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Pain related genes in endometriosis: A meta-analysis

by

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Declaration

I, Manika Saxena hereby declare that the contents of this thesis consist of original work carried out by the author unless otherwise stated and duly acknowledged. To the best of my knowledge no part of this thesis has been submitted in whole or part for the award of any other degree of the university or other institution.

Signature

Manika Saxena

Date
5.03.2015

Abstract

Endometriosis is a benign gynaecological disorder characterised by the presence of endometrial-like glands and stroma occurring outside the uterine cavity. It affects 6-10% women of reproductive age and is often associated with chronic pelvic pain which can be extremely debilitating. Chronic pain in endometriosis may be of nociceptive, neuropathic and/or inflammatory origin. Processes involved in pain generation include neuronal development, peripheral sensitisation due to inflammation, signal transduction, conduction and pain modulation. A range of genes are known to play important roles in these processes and their expression levels are altered in other pain conditions. Dysregulated genes may contribute to pain generation in women with endometriosis. Therefore, the aim of this study was to investigate the expression of pain related genes in women with endometriosis compared to women without the disease by conducting a meta-analysis of available microarray gene expression data and associated clinical information.

Suitable studies and data were identified from electronic databases, gene expression repositories and within a University Obstetrics and Gynaecology department, by limiting the search to peer-reviewed, English language studies. Sixteen published full-text studies and one unpublished thesis were included. Included studies were case-control or cross-sectional design evaluating gene expression of eutopic endometrium from women with and without endometriosis and/or of endometriotic lesions. Study participants were pre-menopausal with regular menstrual cycles and surgically proven to have or not have endometriosis. RNA hybridisation with whole human genome microarray data were extracted and dysregulated gene expression determined through meta-analyses of microarray data.

This study has shown that in the eutopic endometrium from women with endometriosis and endometriotic lesions, pain related genes were significantly upregulated. Genes involved in pain generation were also upregulated in the secretory phase of the menstrual cycle in endometriosis. In particular, genes involved in neuronal development, inflammation leading to sensitisation, signal transduction, conduction and modulation were upregulated.

Upregulation of genes involved in pain generation likely contributes to pain symptoms in women with endometriosis. Increased neuronal development and sensory innervation in the eutopic endometrium and endometriotic lesions may contribute to increased neuronal sensitisation due to the inflammatory microenvironment. This may lead to enhanced signal transduction and conduction of pain signals as well as promotion of pain by pain modulation. An improved understanding of the underlying molecular pain mechanisms may aid in identifying candidate genes for managing endometriosis-associated pain.

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List of Abbreviations

17β-HSD-1: 17β-Hydroxysteroid dehydrogenase-1

17β-HSD-2: Hydroxysteroid dehydrogenase-2

5-HT: Serotonin

ASIC: Acid sensing ion channels

AVIL: Adivilin

BDNF: Brain-derived neurotrophic factor

Ca^{2+}: Calcium ions

CNS: Central nervous system

COX-2: Cyclo-oxygenase-2

DAVID: Database for Annotation, Visualization and Integrated Discovery

DIE: Deep infiltrating endometriosis

DRG: Dorsal root ganglion

EGF: Epidermal growth factor

ER-α: Oestrogen receptor-α

ER-β: Oestrogen receptor β

FDR: False discovery rate

FGF: Fibroblast growth factor

GABA: Gamma-aminobutyric acid

GABBAB: Gamma-aminobutyric acid type B

GABRA2: Gamma-aminobutyric acid A receptor, alpha 2

GAP: Growth associated protein

GEO: Gene expression omnibus

GnRH: Gonadotropin-releasing hormone

GO: Gene ontology

Gp130: Glycoprotein 130

HCL: Hierarchical clustering method

HGF: Hepatocyte growth factor

HPSE: Heparanase

HTR1D: 5-hydroxytryptamine (serotonin) receptor 1D

ICAM-1: Intracellular adhesion molecule-1

IL-1: Interleukin-1

IL-11: Interlukin-11

IL-15: Interleukin-15

IL6ST: Interleukin 6 signal transducer

IL-8: Interlukin-8

JUNB: *Jun B proto-oncogene*

KCNC1: Potassium voltage-gated channel, Shaw-related subfamily, member 1

KCND3: Potassium voltage-gated channel, Shal-related subfamily, member 3

LIF: Leukaemia-inhibiting factor

MAD: Median absolute deviation

MAPK: Mitogen activated protein kinases

mRNA: Messanger ribonucleic acid

MS: Manika Saxena

NCAM: Neural cell adhesion molecule

NGF: Nerve growth factor

NK: Natural killer

NSAID: Non-steroidal anti-inflammatory drugs

NT-3: Neurotrophin-3

NT-4/5: Neurotrophin-4/5

OCs: Oral contraceptives

OSM: Oncostatin M

PNS: Peripheral nervous system

PR: Progesterone receptor

RANTES: Regulated on activation normal T expressed and secreted

RMA: Robust multi-array analysis

RNA: Ribonucleic acid

SE: Standard error

TNF-α: Tumor necrosis factor-α

Treg cells: Regulatory T lymphocytes

TRP: Transient receptor potential

TRPM8: Transient receptor potential M8

TRPV1: Transient receptor potential vallinoid

UNC45A: Unc-45 homolog A (C. elegans)

VCAM-1: Vascular cell adhesion molecule-1

VEGF-A: Vascular endothelial growth factor-A

Chapter 1

Endometriosis

1.1 Introduction

Endometriosis is a benign gynaecological disorder characterised by the presence of endometrial-like glands and stroma outside the uterine cavity (Rahmioglu et al., 2012, Fraser, 2008). It affects approximately 6-10% of women of reproductive age (Fraser, 2008, McLeod and Retzloff, 2010, Simoens et al., 2012). The primary symptoms include pain and infertility (Giudice and Kao, 2004, Fauconnier et al., 2013). It is highly variable in the age of onset; presentation; severity of symptoms; site and extent of pathology; and in the response to treatment, such as recurrence of the disease, alleviation of symptoms and restoration of fertility (Fraser, 2008, McLeod and Retzloff, 2010, Okeke et al., 2011, Kennedy et al., 2005). It is often a debilitating condition, significantly affecting the lives of patients in a variety of ways (Mehedintu et al., 2014).

Endometriotic lesions are an important feature of endometriosis. They usually grow on the peritoneum lining the pelvic/abdominal cavity; occurring on the pelvic/abdominal wall, ovaries, fallopian tubes, outer wall of the uterus and intestines (see Fig. 1.1; Brosens and Benagian, 2011, Koninckx, 1994, Olive and Pritts, 2001). In rare cases, lesions have been observed on the pancreas, pleura, thorax, kidneys, vertebrae and sciatic nerve roots (Fraser, 2008, Olive and Pritts, 2001). Despite extensive research, the aetiology of endometriosis remains poorly understood. Abnormalities of the uterine endometrium as well as changes in the microenvironment around endometriotic lesions may contribute to the development and

maintenance of endometriosis as well as its related symptoms (Ulukus et al., 2006, Jiang and Wu, 2012).

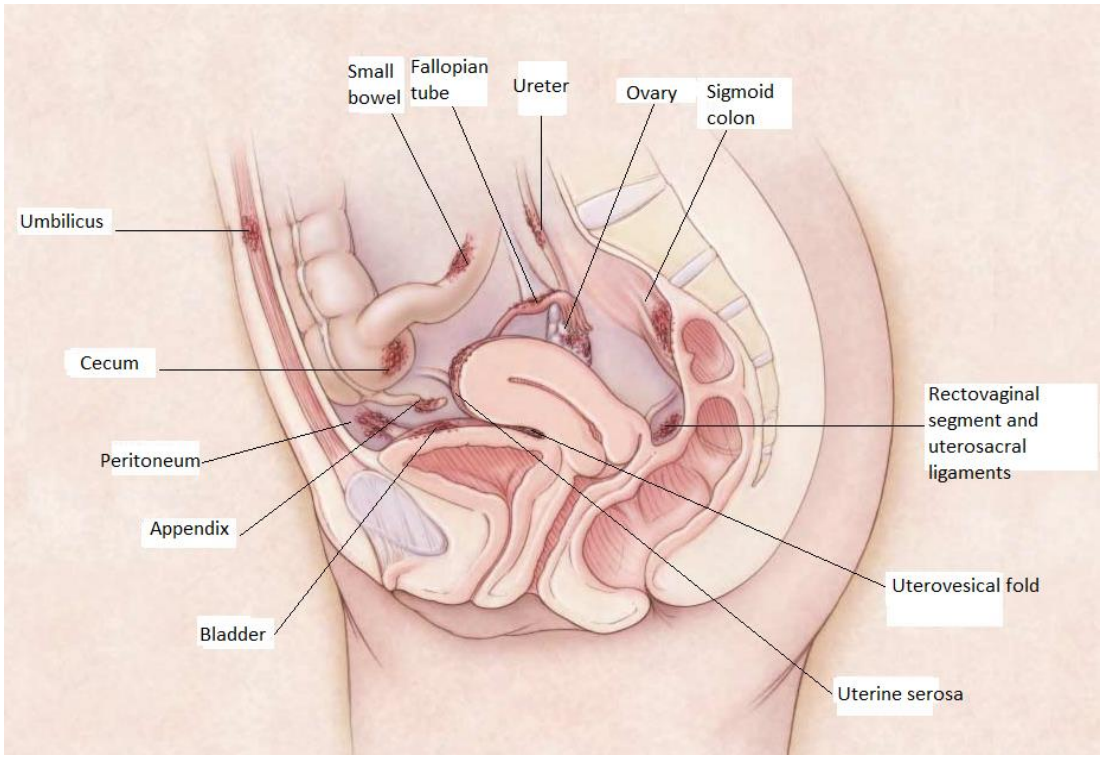


Fig. 1.1: Common sites of endometriosis (Olive and Pritts, 2001).

1.1.1 Heritability

Genetic predisposition plays a role in endometriosis (Speroff, 2005). Although it does not show a clear Mendelian pattern of inheritance, there is a strong familial component (Treloar et al., 1999, Stefansson et al., 2001, Ward et al., 2004, Vigano et al., 2007). There is a six times increased risk of developing endometriosis in first-degree relatives of women with the disease (Coxhead and Thomas, 1993, Moen and Magnus, 1993, Simpson et al., 1980, Kennedy et al., 1995, dos Reis et al., 1999, Augoulea et al., 2012, Simpson and Bischoff, 2002). Specifically, chromosome alterations in arms 5q, 6q, 9p, 11q and 22q and on chromosome 17 have been shown to be associated with endometriosis (Jiang, 1998, Bischoff and Simpson, 2004, Bischoff et al., 2002). A number of gene expression microarray studies

have also identified a range of candidate genes involved in regulating steroid metabolism, neurogenesis, angiogenesis, inflammation and immune response that may be dysregulated in endometriosis, contributing to its development and associated symptoms (Bischoff and Simpson, 2004, Burney et al., 2007, Crispi et al., 2013, Kao et al., 2003, Zondervan et al., 2001, Nyholt et al., 2012, Albertsen et al., 2013).

1.2 Symptoms

The most common symptoms of endometriosis are infertility and pelvic pain. Although a proportion of women with endometriosis may be asymptomatic, women with endometriosis often present with pain. Pain (thoroughly reviewed in Chapter 2) can manifest non-cyclic chronic pelvic pain, dysmenorrhea (menstrual pain), dyspareunia (pain with intercourse) and dyschezia (pain with defecation;Kennedy et al., 2005, Mehedintu et al., 2014). Other associated symptoms may include dysfunctional uterine bleeding, abdominal bloating, pre-menstrual spotting, constipation and chronic fatigue (Bellelis et al., 2010).

1.3 Diagnosis

The complex and highly variable nature of endometriosis makes its diagnosis difficult. A delay in diagnosis is very common as endometriosis shows symptomatic commonalities with other diseases and its diagnosis is invasive (surgical; Mehedintu et al., 2014). A laparoscopy combined with histological confirmation is the gold standard for the diagnosis of endometriosis (Kennedy et al., 2005, Fraser, 2008, Mehedintu et al., 2014). Laparoscopy is a procedure in which an incision is made in the abdomen and the laparoscope (telescopic camera) is inserted, to allow visualisation of the pelvic cavity and biopsies to be taken (Jacobson et al., 2010). Trans-vaginal ultrasound and MRI imaging can diagnose deep infiltrating endometriosis (Marcal et al., 2010, Holland et al., 2010, Bazot et al., 2004). These

techniques are operator-dependent and require both experience and skill to minimise diagnostic error (Fraser, 2008, Valle and Sciarra, 2003, Kennedy et al., 2005). There is an ongoing need for the development of novel non-invasive tools for diagnosis of endometriosis.

1.4 Theories of pathogenesis

Various theories have been put forth to explain the development of endometriosis (Linden, 1996); including, but not limited to, Sampson's retrograde menstruation theory, theory of coelomic metaplasia, theory of lymphatic and vascular induction, and composite theory (Sampson, 1940, Meyer, 1919, Sampson, 1927b, Gazvani and Templeton, 2002). However, no single theory satisfactorily explains the development of endometriosis. The two most popular theories, retrograde menstruation and coelomic metaplasia, are discussed in Sections 1.4.1 and 1.4.2.

1.4.1 Coelomic metaplasia

Metaplasia is a process in which one cell type changes into a different form that is abnormal for that tissue (Iwanoff, 1989, Vercellini et al., 2004, Cullen, 1896). The theory of coelomic metaplasia was proposed by Iwanoff (1989) and then developed by Meyer (1919). It states that normal peritoneal cells may develop into ectopic endometrial cells (Iwanoff, 1989, Meyer, 1919). Evidence linking metaplasia and endometriosis is lacking, but the ultrastructure of pelvic peritoneal tissue from women undergoing surgery suggests that there might be a metaplastic change of peritoneal mesothelial cells into endometrial glandular cells before the establishment of endometriosis in the peritoneum (Matsuura et al., 1999, Nap et al., 2004, Vinatier et al., 2001). An extension to the theory of metaplasia is the induction theory which proposes that one or more endogenous, biochemical or immunological factors

secreted by menstrual endometrium may promote differentiation of peritoneal cells to endometrial-like cells (Nap et al., 2004, Burney and Giudice, 2012).

1.4.2 Retrograde menstruation

In 1927, Sampson proposed the theory of retrograde menstruation, also known as the implantation theory (Sampson, 1927a). According to this theory, endometriosis develops through the retrograde flow of viable endometrial fragments into the peritoneal cavity during menstruation, which then implant on the peritoneum and form lesions (Sampson, 1940). In retrograde menstruation, menstrual fluid flows through the fallopian tubes instead of leaving through the vagina (Nap et al., 2004, Halme et al., 1984).

This theory is currently the most widely accepted as clinical findings suggest that endometriotic lesions tend to cluster around structures closer to the distal ends of the fallopian tubes (Dmowski and Radwanska, 1984, Al-Fozan and Tulandi, 2003). Women with anatomical variations or abnormalities obstructing the menstrual outlet, such as cervical stenosis and other mullerian anomalies, have a higher risk of developing endometriosis due to increased volume of retrograde menstruation (Sanfilippo et al., 1986, Barbieri, 1998, Fallas, 1956). Furthermore, viable endometrial cells are present in the menstrual and peritoneal fluid of women with endometriosis; these cells have the capability to adhere to the peritoneum, followed by implantation (Koninckx et al., 1980, Koks et al., 1997, Nisolle et al., 2007). However, Sampson's theory does not explain why endometriosis does not develop in all women with retrograde flow, as retrograde menstruation happens in 90% of all women with patent fallopian tubes (Vercellini et al., 2004, Nap et al., 2004, Halme et al., 1984). It is becoming increasingly evident that other molecular and biochemical factors are involved in the pathogenesis of endometriosis.

1.5 Eutopic endometrial anomalies

The eutopic endometrium of women with endometriosis shows differences in physiology and biochemistry compared to the endometrium of women without endometriosis (Meresman et al., 2000). Increasing evidence indicates that anomalies of the endometrium such as decreased apoptosis, evasion of immune surveillance, increased cell adhesion and proliferation, increased angiogenesis and neurogenesis and local oestrogen production may contribute to lesion establishment, disease progression and associated symptoms (Agic et al., 2009, Tabibzadeh, 1998, Giudice and Kao, 2004, Sharpe-Timms, 2001, Khoufache et al., 2012).

1.5.1 Decreased apoptosis

Apoptosis is a physiological process of programmed cell death whereby excess and dysfunctional cells are eliminated by a regulated sequence of molecular events without eliciting an inflammatory response (Taniguchi et al., 2011, Kerr et al., 1972, Alison and Sarraf, 1992). During menstruation, apoptosis plays a regulatory role by removing senescent cells from the lining of the endometrium (Nasu et al., 2011, Taniguchi et al., 2011). In women with endometriosis, apoptosis in the endometrium is greatly reduced (Beliard et al., 2004, Taniguchi et al., 2011, Liu and Lang, 2011). This may be attributed to the increased expression of bcl-2, which blocks the apoptotic pathways and decreased expression of bax, which promotes apoptosis, in the eutopic endometrium from women with endometriosis compared to women without the disease (Jones et al., 1998a, Meresman et al., 2000, Harada et al., 2004, Nasu et al., 2011). Moreover, there is dysregulation of genes involved in apoptosis in the eutopic endometrium of women with endometriosis which further inhibits apoptosis (Zubor et al., 2009). This leads to entry of viable endometrial cells into the peritoneal cavity (Beliard et al., 2004, Harada et al., 2004).

1.5.2 Ineffective immune response

Local immune cells facilitate the clearance of endometrial fragments following menstrual shedding (Liu and Lang, 2011, Ulukus et al., 2006). Several immune cell populations are disturbed both in function and numbers in the eutopic of women with endometriosis (Sharpe-Timms, 2001, Berbic et al., 2009, Matarese et al., 2003). Cytotoxicity of natural killer (NK) cells is decreased and T lymphocyte function is defective (Christodoulakos et al., 2007, Giudice et al., 1994, Helvacioglu et al., 1997). Regulatory T lymphocytes (Treg cells) are increased during the secretory phase and suppress the action of other immune cell populations (Berbic et al., 2010). Increased immature dendritic cell density in the eutopic endometrium with decreased presence of mature dendritic cells indicates impaired recognition of foreign or displaced cells (Braun and Dmowski, 1998, Matarese et al., 2003). Moreover, macrophage numbers are decreased during menstruation (Sharpe-Timms, 2001, Sharpe-Timms et al., 2002). In endometriosis, the endometrial immune system appears unable to contain shed endometrial fragments, indicating that more viable shed endometrial cells reach the peritoneal cavity subsequently leading to establishment of the lesions (Sharpe-Timms et al., 2002, Christodoulakos et al., 2007, Ulukus et al., 2006). The resident immune cell populations of the eutopic endometrium also produce pro-inflammatory cytokines/chemokines (Sinaii et al., 2002, Herington et al., 2011). Furthermore, the mRNA levels of genes encoding for immune cells as well as inflammatory cytokines are increased in the eutopic endometrium of women with endometriosis (Chand et al., 2007, Kyama et al., 2008, Akoum et al., 1995). This may trigger an intense inflammatory response and contribute to pain in endometriosis (Berkley et al., 2005).

1.5.3 Increased cell adhesion and proliferation

In the eutopic endometrium of women with endometriosis, both protein and mRNA expression levels of cell adhesion molecules such as integrin-αvβ3, cadherins, intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), CD166, annexin A2, interlukin-11 (IL-11) and leukaemia-inhibiting factor (LIF) are increased (Sundqvist et al., 2012, Dimitriadis et al., 2006, Fowler et al., 2007, Al Jefout et al., 2009, Somigliana et al., 1996, Abu-Asab et al., 2011, Burney et al., 2007). This is thought to lead to the attachment of refluxed endometrial tissue on to the peritoneal surface and promote lesion establishment (Ulukus et al., 2006, Al Jefout et al., 2009, Witz et al., 1999).

Increased cell proliferation has also been observed in the eutopic endometrium of women with endometriosis (Johnson et al., 2005, von Rango et al., 1998, Jones et al., 1998b). For example, there is an increased number of endothelial, epithelial and stromal cells in the eutopic endometrium of women with endometriosis when compared to women without endometriosis (Wingfield et al., 1995, Jones et al., 1998b, Jiang and Wu, 2012). Increased proliferation in the eutopic endometrium likely contributes to endometrial cell survival, implantation and growth in ectopic locations (Lawson et al., 2008, Lessey et al., 1994, Wingfield et al., 1995, Johnson et al., 2005, Kyama et al., 2008).

1.5.4 Angiogenesis

Angiogenesis is the process of formation of new blood vessels from pre-existing blood vessels (Xu et al., 2013). It is an important process for the progression of endometriosis as the lodged endometrial fragments on the peritoneum require blood supply for survival (Liu and Lang, 2011). The eutopic endometrium of women with endometriosis is highly angiogenic compared to the endometrium from women without endometriosis (Laschke and Menger,

2007, Torry and Torry, 1997, Groothuis et al., 2005, Hur et al., 2006). In the eutopic endometrium of women with endometriosis, there is a higher protein and gene expression of angiogenic factors, such as vascular endothelial growth factor-A (VEGF-A), interlukin-8 (IL-8), fibroblast growth factor (FGF), hepatocyte growth factor (HGF) and epidermal growth factor (EGF) compared to endometrium from women without endometriosis (Bourlev et al., 2006, Nisolle et al., 1993, Mihalich et al., 2003, Sugawara et al., 1997, Fukaya et al., 1999, Jiang and Wu, 2012, Mueller et al., 2000, Takehara et al., 2004, Huang and Yeh, 1994). These findings indicate that increased angiogenic capacity of the eutopic endometrium may facilitate establishment of a blood supply for ectopically implanted endometrial fragments and therefore initiation and progression of endometriosis.

1.5.5 Local oestrogen production

In the eutopic endometrium of women with endometriosis, there is evidence of excessive oestrogen production (Dassen et al., 2007, Bukulmez et al., 2008, Aghajanova et al., 2009, Kitawaki et al., 1997). Aromatase, an essential enzyme for oestrogen production, not expressed in normal endometrium, is highly expressed in the eutopic endometrium of women with endometriosis (Kitawaki et al., 1997, Kyama et al., 2008). There are increased levels of 17β-hydroxysteroid dehydrogenase-1 (17β-HSD-1) and decreased levels of 17β-HSD-2 which catalyse the activation and inactivation of oestradiol, respectively (Zeitoun et al., 1998, Andersson and Moghrabi, 1997, Dassen et al., 2007). Aberrant aromatase gene and protein expressions along with defective oestradiol metabolism may increase local oestrogen levels, which correspond with elevated oestradiol concentrations in the menstrual blood of women with endometriosis (Lessey et al., 1988, Nisolle and Donnez, 1997, Attia et al., 2000, Al-Sabbagh et al., 2012, Ulukus et al., 2006, Kyama et al., 2008). Excessive oestrogen

production favours the inflammatory characteristics of endometriosis and lesion growth and persistence (Tsai et al., 2001, Bulun et al., 2001).

1.5.6 Neurogenesis

Neurogenesis is the formation of nervous tissue occurring under the control of neurotrophic factors and their receptors (Asante and Taylor, 2011). In eutopic endometrium from women with endometriosis, there is increased protein and gene expression of neurotrophic factors, such as nerve growth factor (NGF), neurotrophin-3 and neurotrophin-4/5 (NT-3, NT-4/5), and brain-derived neurotrophic factor (BDNF) compared to women without endometriosis (Browne et al., 2012, Tokushige et al., 2008). Increased density of neuroendocrine cells has also been identified in the eutopic endometrium of women with endometriosis, which produce neuromodulatory substances in response to chemical stimulation (Tischler, 1989, Wang et al., 2010). In addition, in the eutopic endometrium of women with endometriosis, nerve fibres have been identified in the functional layers of endometrium and myometrium of women with endometriosis, not found otherwise in the endometrium from women without endometriosis (Tokushige et al., 2007, Tokushige et al., 2006a, Zhang et al., 2009, Aghaey Meibody et al., 2011). These nerve fibres are sensory C, adrenergic and cholinergic, responsible for transmitting dull, throbbing and diffuse pain (Al-Jefout et al., 2009, Al Jefout et al., 2009). Increased neurogenesis as well as the presence of nerve fibres in the eutopic endometrium of women with endometriosis may be responsible for increased peripheral sensitisation contributing to the pain-related symptoms of endometriosis (Bloski and Pierson, 2008, Tokushige et al., 2006a).

Endometriosis remains an enigmatic gynaecological disorder. It is becoming increasingly evident that fundamental changes in the eutopic endometrium of women with endometriosis

may contribute to development of the disease. The presence of aberrantly expressed apoptotic, immuno-modulatory, adhesive, proliferative, hormonal, angiogenic and neurogenic factors within the eutopic endometrium may contribute to the development of the endometriosis and its associated symptoms. The pro-inflammatory microenvironment of the eutopic endometrium along with the presence of small unmyelinated sensory nerve fibres may also contribute to the associated pain symptoms. However, it should be noted that exact mechanisms of pain generation remain unknown and require in-depth study of the involved molecular mechanisms (discussed further in Chapter 2).

1.6 Endometriotic lesions

There are three broad types of endometriotic lesions: superficial peritoneal endometriosis, ovarian endometriomas and deep infiltrating endometriosis (DIE; described in more detail in Table 1.1). Typical endometriotic lesions show histological features similar to the endometrium, with stroma and glandular epithelium that respond to hormonal stimuli and exhibit characteristics of cyclic growth (Weitzman and Buttram, 1989). However, there are many differences between the cells of endometriotic lesions and those of the surrounding/normal peritoneum or the eutopic endometrium, including differences related to angiogenesis, hormone production and responsiveness, immune environment and neurogenesis.

Table 1.1: Types of endometriotic lesions.

Lesion type	Appearance	Characteristics	Location
Peritoneal endometriotic lesions[1]	Clear	Papules that resemble normal endometrium	Around the peritoneum, fallopian tubes and bowel
	Red flare	Considered the most "active"; highly vascularised	
	Blue-black	Puckered; presence of pigmented haemosiderin deposits from "old blood"; older, more advanced than red flare and considered less active	
	White	Surrounded by dense collagen and connective tissue deposits; thought to be older and the least active	
Ovarian endometriomas[2]	Brown tar-like filled cysts	Contain shed menstrual debris; arise after endometrial ectopic implantation	On the ovaries
Deep-infiltrating endometriosis[3]	Nodular in appearance	Firm, solid, tumour-like mass that extends more than 5 mm from peritoneal surface into adjacent structures	Posterior cul-de-sac, uterosacral ligaments, bowel, bladder and the rectovaginal septum

1(Brosens et al., 2012, Nisolle et al., 1997, Donnez et al., 2003)

2(Nisolle et al., 1997)

3(Nisolle et al., 1997)

1.6.1 Angiogenesis

Angiogenesis is essential for the growth and persistence of endometriotic lesions, as lesions derive their blood supply from the surrounding vasculature (Xu et al., 2013). A number of angiogenic factors are synthesised by endometriotic lesions, the most potent and strongly expressed being VEGF-A (Donnez et al., 1998, Machado et al., 2008, Tan et al., 2002,

Takehara et al., 2004). VEGF-A gene and protein expression has been observed to be higher in endometriotic lesions compared to eutopic endometrium (Di Carlo et al., 2009, Donnez et al., 1998, Bourlev et al., 2006, Tan et al., 2002). Angiogenic properties also tend to differ between lesion types, for example, active, early-developing, red flare lesions show greater vascularisation compared to less active black or white scarred lesions (Matsuzaki et al., 2001). In general, peritoneal lesions have greater expression of VEGF-A compared to ovarian (Tan et al., 2002, Takehara et al., 2004). Furthermore, deep infiltrating lesions show higher expression of VEGF-A and greater blood vessel density compared to peritoneal or ovarian lesions (Machado et al., 2008).

1.6.2 Hormone production and responsiveness

Oestrogen is the key hormone that regulates growth and development of endometriotic lesions (Jones et al., 1995). Oestradiol, biologically active oestrogen, is locally produced within lesions (Bulun et al., 2012), attributable to increased aromatase at both transcriptional and protein levels (Kitawaki et al., 1997, Zeitoun et al., 1998, Vinatier et al., 2000, Kyama et al., 2008, Bukulmez et al., 2008). In lesions, cyclo-oxygenase-2 (COX-2) which stimulates oestrogen production (and vice versa) is also upregulated, creating a positive feedback loop favouring continuous oestrogen production (Attar and Bulun, 2006, Tsai et al., 2001). Increased expression of enzymes such as 17β-HSD-1 in endometriotic lesions also contributes to local oestrogen production (Huhtinen et al., 2012, Rižner, 2009, Smuc et al., 2007, Cheng et al., 2008, Borghese et al., 2010).

The actions of oestrogen and progesterone are mediated through their receptors, oestrogen receptor (ER-α and -β) and progesterone receptor (PR) (Bulun et al., 2012, Bukulmez et al., 2008, Bulun et al., 2010). Significantly lower transcriptional and protein levels of

progesterone receptors and ER-α have been observed in endometriotic lesions compared to the eutopic endometrium from women with endometriosis (Attia et al., 2000, Bulun et al., 2006, Bukulmez et al., 2008). These changes may contribute to the loss of control of oestrogen production and resistance to progesterone observed in women with endometriosis, thought to facilitate development and progression of the disease (Bulun et al., 2010, Xue et al., 2007, Attia et al., 2000).

1.6.3 Immune alterations

Macrophages, immature dendritic cells, natural killer cells and T cells are recruited directly to the site of endometriotic lesions, possibly in an attempt to clear the lesion (Tran et al., 2009, Jones et al., 2002, Schulke et al., 2009, Berbic and Fraser, 2011). However, the local immune environment is dysfunctional and lesions persist (Herington et al., 2011, Berbic and Fraser, 2011). These immune cells produce cytokines, chemokines, growth factors and potent angiogenic factors which actually contribute to the survival and ectopic growth of endometrial tissue fragments (Lebovic et al., 2001). An inflammatory response is initiated and mediators are released which stimulate blood flow and extravasation of leukocytes (neutrophils and monocytes) from blood vessels into the tissue, further favouring lesion persistence (Berbic and Fraser, 2011, Christodoulakos et al., 2007, Sidell et al., 2002).

1.6.4 Neurogenesis

Neuronal growth has been observed in endometriotic lesions (Wang et al., 2009, Guo and Wang, 2006, Mechsner et al., 2007). The protein and mRNA expressions of NGF and other neurotrophins; such as NT-3, NT-4 and BDNF; and their receptors are increased in endometriotic lesions (Tokushige et al., 2010, Tokushige et al., 2006a, Anaf et al., 2002, Abu-Asab et al., 2011). Increased angiogenesis and immune cell populations produce

neuroattractant cytokines which promote nerve fibre growth into lesions (Tokushige et al., 2006a, Tlandi et al., 2001, Tamburro et al., 2003, Anaf et al., 2006, Asante and Taylor, 2011, Berbic et al., 2009). Moreover, abnormal hormonal environment promotes higher expression of neurotrophic factors and neuronal growth (Anaf et al., 2002, Tokushige et al., 2006b).

Furthermore, nerve fibres have been observed in all types of endometriotic lesions (Tokushige et al., 2006b, Tokushige et al., 2010, Herington et al., 2011, Mechsner et al., 2007, Anaf et al., 2002). These nerve fibres are a mixture of sensory Aδ, sensory C, adrenergic and cholinergic (Tokushige et al., 2006b, Mechsner et al., 2007). Presence of sensory nerve fibres in the endometriotic lesions may contribute to the pain symptoms associated with endometriosis (Tokushige et al., 2006a, Morotti et al., 2014b). Interestingly, higher densities of nerve fibres and neurotrophins have been observed in DIE lesions compared to peritoneal or ovarian lesions, which correlates with increased pain in women with DIE (Herington et al., 2011, Vercellini et al., 2007, Stratton and Berkley, 2011, Gruppo Italiano per lo Studio, 2001). A recent study also suggests that women who complain of moderate to severe pain have higher densities of endometriosis-associated nerve fibres (Mechsner et al., 2009).

Overall, it appears that abnormal eutopic endometrium predisposes susceptible women to develop endometriosis. In addition, it is likely the presence of endometriotic lesions further regulates the eutopic endometrium. Ongoing processes in endometriotic lesions not only contribute to disease progression, but apparently also to the development of associated symptoms such as pain. However, mechanisms of pain generation in women with endometriosis are not well understood (further explored in Chapter 2).

Chapter 2

Pain in Endometriosis

2.1 Introduction

The most common symptom of endometriosis is pain, however pain mechanisms in endometriosis remain poorly understood (Taylor et al., 1999, Ozkan et al., 2008, Martinez-Roman et al., 1997, Kao et al., 2003, Triolo et al., 2013, Kobayashi et al., 2013, Morotti et al., 2014b). As introduced in Chapter 1, pain associated with endometriosis can be broadly described as the common triad of dysmenorrhoea (painful menses), dyspareunia (painful sexual intercourse) and dyschezia (pain with defecation; Nasir and Bope, 2004, Fraser, 2008). Pain intensity does not correspond with the anatomical severity or other parameters of endometriosis (Mathias et al., 1996 , Fraser, 2008). It has been linked to the presence of unmyelinated sensory nerve fibres in the eutopic endometrium and endometriotic lesions; interaction between peripheral nerves, the peritoneal environment and the central nervous system; as well as to altered hormonal, immune and inflammatory environments in the pelvis (Evans et al., 2007, Tokushige et al., 2006a, Reis et al., 2013, Morotti et al., 2014b, Stratton and Berkley, 2011, Asante and Taylor, 2011).

2.2 Nervous system

The nervous system is divided into the central nervous system (CNS) and peripheral nervous system (PNS). The CNS consists of the brain and spinal cord; the PNS of sensory neurons, ganglia and nerves, which connect to the CNS (Amann and Constantinescu, 1990, Barker, 1901). The divisions and functions of the CNS and PNS are summarised in Fig. 2.1.

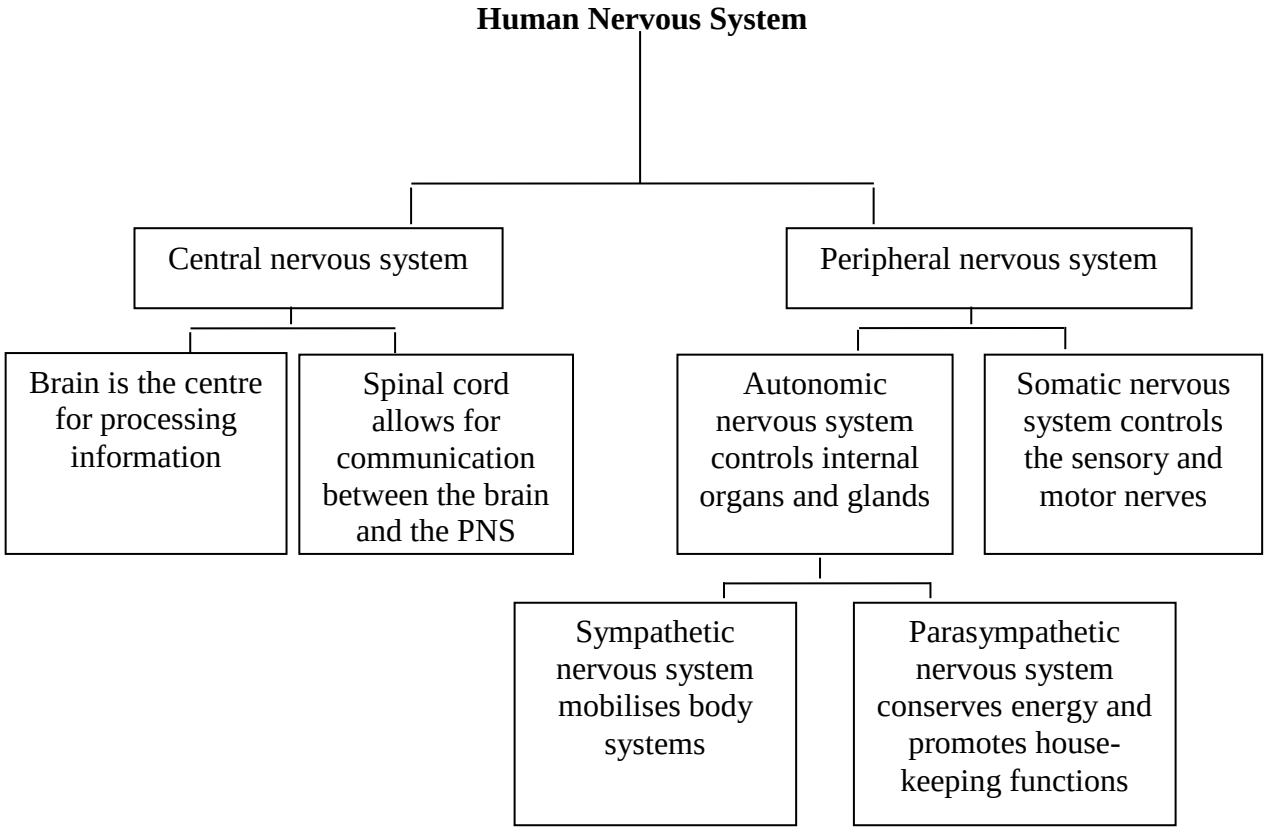


Fig. 2.1: Organisation of the nervous system (adapted from Barker, 1901).

Neurons are the basic units of the nervous system, connecting to form neural networks (Luse, 1956, DeFelipe, 1997). Each neuron consists of dendrites (projections that receive electric stimuli), a cell body and axons (Bohler et al., 2007). Axons are specialised structures that conduct and transmit action potentials to adjacent neurons via synapses (Liu and Bahu, 1975). Once the signal reaches the axon terminal a neurotransmitter is released which rapidly crosses over to the receptor site of the next neuron (DeFelipe, 1997).

Specialised neurons are triggered by specific stimuli (Dubin and Patapoutian, 2010). Sensory neurons**,** also known as afferent neurons, respond to stimuli such as sound, touch, light and changes in the pH. The Aδ and C afferent sensory neurons that respond to painful stimuli are known as nociceptors (Barker, 1901, Dubin and Patapoutian, 2010). Nociceptors have high

sensitivity and are sensitised by mechanical, thermal or chemical stimuli leading to pain generation (Dubin and Patapoutian, 2010, Basbaum et al., 2009, Millan, 1999).

2.2.1 Female pelvic innervation

The female pelvis is a complex structure and any dysfunction within it can lead to pelvic pain (Wasnik et al., 2011). The female pelvis has both sympathetic and parasympathetic nerve supplies (Ferner, 1964, Keast, 2006). Furthermore, the pelvic viscera are innervated with both sensory and motor fibres. The motor nerve fibres extend from the spinal cord or the brain to the organ and sensory fibres bring information back to the spinal cord or brain (Frank and Netter, 2006). The complex innervation of the pelvis comes from the superior hypogastric plexus, sympathetic chain (L1–L5), parasympathetic fibres (S2–S4) and sacral plexus (sacral splanchnic nerves, S1–S5; see Fig. 2.2; Cervero, 1994, Keast, 2006). Visceral sensory nerve fibres respond to noxious stimuli and can evoke the sensation of pain which is generally poorly localised (Cervero, 2010, Cervero, 1991). Most visceral sensory nerve fibres are Aδ and C unmyelinated fibres, as observed in the eutopic endometrium and endometriotic lesions of women with endometriosis (Cervero and Laird, 2004, Tokushige et al., 2006a, Tokushige et al., 2007, Wang et al., 2009). These fibres are responsible for transmitting dull, throbbing pain (Bielefeldt et al., 2006).

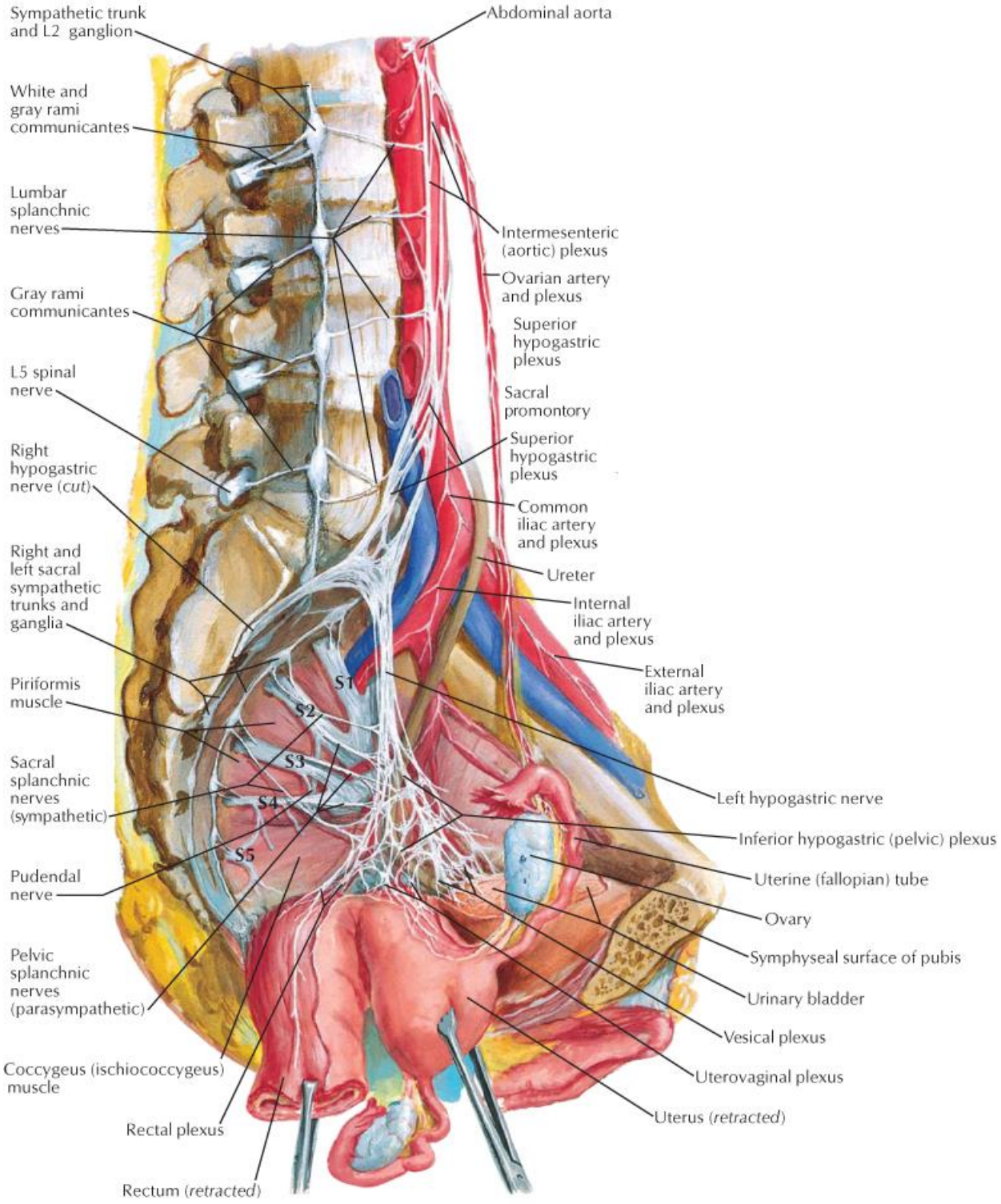


Fig 2.2.: Female pelvic innervation (Frank and Netter, 2006).

2.3 Pain

According to the International Association for the Study of Pain, pain is defined as an unpleasant emotional and sensory experience due to noxious stimuli associated with actual or potential tissue damage (Merskey and Bogduk, 1994, Anand and Craig, 1996, Schaible, 2007, Howard, 2009). Pain can be acute or chronic. Acute pain is the normal processing that warns the body against noxious stimuli. In contrast, chronic pain is caused by disease or when noxious stimuli persist for longer periods (six months or more; Schaible, 2007, Calvino and Grilo, 2006, Russo and Brose, 1998). Pain is also influenced by social and psychological factors (Merskey, 1994, Chapman and Gavrin, 1999, Kendall, 1999) and can promote a stress response leading to fatigue, impaired mental and physical function (Chapman and Gavrin, 1999, Kendall, 1999).

Pain is generated when potentially noxious stimuli sensitise the surrounding specialised sensory neurons known as nociceptors responsible for transmitting painful signals, thus generating an action potential which is conducted along the nerve axons to the spinal cord and the CNS (Latremoliere and Woolf, 2009, Schaible, 2007, Ji and Woolf, 2001). The CNS then processes the received information and generates responses of pain recognition such as discrimination and localization, arousal and aversive reactions due to the noxious event (Schaible, 2007, Cervero, 1995, Cervero and Laird, 2004). Application of noxious stimuli can either lead to spontaneous pain (pain in the absence of any intentional stimulation), hyperalgesia (extreme pain from a stimulus that evokes pain) and/or allodynia (pain due to a stimulus that does not usually provoke pain; Jensen and Finnerup, 2014).

Pain can be further classified into nociceptive, neuropathic and inflammatory. Nociceptive pain typically originates from the peripheral tissue to warn of potentially noxious stimuli

(Asante and Taylor, 2011, Cervero, 1988, Fraser, 2010, Grimm et al., 2011, Howard, 2009). It includes four basic processes: transduction, transmission, modulation and perception (described in detail in Section 2.4; Howard, 2009). It may be somatic or visceral in origin. Somatic pain is localised and is often recognised as sharp pain, whereas visceral pain is diffuse and often difficult to assess (Vercellini et al., 2009, Gebhart, 2000). Neuropathic pain is caused by damage to the central or peripheral nervous system (Latremoliere and Woolf, 2009, Campbell and Meyer, 2006). It generally does not trigger an acute event but leads to a state of chronic pain (Howard, 2009, Sivilotti and Woolf, 1994). Following nerve injury, persistent axonal discharges set up abnormal neural circuits via the spinal cord resulting in persistent, prolonged or intermittent signals to the brain and even after the original stimulus has been removed (Wu et al., 2001, Djouhri et al., 2006, Obata et al., 2003). In inflammatory pain, sensitisation lowers the threshold of polymodal nociceptors as well as recruits insensitive nociceptor which evokes an intense response and renders non-painful stimuli to be painful (Schaible, 2007, Voscopoulos and Lema, 2010, Staud, 2011). However, pain may not strictly be nociceptive, neuropathic or inflammatory as all three may contribute to one another (Schaible, 2007).

2.3.1 The pain matrix

The pathways and processes in the body associated with pain perception are complex and may collectively be referred to as the pain matrix (Tracey and Mantyh, 2007). The processes involved in pain generation include neuronal development, peripheral sensitisation due to inflammation, transduction, conduction via synaptic transmission and modulation (see Fig. 2.3; Foulkes and Wood, 2008). These processes are described in more detail below in Sections 2.3.1.1-2.3.1.5.

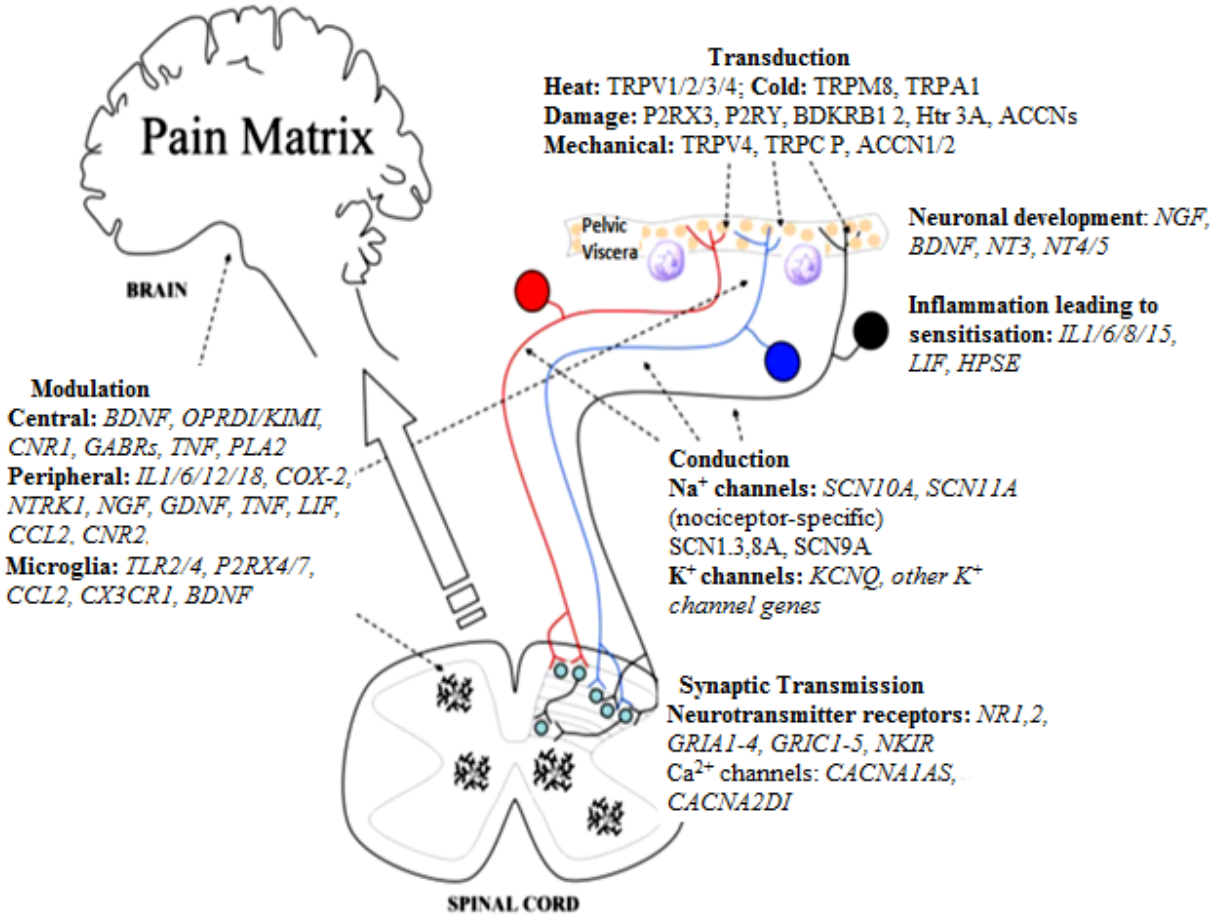


Fig. 2.3: Figure illustrating pain pathways and processes from the site of injury through the spinal cord to the brain; as well as the genes involved in the transduction, conduction, transmission and modulation of pain (adapted from Foulkes and Wood, 2008).

Briefly, in the periphery, enhanced neuronal remodelling and development may lead to increased peripheral sensitisation due to pro-inflammatory mediators produced following a noxious event (Schaible, 2007). This activates the nociceptors on the peripheral nerves to create action potentials, causing depolarisation of the local membranes and transmission along the axons (Foulkes and Wood, 2008, Cervero and Laird, 2004). Synaptic transmission takes place in the spinal cord. Cytokines, released in response to injury, alter the excitability of sensory neurons leading to pain modulation (Cervero and Laird, 2004, Sivilotti and Woolf, 1994). From the spinal cord, information is transmitted to the brain and processed (Foulkes

and Wood, 2008, Apkarian et al., 2005, Gangadharan and Kuner, 2013, Kuner, 2010, Kitahata, 1993, Willis, 1985, Millan, 1999, Derbyshire, 2000).

Pathways and processes in chronic pain are more complex. Chronic pain persists even after the original injury heals, and is influenced by an individual's genetically determined pain sensitivity combined with changes in the neuroplasticity of the CNS (Phillips and Clauw, 2011, Sarzi-Puttini et al., 2011, Staud, 2011). Individuals with chronic pain have enhanced sensitisation to stimuli and increased levels of pro-inflammatory mediators involved in pain modulation (Vincent et al., 2011, Kaya et al., 2013).

2.3.1.1 Neuronal development

Neurotrophic factors such as NGF and BDNF are responsible for the development, survival and maintenance of sensory neurons in the periphery (Lindsay, 1996, Huang and Reichardt, 2001). Both protein and mRNA expressions of these growth factors are known to be increased during pain generation, which may contribute to increased neuronal development in the periphery (Cho et al., 1997b, Zhu et al., 2001, Hinsby et al., 2004, Lin et al., 2011, McKelvey et al., 2013). The sensitisation of the peripheral sensory neurons by pro-inflammatory mediators contributes to pain generation (Cervero, 1995, Voscopoulos and Lema, 2010, Gangadharan and Kuner, 2013).

Persistent noxious stimulation leads to remodelling of the neurons as well as neuronal synapses which intensify signal transmission (Voscopoulos and Lema, 2010, Treede, 1999). This leads to the sensory neurons becoming more sensitive to noxious stimulation and evoking a stronger response to even non-painful stimuli (Russo and Brose, 1998, Schachner, 1997, Voscopoulos and Lema, 2010). Moreover, the remodelled neurons tend to develop

more connections with the neurons in the dorsal root ganglion (DRG) of the spinal cord and CNS in order to transmit more painful signals contributing to the development of chronic pain (Ji and Woolf, 2001, Woolf and Salter, 2000).

2.3.1.2 Sensitisation due to inflammation

Peripheral sensitisation leads to lowering of threshold of peripheral sensory neurons and activating the nociceptors at the peripheral nerve ends (Gangadharan and Kuner, 2013, Kitahata, 1993, Staud, 2011, Schaible, 2007). This generates an action potential which is transferred from the nerves to the spinal cord and the brain (Schaible, 2007, Voscopoulos and Lema, 2010). Following a noxious event, the pro-inflammatory mediators such as cytokines and growth factors, released by the damaged cells directly sensitise the nociceptors (Sommer and Kress, 2004, Kawasaki et al., 2008, Pezet and McMahon, 2006). Furthermore, inflammatory mediators such as prostaglandins, serotonin and bradykinin alter the sensitivity of the sensory neurons to mechanical and thermal stimuli (Dray and Perkins, 1993, Bardin, 2011, Voscopoulos and Lema, 2010).

Due to persistent sensitisation due to inflammation, the threshold of the peripheral sensory neurons lowers to an extent that innocuous stimuli can activate the nociceptors (Schaible, 2007). Moreover, mechano-insensitive nerve fibres become mechano-sensitive fibres leading to a much more pronounced input to the spinal cord (Schaible, 2007, Russo and Brose, 1998, Voscopoulos and Lema, 2010). Following injury, both protein and gene levels of inflammatory mediators upregulate contributing to increased peripheral sensitisation thereby leading to pain generation (Banner and Patterson, 1994, Gadient and Patterson, 1999, Page et al., 2005, Homma et al., 2013).

2.3.1.3 Transduction

Transduction is the conversion of noxious stimuli to electrical impulses. It takes place when nerve endings of nociceptors (C and Aδ fibres) respond to noxious stimuli (Foulkes and Wood, 2008, Xu et al., 2008, Cervero and Laird, 2004, Treede, 1999). Nociceptors are distributed in the skin, muscles, connective tissue, bones, joints and viscera. Their characteristics and functions are detailed in Table 2.1 (Millan, 1999, Binshtok, 2011). Once a noxious stimulus is received by the nociceptor, an action potential is generated due to the opening of ion channels and a flux of ions across cell membranes within the afferent sensory neurons (Foulkes and Wood, 2008). Information regarding the intensity and site of injury is sent to the CNS via these action potentials (Gangadharan and Kuner, 2013, Dussor et al., 2009).

Table 2.1: Types of nociceptors

Type of nociceptor	Type of stimuli	Receptors	Acute or chronic pain	Type of nerve fibre
Thermal[1]	Noxious heat (~40-45°C); cold (10-15°C)	TRPV1, TRPM8	Acute pain	Small diameter, myelinated Aδ fibres
Mechanical[2]	Change in pressure; distension; cuts; blows	TRPV4, Vesicular glutamate transporter	Acute pain	Small diameter, myelinated Aδ fibres
Chemical[3]	Changes in pH; inflammatory mediators; capsaicin	Acid sensing ion channels (ASIC),	Chronic pain	Small diameter, unmyelinated C fibres
Polymodal[4]	Change in temperature, pressure and pH; inflammatory mediators	TRPA1, tachykinin NK1 receptor	Chronic pain	Small diameter, unmyelinated C fibres

1 (Dubin and Patapoutian, 2010, Foulkes and Wood, 2008, Lee et al., 2005b, Levine and Alessandri-Haber, 2007, Liu et al., 2013)

2 (Dubin and Patapoutian, 2010, Lee et al., 2005b)

3 (Dubin and Patapoutian, 2010, Lee et al., 2005b, DeFelipe, 1997)

4 (Dubin and Patapoutian, 2010, Lee et al., 2005b, Treede, 1999)

Genes involved in transduction are expressed in the primary sensory neurons (Treede, 1999, Foulkes and Wood, 2008, Zakir et al., 2012, Urano et al., 2012). Some genes are specifically expressed following tissue damage, mediate the release of soluble mediators following sensitisation and increase the excitability of sensory neurons (Trang et al., 2006, Chessell et al., 2005, Binshtok, 2011, Lee et al., 2005b).

2.3.1.4 Conduction and transmission

Pain impulses are conducted from the site of transduction along sensory nerve fibres and transmitted to the dorsal horn neurons of the spinal cord via synapses, and then to the brain (see Fig. 2.4; Schaible, 2007, Foulkes and Wood, 2008, Argoff, 2011, Gangadharan and Kuner, 2013, Lee et al., 2005b).

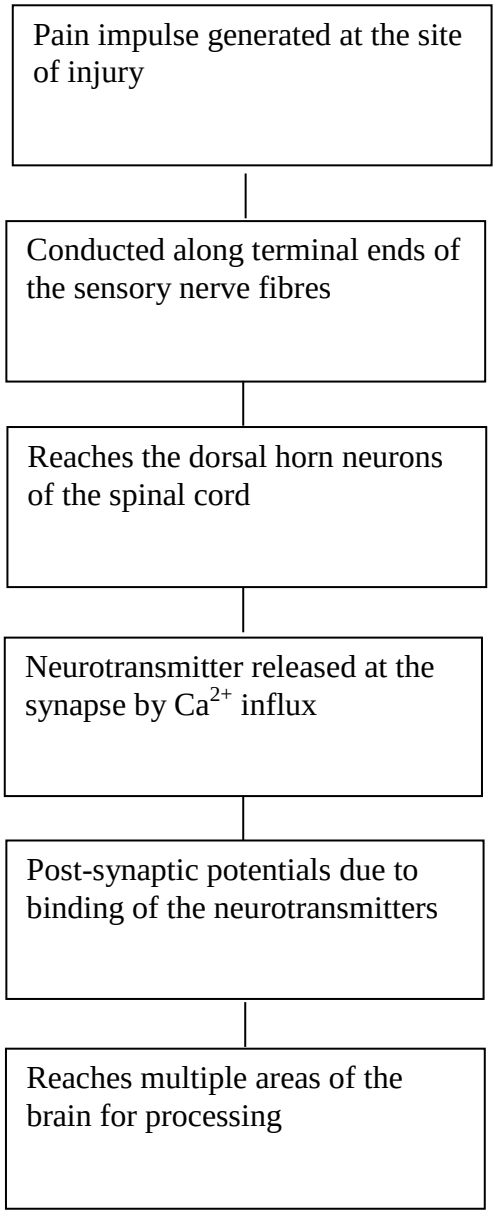


Fig. 2.4: Schematic presentation of conduction and transmission of pain impulses from the site of injury to the brain.

Voltage-gated sodium ion channels conduct action potentials along the axons to the spinal cord (Waxman et al., 1999, Lee et al., 2005b, Wood, 2004, Foulkes and Wood, 2008). In response to depolarisation of local membranes, sodium channels open and allow an influx of sodium ions generating a potential in the terminal ends of the sensory neurons and conducting them along the axons (Dib-Hajj et al., 2010, Binshtok, 2011, Waxman, 2010, Waxman et al., 1999, Lee et al., 2005b).

The action potential is transmitted from the peripheral nerve fibres to the DRG of the spinal cord (Foulkes and Wood, 2008, Kitahata, 1993, Argoff, 2011), which is mediated by the influx of calcium ions (Ca^{2+}) through the voltage dependent calcium ion channels (Rahman and Dickenson, 2013). This leads to the release of neurotransmitters from the presynaptic membrane of the neuron transmitting the action potential by interacting with the receptors of postsynaptic membrane of the receiving neuron (Kitahata, 1993, Cervero and Laird, 2004, Schaible, 2007). Synaptic transmission is modulated by neurotransmitters and may either inhibit or enhance the signal transmission (Schaible, 2007).

The genes involved in conduction of action potentials include gated sodium-ion channel genes (*SCN10A*, *SCN9A*, *SCN3*, and *SCN11A*) and gated potassium ion genes (*KCNQ*). Their expressions have been shown to be altered during pain (Dib-Hajj et al., 2013, Black et al., 2004, Wang et al., 2011, Rahman and Dickenson, 2013, Yoshimura and de Groat, 1999, Waxman, 2010, Lee et al., 2005b). Moreover, inflammatory mediators such as cytokines, NGF, tumor necrosis factor-α (TNF-α) and prostaglandins can increase the expression of sodium ion channels (Gould et al., 2000, Black et al., 2004) and may contribute to increased action potential generation and conduction.

2.3.1.5 Pain modulation

Pain modulation is the alteration of the excitability of sensory neurons, leading to promotion or inhibition of ascending or descending pain impulses (Gangadharan and Kuner, 2013, Yarnitsky, 2010, Schaible, 2007, Millan, 1999, Kitahata, 1993). Changes in neuronal function following persistent nociceptive activity can contribute to the enhancement of signal transmission as well as increased neuronal excitation, leading to persistent pain (Ossipov et al., 2010, Millan, 2002, Tracey and Mantyh, 2007).

Receptors involved in determining enhancement and inhibition of signal transmission include ligand gated ion channels, G-protein coupled receptors and receptor tyrosine kinases, serotonin (5-HT) receptors 1A and 5A, norepinephirine receptors, gamma-aminobutyric acid (GABA) receptors and adrenergic receptors (Ahmad and Dray, 2004, Bolay and Moskowitz, 2002, Pan et al., 2008, Yarnitsky, 2010, Ossipov, 2012, Ossipov et al., 2010, Lindstedt et al., 2011, Treister et al., 2011, Lambe et al., 2011). Genes encoding for these receptors may have both enhancing and inhibitory effects on the ongoing pain pathways. For example, genes encoding for serotonin receptor 1A and 5A, inhibit pain, whereas genes encoding for serotonin receptors 2A and 7A promote pain (Treister et al., 2011, Foulkes and Wood, 2008, Lambe et al., 2011). Moreover, inhibitory receptors may become excitatory in cases of intense activation, such as following axonal injury and contribute to chronic pain (Staley et al., 1995, Owens et al., 1996, Cho et al., 1997a).

The pain modulating receptors are activated by a number of neurotransmitters which are released by sensory nerve fibres following persistent noxious stimulation (Woolf and Salter, 2000). An upregulation in the expression of excitatory receptors may contribute to maintenance of pain. Neurotransmitters involved in excitatory pain modulation include brain derived neurotrophic factor (BDNF), nerve growth factor (NGF), cytokines such as interleukin-1 (IL-1), prostaglandins and substance P (Foulkes and Wood, 2008, Kitahata, 1993). These factors not only sensitise the sensory neurons directly but also modulate them to respond to low-intensity stimuli (Foulkes and Wood, 2008, Millan, 1999, Schaible, 2007). Gene expression of excitatory neurotransmitters upregulates in chronic pain conditions (di Mola et al., 2000, Obata et al., 2003, Lin et al., 2011, Browne et al., 2012).

2.4 Current understanding of pain in endometriosis

Pain symptoms often debilitate women with endometriosis for years (see Table 2.2). The compression of the nerve fibres by endometriotic lesions and/or sensitisation of the infiltrating nerve fibres in the lesion may contribute to endometriosis pain (Triolo et al., 2013, Morotti et al., 2014b, Neziri et al., 2014, McKinnon et al., 2015). Peripheral sensitisation in endometriosis may be promoted due to increased production of pro-inflammatory mediators by eutopic endometrium and endometriotic lesions, enhancing signal transduction, conduction and modulation which may contribute to the associated pain symptoms (Stratton and Berkley, 2011, Triolo et al., 2013). Moreover, pain in endometriosis may be due to nociceptive, inflammatory and/or neuropathic mechanisms (Howard, 2009, Fraser, 2010, Grimm et al., 2011).

Table 2.2: Pain symptoms associated with endometriosis.

Symptoms	Description and characteristics	Prevalence
Chronic pelvic pain	• Non-cyclic pain lasting more than six months	(34-90%)[1]
Dysmenorrhoea	• Uterine pain during menstruation • Sharp pelvic cramps at the start of menstrual flow radiating to the lower back or thighs or deep, dull aches	(40-90%)[2]
Dyspareunia	• Pain during sexual intercourse • May be at the vaginal canal, at the level of the cervix or in the pelvic/uterine/abdominal region or the vulvar region and/or the vaginal introitus	(24-80%)[3]
Dyschezia	• Pain in defecating • Can worsen with menstruation	(7-51%)[4]
Dysuria	• Pain and burning sensation during urination in the absence of urinary tract infection	(5-27%)[5]

1(De Graaff et al., 2013, Fauconnier et al., 2002, Mahmood et al., 1991, Porpora et al., 1999, Milingos et al., 2006, Leng et al., 2007, Ling, 1999)

2(De Graaff et al., 2013, Fauconnier et al., 2002, Mahmood et al., 1991, Porpora et al., 1999, Chapron et al., 2003, Milingos et al., 2006)

3(Bernuit et al., 2011, Denny and Mann, 2007, Ferrero et al., 2005, De Graaff et al., 2013, Fauconnier et al., 2002, Mahmood et al., 1991, Porpora et al., 1999)

4(Fauconnier et al., 2002, Roman et al., 2012, Hao et al., 2009, Leng et al., 2007, Dai et al., 2012, MacDonald et al., 1999)

5(Gabriel et al., 2011, Camanni et al., 2009, MacDonald et al., 1999)

6(Preciado Ruiz et al., 2005, Schrager et al., 2013, Meuleman et al., 2009, Khawaja et al., 2009, Holoch and Lessey, 2010, Ozkan et al., 2008)

2.4.1 Nociceptive pain in endometriosis

Pain in endometriosis involves the pelvic viscera, evidence for which includes high density of unmyelinated C fibres in the eutopic endometrium and endometriotic lesions (Tokushige et al., 2006a, Tokushige et al., 2010, Wang et al., 2009). Also, chemical mediators, such as cytokines, released by local immune cell populations may contribute to the activation of nociceptors (Fraser, 2010, Cervero and Laird, 2004, Cervero, 1995, Simone and Kajander, 1997, Perl, 2007, Basbaum et al., 2009, Giudice and Kao, 2004, Schmidt et al., 1995). Typical nociceptive pain ceases when noxious stimuli are removed. Studies have shown significant improvement in pain symptoms after surgical removal of endometriotic lesions (Grimm et al., 2011, Howard, 2009, Sutton et al., 1994, Abbott et al., 2004). However, in some cases total pain relief is not achieved and some degree of pelvic pain persists, indicating

that pain in endometriosis is not only nociceptive but may also be of inflammatory and/or neuropathic origin (Howard, 2009).

2.4.2 Inflammatory pain

Inflammatory pain occurs due to tissue injury and is a major cause of visceral pain. Many processes in endometriosis increase the production of pro-inflammatory mediators (Costigan et al., 2002, Cakmak et al., 2009, Hirata et al., 2008, Anaf et al., 2002, Noble et al., 1997). For example, macrophage migration inhibitory factor, TNF-α, IL-1β, IL-6, IL-8, regulated on activation normal T expressed and secreted (RANTES) and monocyte chemotactic protein-1 have increased levels in the eutopic endometrium and peritoneal fluid of women with endometriosis compared to women without endometriosis (Hille, 1992, Mannion et al., 1999, Bedaiwy et al., 2007, Bersinger et al., 2006, Velasco et al., 2010, Arici, 2002, Akoum et al., 2001, Morin et al., 2005). These may contribute to sensitisation of peripheral sensory neurons leading to pain generation.

Pro-inflammatory factors released by the eutopic endometrium as well as endometriotic lesions may contribute to inflammatory pain (Longhurst and Dittman 1987; Bulmer, Lunny et al. 1988; Bennett 2001; Malcangio and Lessmann 2003; Antsiferova, Sotnikova et al. 2005; Tegeder, Costigan et al. 2006; Merighi, Salio et al. 2008; Borghese, Vaiman et al. 2010; Tremblay and Hamet 2010; Browne, Yu et al. 2012). For example, NGF contributes to inflammatory pain by inducing the expression of neuropeptides and modulating central pain transmission (Gould et al., 2000, Pezet and McMahon, 2006). Excessive oestrogen production leads to production of prostaglandins, which can directly activate nerve endings thereby aiding in inflammatory pain generation (Kauppila et al., 1979, Koike et al., 1992). Although the number of studies indicating that pain in endometriosis is inflammatory is

increasing, it remains to be determined whether the inflammatory microenvironment is causal or a consequence of endometriosis.

2.4.3 Neuropathic pain

The presence of nerve fibres both in the eutopic endometrium and endometriotic lesions as well as their association with endometriosis-associated pain has been reported (Anaf et al., 2002, Tokushige et al., 2007, Berkley et al., 2005). Direct evidence for neuropathic pain in endometriosis is lacking; however, there are studies to support this (McAllister et al., 2012, Bajaj et al., 2003, Pacchiarotti et al., 2013). For example, Anaf et al. (2000) reported that pain in endometriosis may be due to the physical interaction between nerve fibres and endometriotic lesions. However, these findings have been limited to only DIE lesions (Anaf et al., 2002). Moreover, women with peritoneal lesions associated with high nerve fibre densities reported more pain than women with peritoneal lesions not associated with nerve fibres (McKinnon et al., 2012).

In peritoneal lesions, there is an increased expression of markers for sensory, sympathetic and parasympathetic nerves compared to normal peritoneum (Tokushige et al., 2006b). Studies have confirmed the innervation of endometriotic lesions by slow unmyelinated sensory C and the faster myelinated Aδ nerve fibres which are responsible for mediating painful stimuli (Berkley et al., 2004, Tokushige et al., 2006b). Research by Mechsner et al. (2007) has shown growth associated protein (GAP) 43, a marker for neural outgrowth and regeneration, to be strongly expressed in nerve fibres associated with endometriotic lesions. All these suggest that endometriosis may have neuropathic properties that can lead to changes in the nervous system, however the exact mechanisms remain unclear (Howard, 2009, McKinnon et al., 2015).

2.4.4 Central pain processing in endometriosis

It has been observed that in chronic pelvic pain conditions such as endometriosis, women exhibit enhanced pain processing by the CNS (Bajaj et al., 2003, Weiwei He et al., 2010, Laursen et al., 2005, As-Sanie et al., 2012, Neziri et al., 2014). Chronic pain, as experienced by many women with endometriosis, is a consequence of deficits in conditioned pain modulation, which inhibits pain by the descending pathways, and increased sensitivity to noxious stimulation (Calvino and Grilo, 2006, Fornasari, 2012).

In endometriosis, the pro-inflammatory microenvironment together with hyper sensory innervation in the pelvic viscera may lead to intense nociception, which contributes to increased sensitisation of the neurons in the DRG and CNS, also known as central hyper-excitability (Triolo et al., 2013, Evans et al., 2007, Kobayashi et al., 2013). The central hyper-excitability involves loss of inhibitory mechanisms, contributing to increased pain and enlarged referred areas, which is pain perceived at a site distant from the site of painful stimulus (Dubner, 1991, Dubner, 1994, Bajaj et al., 2003). Central hyper-excitability is further aggravated during menstruation due to abrupt changes in hormonal production and increased production of pro-inflammatory neuropeptides such as prostaglandins, leading to decreased threshold of the neurons to pressure and heat (Bajaj et al., 2003, Bajaj et al., 2002, Brawn et al., 2014). The aggravated central hyper-excitability may lead to persisting pain even after the surgical removal of endometriotic lesions (Bajaj et al., 2003). Furthermore, women with endometriosis-associated pain demonstrate increased sensitivity to noxious stimulation due to inflammation than women without endometriosis (Bajaj et al., 2003, Brawn et al., 2014, Neziri et al., 2010).

In addition to central hyper-excitability, women with endometriosis show changes in the brain that relate to pain processing. Morphological changes in the brain such as reduced grey matter volume have been observed in chronic pain (Rodriguez-Raecke et al., 2009, Baliki et al., 2011). In a recent study by As-Sanie et al. (2012), a reduction in the volume of brain grey matter was demonstrated in women with endometriosis-associated pain compared to women with endometriosis but no pain. Reduced volume of grey matter, which processes the sensory signals from the viscera, means that noxious stimulation is no longer required for pain generation and the constant pain experience is being driven by the brain itself (Rodriguez-Raecke et al., 2009, As-Sanie et al., 2012, Baliki et al., 2011). Longer duration of noxious stimulation and neuronal remodelling of the pain network contributes to reduced grey matter volume and transition to a chronic pain state (As-Sanie et al., 2012).

In summary, pain in endometriosis ranges from mild to severe with some women being asymptomatic. Complex mechanisms, along with genetic and environmental factors and prior experiences may contribute to variability in pain experiences by women with endometriosis. Pain in endometriosis may be of nociceptive, inflammatory or neuropathic origin. However, pain mechanisms in endometriosis remain poorly understood due to lack of research as well as the multifaceted nature of the disease and associated molecular mechanisms. Studies focusing on elucidating pain mechanisms have generally been hampered by factors such as insufficient sample size, loss to follow up and improper study designs.

2.5 Impact of pain on women's lives

Endometriosis pain has a negative impact on women's professional and personal lives (Mathias et al., 1996 , Huntington and Gilmour, 2005, Oehmke et al., 2009, Culley et al., 2013). It is entwined with a wide range of other symptoms such as bowel problems, being

generally unwell, fatigue and depression (Huntington and Gilmour, 2005). Delay in diagnosis as well as uncertainty of response to treatment impacts the duration and severity of the pain experienced by these women (Denny, 2004, Oehmke et al., 2009). Absenteeism from work, reduced productivity, financial hardship due to lost work hours, cost of treatment and lack of understanding by employers and colleagues often hampers professional lives of women with endometriosis (Denny, 2004, Culley et al., 2013, Huntington and Gilmour, 2005).

In terms of their personal lives, many women are embarrassed to talk about endometriosis pain due to the taboos surrounding menstruation, sexual problems and pelvic pain, leading to social isolation (Huntington and Gilmour, 2005, Gilmour et al., 2008, Jones et al., 2004, Denny, 2004). Women may not be able to participate in daily chores due to pain associated with endometriosis (Oehmke et al., 2009). Endometriosis pain impacts not only women with the disease but also those who surround them, and society as a whole. The combined annual costs of healthcare and loss of productivity associated with pain due to endometriosis have been estimated at AUD 12,094.25 (approximately €9579) per patient (Simoens et al., 2012).

2.6 Pain management

The complex and highly variable nature of endometriosis pain makes its successful management difficult. Conservative surgery for treating pain in endometriosis provides relief in 60-80% patients (Abbott et al., 2004). This type of surgery includes endometriotic lesion excision and ablation, with both providing same level of pain relief (Healey et al., 2010). In women with ovarian endometriosis, excision of the endometrioma cyst wall results in reduced pain rates compared to ablation (Hart et al., 2008). Complete removal of lesions may provide relief from pain symptoms, however pain symptoms can recur after surgery. Almost

half of women relapse within five years of the surgery and almost half of these patients require further surgery (Sutton et al., 1997, Fauconnier and Chapron, 2005, Medicine, 2006).

Disruption of neural pathways serving the pelvis may also provide relief from pain due to endometriosis (Hansen et al., 2010, The Practice Committee of the American Society for Reproductive, 2014, Lee and Yang, 2008, Yuan, 2006). These include laparoscopic uterosacral nerve ablation, the disruption of efferent nerve fibres in the uterosacral ligaments and presacral neurectomy, interruption of sympathetic innervations at the level of superior hypogastric plexus (Howe et al., 2010, Medicine, 2006, Valle and Sciarra, 2003, Kennedy et al., 2005). Laparoscopic uterosacral nerve ablation provides no significant pain relief when compared to conservative surgery (The Practice Committee of the American Society for Reproductive, 2014, Davis, 1996). On the other hand, presacral neurectomy has been proposed for treating midline pain, however it is a technically challenging procedure and involves significant risk of bleeding from the adjacent venous plexus so is unpopular (Valle and Sciarra, 2003, Howe et al., 2010, Kennedy et al., 2005, Hansen et al., 2010).

Radical surgery may be offered to women who do not wish to conceive or for whom all other therapies for relieving pain have failed (Hansen et al., 2010, The Practice Committee of the American Society for Reproductive, 2014). This includes hysterectomy, bilateral oophorectomy and removal of all endometriotic implants. Radical surgery is generally thought to provide definitive pain relief, however if ovaries are not removed at the time of surgery pain may recur (Hansen et al., 2010).

Currently available medical management approaches for endometriosis pain include analgesics and hormonal suppression (Bruner-Tran et al., 2013, Huang, 2008). When

investigations reveal no definite diagnosis, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), available over the counter or through prescription, are offered for controlling pain symptoms (Kennedy et al., 2005). Analgesics such as Paracetamol, the daily dose for which is 4000 mg or 1000 mg four hourly, reduce pain by blocking existing pain however do not alter any disease mechanism in the body (Huang, 2008, Bruner-Tran et al., 2013, Nasir and Bope, 2004, Kennedy et al., 2005). In cases where these are not able to alleviate endometriosis pain, stronger pain killers such as co-analgesics, dihydrocodeine or opioids may be prescribed (Kennedy et al., 2005). However, these cannot be used for long term as they have side effects such as dependency (Medicine, 2014, Kennedy et al., 2005). NSAIDS such as ibuprofen, naproxen sodium, ketoprofen and mefenamic acid alleviate pain symptoms by blocking cyclooxygenase and therefore the production of prostaglandins (Lethaby et al., 2007). They must be taken 24 hours before the expected pain experience as well as six-hourly in order to be effective (Lethaby et al., 2007). Although effective, they can have serious side effects such as nausea, vomiting, diarrhoea, irritation of the stomach and stomach ulcers (Medicine, 2014).

Hormonal treatment involves providing a steady hormonal environment that suppresses eutopic endometrium and endometriotic lesions to provide relief from the associated pain. It is used as primary medical therapy as well as in conjunction with surgical resection for managing endometriosis pain (Surrey, 2006, Brown et al., 2012, Zito et al., 2014, Angioni et al., 2014, Schweppe, 2001). Hormonal treatment includes the combined oral contraceptive (OCs); progestins taken as tablet, injection once in three months or continuously as a rod inserted under the skin or released from an intrauterine system (levonorgestrel-releasing intrauterine system; LNG-IUD); and gonadotropin-releasing hormone (GnRH) analogues (Prentice et al., 2004, Moore et al., 2004, Kennedy et al., 2005). Combined oral contraceptive

pills alleviate pain symptoms by suppressing endometriotic lesion growth as well as reducing production of prostaglandins thereby decreasing inflammation (Moore et al., 2004, Moore et al., 2000). Both traditional OCs containing androgenic progestogens (19-nortestosterone derivatives) as well as new generation OCs containing progestogen and desogestrel provide relief from endometriosis pain symptoms in up to 75% patients (Moore et al., 2004, Hansen et al., 2010, Proctor et al., 2001, Harada et al., 2008). Continuous low dose OCs are more effective in controlling pain symptoms than cyclic doses (Zorbas et al., 2015, Vercellini et al., 2003, Seracchioli et al., 2010).

Progestins relieve endometriosis pain symptoms by creating a state of pseudopregnancy and atrophy of endometriotic lesions (Schweppe, 2001). The variety of available agents have varying pros and cons (see Table 2.3), however no single agent can be considered more efficacious than another (Schweppe, 2001, Zito et al., 2014, Surrey, 2006, Bahamondes et al., 2007, Fedele and Berlanda, 2004). This may be due to lack of appropriate randomised controlled trials and standardised evaluation of pain in women with endometriosis (Surrey, 2006, Fedele and Berlanda, 2004). All available progestins have similar side effects such as weight gain, acne, increased hair growth, breast tenderness, cramps and mood swings (Schweppe, 2001).

Table 2.3: Types of available progestins

Name	Form	Dosage	Advantages
Dienogest[1]	Tablet	2 mg/day	• Fewer side effects than Danazol and GnRH analogues • Safe
Dydrogesterone[2]	Tablet	10-30 mg/day	• Compatible with conception • Reduces bleeding
Medroxyprogesterone acetate[3]	Tablet	30-60 mg/day	• Fewer side effects than Danzol and GnRH analogues
Norethisterone[4]	Tablet	2.5-5 mg/day	• Controls uterine bleeding • Positive effect on calcium metabolism • No negative effects on lipoprotein metabolism at low dosages
Depot medroxyprogesterone acetate[5]	Long-acting injection	50 mg injection/week or 100 mg injection/2 weeks or 150 mg injection/2-3 months	• Fewer side effects than Danzol and GnRH analogues • Compliance with long-term administration
Levonorgestrel intrauterine system[6]	T-shaped intrauterine device	52 mg levonorgestrel released into the uterus over a period of 5 years	• Avoidance of repeated administrations • Increase of compliance in long-term administration • Greater efficacy compared to GnRH analogues

1 (Harada and Taniguchi, 2010, Morotti et al., 2014a, Strowitzki et al., 2010)

2 (Brown et al., 2012, Fedele and Berlanda, 2004, Zito et al., 2014, Schweppe, 2001)

3 (Schlaff et al., 2006, Fedele and Berlanda, 2004)

4 (Morotti et al., 2014a, Schweppe, 2001)

5 (Schlaff et al., 2006)

6 (Bahamondes et al., 2007, Petta et al., 2005, Vercellini et al., 2005, Lockhat et al., 2005)

GnRH analogues provide pain relief by inducing amenorrhea and progressive endometrial atrophy (Huang, 2008, Medicine, 2006, Zito et al., 2014). They are administered either by a calibrated nasal spray of nafarelin acetate two times a day, or by injection of a short-acting formulation daily or a longer acting formulation every 1-3 months (Brown et al., 2010, Sagsveen et al., 2003). They are as effective as progestins or OCs in providing relief from

endometriosis pain symptoms and they are particularly effective in providing relief from dysmenorrhea since they cause amenorrhea (Medicine, 2014, Vercellini et al., 1993). Side effects of GNRH analogues include hot flushes, vaginal dryness, decreased libido, mood swings, headache and bone mineral depletion, hence they are not widely recommended (Sagsveen et al., 2003, Zito et al., 2014). Although hormonal treatment can be effective in providing relief, pain relapses at suspension of treatment as the endometriotic lesions become active again (Vercellini et al., 2008, Minjarez and Schlaff, 2000, Medicine, 2006).

Pain symptoms in some patients persist even after medical and/or surgical treatment. Overall, there is 10-50% recurrence rate of endometriosis pain symptoms and up to 20% of women do not respond to any treatment (Davis and McMillan, 2003, Abbott et al., 2004, Lindsay et al., 2015). Therefore, individualised and multidisciplinary approaches may be required in the treatment of endometriosis pain (Kennedy et al., 2005). For example, since the efficacy of available pain treatments is similar, women need to be informed regarding the expense, side-effects and invasiveness of therapy to make an informed decision regarding the approach most appropriate for them (The Practice Committee of the American Society for Reproductive, 2014, Kennedy et al., 2005, Dunselman et al., 2014).

Problematic pain due to endometriosis can call for a multidisciplinary treatment approach (Rocha et al., 2012, Greco, 2003, Metzger, 1997). This may combine medical therapy, counselling and alternative therapies in order to improve women's responses to treatment (Greco, 2003, Kames et al., 1990, Ortiz, 2008). Counselling should be offered to certain patients so they can return to their routine social and family lives (Greco, 2003, Townsend et al., 2006, Gilmour et al., 2008). Alternative therapies such as acupuncture, herbal medicines, dietary changes and yoga have also been successful in reducing endometriosis-associated

pain (Medicine, 2014, Kennedy et al., 2005). The complexities and inadequacies of pain management in endometriosis indicate the importance of understanding molecular mechanisms underlying pain generation in women with the disease. Improved understanding of mechanisms will facilitate development of better pain management techniques.

Aims and Hypotheses

Aims

The overall aim of this thesis was to investigate the expression of pain related genes in women with endometriosis compared to women without the disease.

This thesis also aimed to investigate the relationship between endometrial and endometriotic lesion gene expression and menstrual cycle phase.

Hypotheses

1. Pain related genes are dysregulated in eutopic endometrium from women with endometriosis and in endometriotic lesions.
2. The endometrial and endometriotic lesion expression levels of pain related genes vary during different phases of the menstrual cycle.
3. The expression levels of different pain related genes correlate with each other in the eutopic endometrium from women with endometriosis and in endometriotic lesions.

Chapter 3

Methodology

3.1 Introduction

In order to gain insights into the mechanisms involved in pain generation in women with endometriosis, a meta-analysis of microarray gene expression was conducted between eutopic endometrium from women with and without endometriosis; and endometriotic lesions. Microarray technology is a powerful tool for analysing expression of numerous genes simultaneously in a single tissue specimen in a highly efficient manner (Ramasamy et al., 2008). A number of studies have used this technology to understand the underlying biological mechanisms in endometriosis (Burney et al., 2007, Hurst et al., 2014, Kao et al., 2003, Khan et al., 2012). Through a meta-analysis, the statistical power for obtaining a more precise estimate of differential gene expression increases (Ramasamy et al., 2008, Taminau et al., 2014). This may aid in developing a more accurate picture of the biological pathways underlying pain generation in women with endometriosis.

This meta-analysis will utilise the primary two types of microarray gene expression data:

- individual participant raw or normalised data which represent measurement of expression for every gene in a sample (Ioannidis et al., 2002, Stewart and Parmar, 1993); and
- lists of dysregulated genes published in the studies (Miller and Stamatoyannopoulos, 2010, Cahan et al., 2007, Griffith et al., 2006).

Figure 3.1 provides an overview of the present meta-analyses highlighting the type of data used, number of included studies, tissue types being compared, primary outcomes of the meta-analyses and results convergence. This meta-analysis was conducted by separately

analysing individual participant gene expression data and published gene lists. For both data types, comparisons were made between eutopic endometrium from women with and without endometriosis as well as between eutopic endometrium and endometriotic lesions from women with endometriosis. Individual participant gene expression data were adjusted for menstrual cycle phase. However, this could not be done for the published gene list data as lists of genes dysregulaed in different menstrual cycle phases were not available. The primary outcome measure for all the analyses was dysregulated genes involved in pain generation. In order to find genes that are consistently dysregulated throughout the datasets, results comparing gene expression of eutopic endometrium from women and without endometriosis as well as of eutopic endometrium from women with endometriosis and endometriotic lesions from both the individual participant gene expression data and published gene lists were converged.

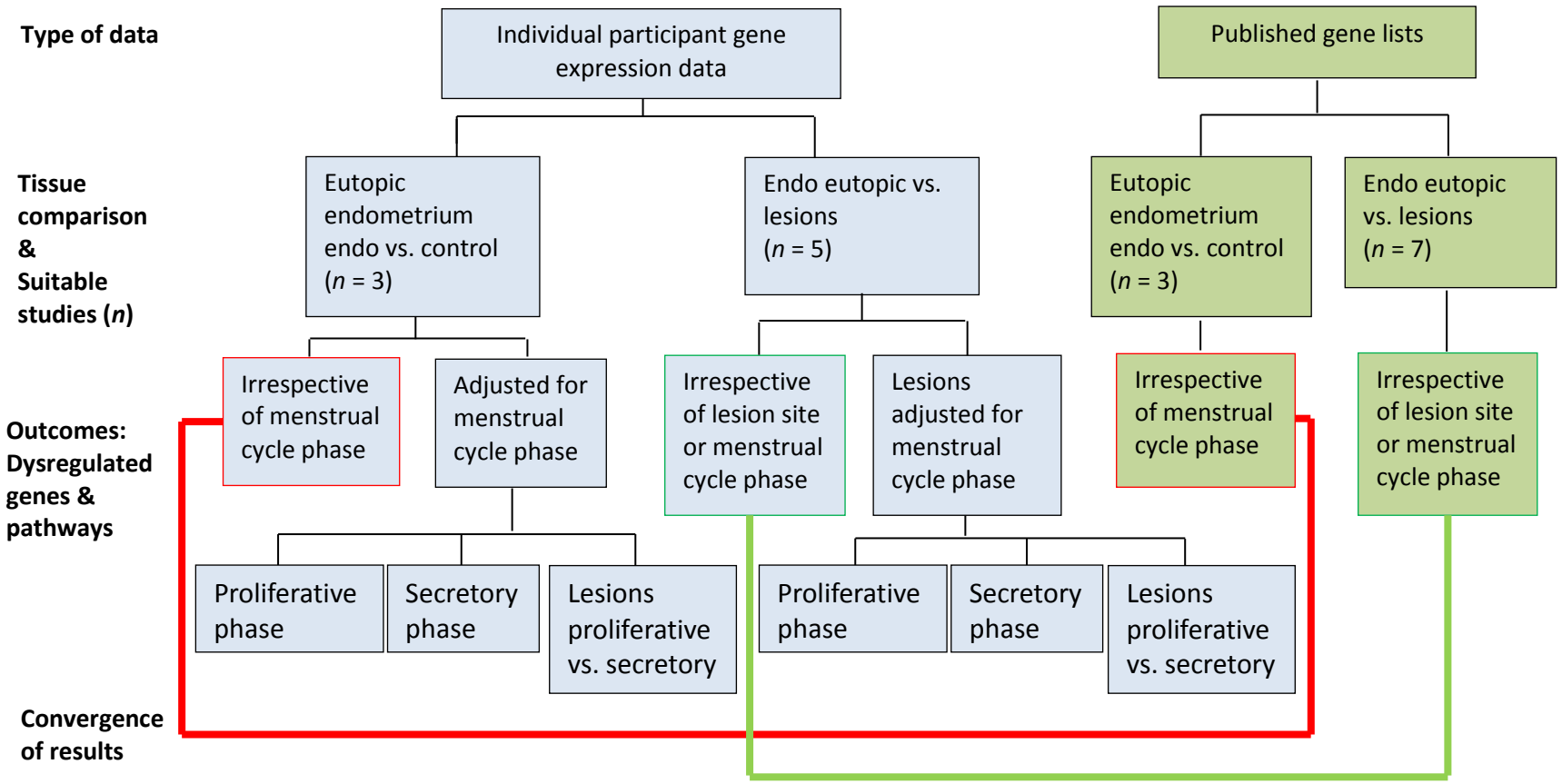


Fig 3.1: Flow-chart illustrating an overview of the present meta-analyses highlighting the data type used, the no. of suitable studies (*n*), the tissue type being compared, the groups being compared to get the outcomes and result convergence. Data for published gene lists could not be adjusted for menstrual cycle phase since related information and data were not available. Endo = endometriosis

3.2 Criteria for considering studies for the review

Inclusion and exclusion criteria for study selection are summarised in Table 3.1. Further details regarding criteria for study design, participant characteristics, study methods and outcome measures are provided below.

Table 3.1: Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Studies investigating gene expression profiles in endometrium and endometriotic lesions • Participants: premenopausal with normal menstrual cycles • Presence or absence of endometriosis confirmed laparoscopically • Eutopic endometrial and endometriotic lesion specimens obtained through endometrial biopsy/curetting/excision • Use of whole human genome microarray chips • Availability of individual participant gene expression data or published gene lists • Peer-reviewed studies	• Participants on hormonal treatment • Individual participant gene expression data or published gene lists unavailable

Study design

Studies included in the meta-analysis were one of two designs: (1) case-control type studies that recruited women with a confirmed diagnosis of endometriosis and women without endometriosis, and compared gene expression of eutopic endometrial tissue samples; or (2) cross-sectional type studies that either recruited women with a confirmed diagnosis of endometriosis and compared gene expression of endometriotic lesions and eutopic endometrial samples, or recruited women without endometriosis and profiled gene expression of the endometrium.

Participant characteristics

Within the studies, premenopausal women with regular menstrual cycles and laparoscopic evidence of being with or without endometriosis were suitable for inclusion. Women taking hormonal treatment were excluded.

Types of interventions (study methods)

In the included studies, endometrial samples of the participants with or without endometriosis were obtained by biopsy or curettage. Samples for endometriotic lesions from women with endometriosis were obtained by surgical excision. Tissues were processed for ribonucleic acid (RNA) extraction and hybridisation with whole human genome microarray chips.

Outcome measures

The primary outcome measure for the included studies was dysregulated gene expression along with availability of either individual participant gene expression data or published lists of genes declared to be dysregulated in the eutopic endometrium from women with and without endometriosis as well as in endometriotic lesions.

Secondary outcome measures from included studies of particular interest were

- expression of genes involved in pain generation;
- gene expression in different menstrual cycle phases; and
- dysregulated biological pathways revealed by gene ontology analyses.

Adverse outcomes

Adverse outcomes were not applicable in this meta-analysis since treatment effects were not being considered.

3.3 Search methods

Literature and gene database searches were conducted from 1/8/2013 to 30/11/2013 and 4/9/2014 to 6/10/2014. Searches were limited to studies in peer-reviewed scientific journals published in English. Of the 116 studies found, 24 studies analysing microarray gene expression of whole eutopic endometrium from women with and without endometriosis as well as endometriotic lesions were further reviewed. Out of these, 16 were suitable as per the inclusion criteria (see Fig. 3.2 and Table 3.1). The excluded studies were either not peer reviewed, had insufficient data or had compared data from single cell types.

An in-house departmental search was also conducted in order to look for suitable studies that could be included in this meta-analysis. The search revealed one study by Zevallos (2012) which compared the expression of neurotrophins in the eutopic endometrium of women with and without endometriosis. The study was suitable for inclusion as per the inclusion criteria (Table 3.1) and had individual participant gene expression data available.

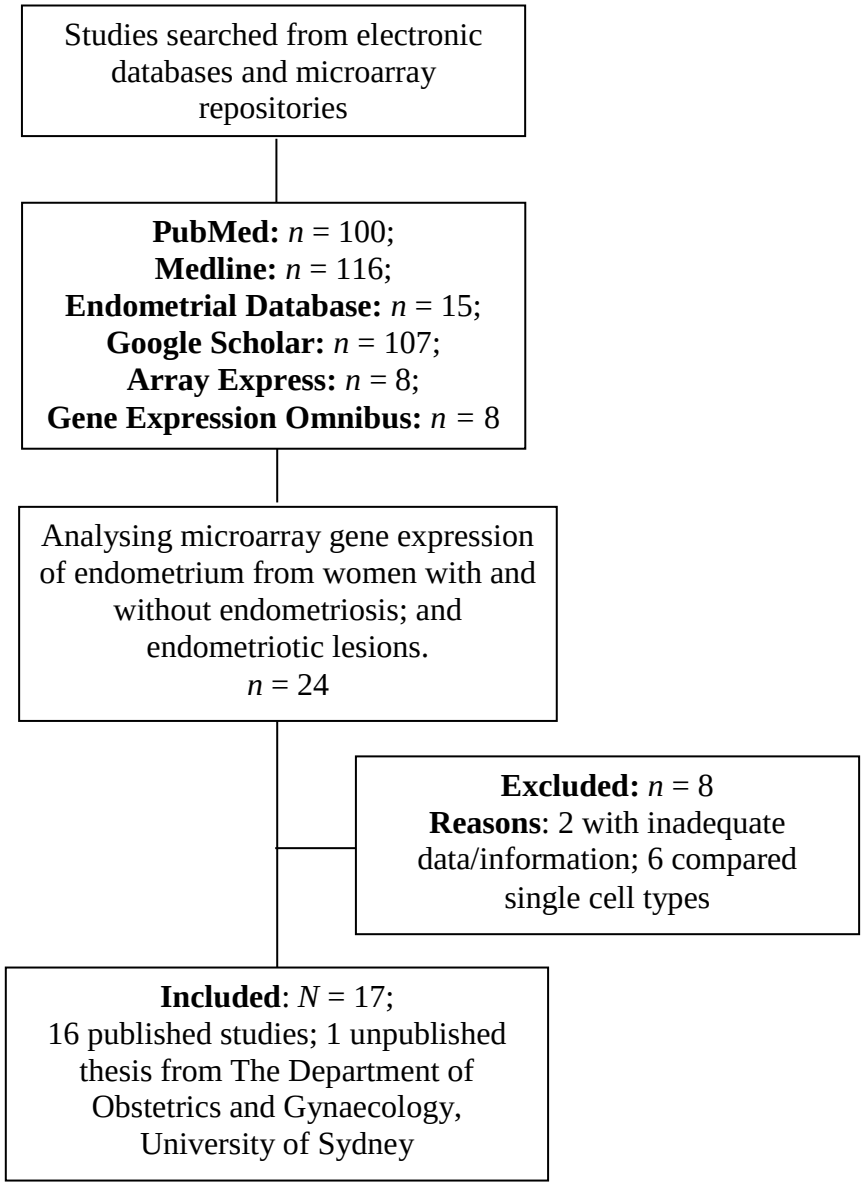


Fig. 3.2: Summary of search results.

Electronic searches

The following electronic databases were searched for eligible studies using the search terms endometriosis, endometrium, eutopic, ectopic, endometriotic lesion, microarray and gene expression.

- Medline via Ovid (http://www.nlm.nih.gov/pubs/factsheets/medline.html)
- Pubmed (www.ncbi.nlm.nih.gov/pubmed/)
- Google Scholar (http://scholar.google.com.au/)
- Endometrium Database Resource (http://edr.research.bcm.edu/edr/ui_home.seam?cid=76228)

Other resources

Reference lists of relevant publications and included studies were also explored to ensure all relevant manuscripts were identified. In addition, a search for microarray gene expression data was performed; using the terms endometriosis, endometrium, eutopic, ectopic and endometriotic lesion, and limiting the search to species *Homo sapiens*; in the following repositories:

- Array express (available from http://www.ebi.ac.uk/arrayexpress/)
- Gene expression omnibus (GEO; available from http://www.ncbi.nlm.nih.gov/geo/).

3.4 Study selection and data assessment

3.4.1 Selection of studies

A single reviewer (MS) scanned all 116 article titles and abstracts retrieved from the searches. Studies that did not conduct a microarray analysis were removed. Full text manuscripts of 24 studies were retrieved out of which those that did not analyse gene expression of whole tissue samples or had inadequate information available were removed.

The reviewer assessing the relevance was not blinded to the information about the articles, such as the publishing journal, names of authors, institution and results. Studies that did not meet the inclusion criteria (criteria summarised previously in Table 3.1) were discarded. See Table 3.2 and Appendix 1 for characteristics of included studies and Appendix 2 for those of excluded studies.

Table 3.2: Studies included in meta-analysis.

Citation	Tissue	Data type (available from/accession no.)	Type of microarray used	Sample #	Age-group (years)	Study type
Hull et al. (2008)	Eutopic endometrium; peritoneal lesions	Individual participant gene expression data (Pubmed accession no.: GSE11691)	HG U133A	EU = 9; EL = 9	20-46	Cross-sectional
Hever et al. (2007)	Eutopic endometrium; ovarian lesions	Individual participant gene expression data (Pubmed accession no.: GSE7305)	HG U133A plus 2.0	EU =10; EL = 10	Not given	Cross-sectional
Burney et al. (2007)	Eutopic endometrium	Individual participant gene expression data (Pubmed accession no.: GDS2737)	HG U133A plus 2.0	EU = 21; EL = 16	22-44	Case-control
Khan et al. (2012)	Eutopic endometrium; ovarian lesions	Individual participant gene expression data (Pubmed accession no.: GSE 37837)	Agilent Whole Human Genome 60-mer 4X44K	EU = 18; EL = 18	24-45	Cross-sectional
Talbi et al. (2006)	Eutopic endometrium	Individual participant gene expression data (Pubmed accession no.: GDS2052)	HG U133A plus 2.0	EU = 27	22-50	Cross-sectional
Zevallos (2012)	Eutopic endometrium	Individual participant gene expression data (http://pwbc.garvan.unsw.edu.au/caarray)	HuGene 1.0 ST array	EU = 12 NE = 18	25-43	Case-control
Crispi et al. (2013)	Eutopic endometrium; peritoneal lesions	Individual participant gene expression data (Pubmed accession no.: GSE25628)	HG U133A plus 2.0	EU = 8 EC = 8 NE = 6	22-46	Case-control
Sohler et al. (2013)	Eutopic endometrium; peritoneal lesions	Individual participant gene expression data (Array Express accession no.: E-MTAB-694)	HG U133A plus 2.0	EU = 27 EC =27	21-52	Cross-sectional

Citation	Tissue	Data type (available from/accession no.)	Type of microarray used	Sample #	Age-group (years)	Study type
Sherwin et al. (2008)	Eutopic endometrium	Prioritised gene list (Pubmed accession no.: 18353903)	Custom made (containing oligonucleotides specific for 22000 human transcripts)	EU = 10 NE = 6	Not given	Case-control
Kao et al. (2003)	Eutopic endometrium	Prioritised gene list (Pubmed accession no.: 12810542)	Affymetrix Genechip Hu95A	EU = 8 NE = 7	28-39	Case-control
Hurst et al. (2014)	Eutopic endometrium	Prioritised gene list (Pubmed accession no.: 24292148)	Affymetrix 8500 array	EU = 10 NE = 5	18-40	Case-control
Zafrakas et al. (2008)	Eutopic endometrium; ovarian lesions	Prioritised gene list (Pubmed accession no.: 18288381)	Affymetrix Gene Chip HG-U133	EU = 4 EC = 4	Not given	Case-control
Gaetje et al. (2007)	Eutopic endometrium; peritoneal lesions	Prioritised gene list (Pubmed accession no.: 17952761)	HG U133A	EU = 3 EC = 3	Not given	Case-control
Eyster et al. (2007)	Eutopic endometrium; ovarian & peritoneal lesions	Prioritised gene list (Pubmed accession no.: 17462640)	CodeLink Whole Human Genome Bioarrays	EU = 11 EC = 11	28-45	Cross-sectional
Borghese et al. (2008)	Eutopic endometrium; ovarian lesions	Prioritised gene list (Pubmed accession no.: 18818281)	Institut Cochin HG18 60mer expression array 47K	EU = 12 EC = 12	Not given	Cross-sectional
Mettler et al. (2007)	Eutopic endometrium; ovarian lesions	Prioritised gene list (Pubmed accession no.: 17333364)	Atlas Human 1,2 array	EU = 5 EC = 5	22-40	Cross-sectional

Citation	Tissue	Data type (available from/accession no.)	Type of microarray used	Sample #	Age-group (years)	Study type
Sun et al. (2014)	Eutopic endometrium; ovarian lesions	Prioritised gene list (Pubmed accession no.: 24502888)	SurePrint G3 Human Gene Expression 8x60K v2	EU = 4 EC = 4	24-45	Cross-sectional
Vouk et al. (2011)	Eutopic endometrium; Ovarian lesions	Prioritised gene list (Pubmed accession no.: 21397694)	TaqMan low-density array	EU = 9 EC = 11	24-50	Cross-sectional

*EU= Eutopic endometrium from women with endometriosis; EC= Endometriotic lesions; NE= No endometriosis

3.4.2 Data extraction

According to the type of available data, information from the included studies was extracted. Individual participant gene expression data were downloaded from public repositories - GEO and Array Express. Data for individual participants were extracted from eligible studies, including (where available) participant identification code, age, menstrual cycle phase, surgically confirmed diagnosis/exclusion of endometriosis and whether the participant was taking any hormonal treatment. Appendix 3 shows participant characteristics from studies with individual participant gene expression data.

Published gene lists were collected from the included studies for which individual participant gene expression data were not available. Information extracted for gene lists included information regarding the groups being compared for gene expression, gene symbols, unique identifiers (Accession ID, Affymetrix probe ID, UniGene ID, etc.), fold change and significance values. All data extraction was conducted by a single person (MS).

3.4.3 Assessment of risk bias in included studies

Bias is a systematic error which can over- or under-estimate the results of a study. In order to anticipate the validity of the included studies in this meta-analysis, the methodology of each study was critically assessed. Factors that were assessed to evaluate potential sources of bias in the studies included: sample size of the studies, blind histological assessment of tissue samples to determine stage of endometriosis, established criteria for assessing menstrual cycle phase, quality of RNA sample used for microarray hybridisation, validation of microarray results and unavailable participant information.

All these factors were evaluated for every individual study by a single reviewer (MS). The sample size of the studies was considered to be adequate if the number of participants in each group was more than 20, as this is thought of as acceptable for small qualitative research projects (Mason, 2010, Guest et al., 2006, Hedges and Bliss-Holtz, 2006). The histological assessment of the endometrial samples was required to be conducted by a histopathologist who was not aware of the participant's history and other details. The criteria for assessing the menstrual cycle phase of the endometrial samples were published such as the Noyes criteria. The quality of RNA used for hybridisation with the microarray chips should have been assessed by either gel electrophoresis or Agilent's Bioanalyzer. The results obtained by microarray analysis should have been further validated by RT-PCR. The clinical characteristics of the individual participants should have been available.

After assessing the methodology of every individual study included in this meta-analysis for the above-mentioned factors it was found that all the studies had potential risk of bias. However, the potential for risk was low for the studies; hence all the studies were included in the meta-analysis.

3.4.4 Measures of effect

In this meta-analysis of gene expression data comparing eutopic endometrium from women with and without endometriosis and endometriotic lesions, the fold-change values of genes were considered to be the measures of effect. Gene expression and dysregulation data were continuous. For individual participant gene expression data, the results were expressed as mean difference ± standard error (SE). For published gene lists, the results were continuous and expressed as ranks given to the genes (Kolde et al., 2012).

3.4.5 Dealing with unavailable data

Information regarding menstrual cycle phase was unavailable for Hull et al. (2008). Individual participant data describing menstrual cycle phase was required for sub-group analyses to determine dysregulated genes in different menstrual cycle phases in women with and without endometriosis. Corresponding author was contacted in an attempt to obtain the unavailable participant data, but unfortunately no replies were received. Therefore, Hull et al. (2008) was excluded from menstrual cycle sub-group analyses.

3.4.6 Assessment of heterogeneity

Participant characteristics from different studies were reviewed for heterogeneity to explore their influence on the results of the meta-analysis. The characteristics for which information was available, such as severity or stage of endometriosis and parity, are not known to impact pain and so were not formally assessed for heterogeneity (Vercellini et al., 2007, Gruppo Italiano per lo Studio, 2001, Fauconnier and Chapron, 2005). Moreover, participant characteristics were not available for all of the included studies; therefore, were not assessed for heterogeneity.

3.4.7 Assessment of reporting bias

Reporting bias may arise when dissemination of studies gets influenced by the nature of the results. Positive and significant results increase the likelihood of such studies to be published quicker, in English, in significant journals and occasionally more than once. In order to reduce the chances of reporting bias, a comprehensive literature review, including searching of microarray data repositories, for eligible studies was conducted to minimise any potential reporting bias. Care was taken not to include data that have been published more than once.

3.5 Data analysis

Analyses of data are detailed below. Briefly, analyses were conducted by grouping the studies according to the type of data available, i.e. individual participant gene expression data or published gene lists, analysing for dysregulated genes and pathways, and then converging the results from both the analyses to determine consistently dysregulated genes. Figure 3.2 provides an overview of the steps undertaken in this meta-analysis.

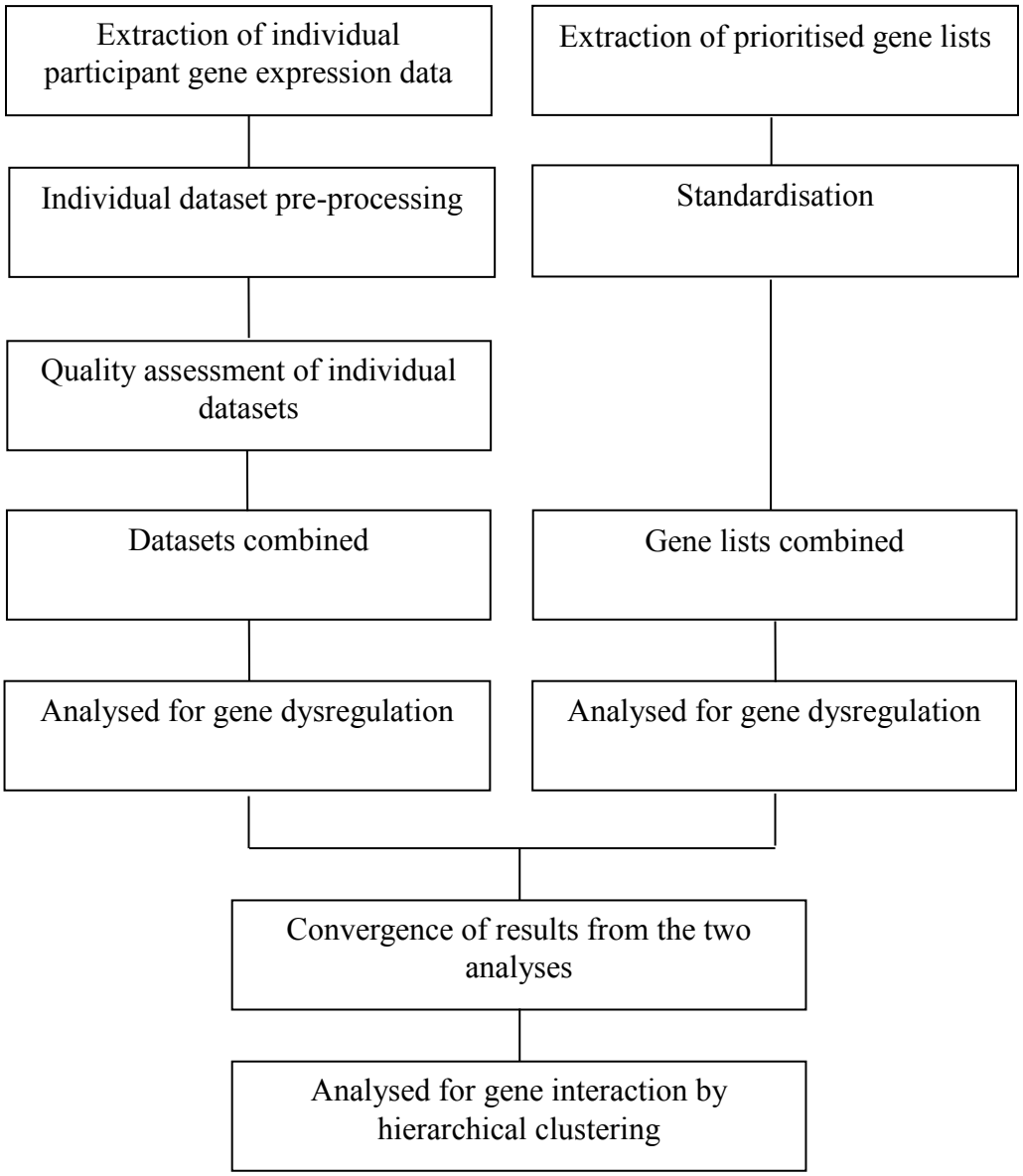


Fig. 3.3: Flow-chart illustrating an overview of the steps undertaken in the present meta-analysis.

For both the individual participant gene expression data and published gene lists, gene expression was compared between eutopic endometrium from women and without endometriosis as well as endometriotic lesions and eutopic endometrium from women with endometriosis. For individual participant gene expression data, the groups were further analysed after adjusting for menstrual cycle phases. This could not be done for published gene lists as the required information and data were not available.

For every study, the individual participant gene expression data were extracted from their respective accession sites, pre-processed and assessed for quality. All the datasets were then integrated into one global dataset and analysed for dysregulated genes and pathways. The dysregulated genes were further analysed to determine the correlation amongst their expression levels.

The published gene lists were extracted from their respective studies, standardised and integrated for analysis of dysregulated genes. The dysregulated gene were further analysed to determine the pathways most affected by them. Lists of dysregulated genes obtained from both the analyses of individual participant gene expression data and published gene lists were then converged to determine gene that are consistently dysregulated across the datasets.

3.5.1 Meta-analysis of individual participant gene expression data

In conducting a gene expression meta-analysis, individual participant gene expression data are preferable as this allows for consistent handling of all the datasets by standardised preprocessing (Ioannidis et al., 2002, Stewart and Parmar, 1993). Another advantage of using individual participant gene expression data is that along with published data, unpublished data can be also included (for example, the Zevallos 2012 dataset included in this meta-analysis). Array quality can also be evaluated and the poorer quality ones subsequently removed from further analyses (Ramasamy et al., 2008).

3.5.1.1 Data pre-processing and normalisation

Pre-processing of all individual datasets was performed using GeneSpring version 12.6.2. This is an essential step in microarray analyses as it allows the assessment of data quality and conversion of microarray data to gene expression values which can be further analysed. It also minimises any differences that might occur due to technical reasons, also known as noise, and ensures that results attained are of highest quality (Zhang et al., 2006, Lu et al., 2012, Agilent, 2013).

Data uploaded to GeneSpring, were automatically pre-processed depending on the type of microarray used (see Appendix 4). Pre-processing consists of the following steps:

- background correction to ensure accurate measures of intensity for each spot on the microarray chip by reducing affects arising due to non-specific sources;
- normalisation to ensure that any differences that exist between samples are due to biological rather than technical variations;
- correction for non-specific binding to ensure that all the miss-matched spots are removed; and
- summarisation of the data into an expression value for the gene in question (Agilent, 2013, Wu, 2009).

For Affymetrix platform data, pre-processing was performed using robust multi-array analysis (RMA) algorithm. RMA algorithm converts probe-level data to measures of gene expression using positive signal intensities for probe-level normalisation, and reduces noise in the data (Irizarry et al., 2003). The probe intensities are corrected using a global model for probe intensity distribution. Observed probes are modelled as the sum of a normal noise component *N* (normal with mean μ and variance σ2) and an exponential signal component *s* (exponential with mean α). To avoid any possibilities of getting any negative values the normal is truncated at zero. Given there are *O* observed intensities, the following adjustment is applied:

$$E\left(s \middle/ O = 0\right) = a + b\frac{\varphi\left(\frac{a}{b}\right) - \varphi\left(\frac{0-a}{b}\right)}{\Phi\left(\frac{a}{b}\right) + \varphi\left(\frac{0-a}{b}\right) - 1}$$

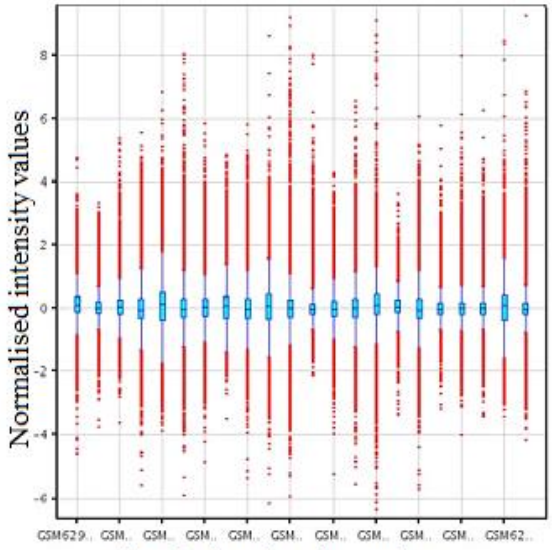
where $a = s - \mu - \sigma 2\alpha$ and $b = \sigma$. Note that φ and Φ are the standard normal distribution density and distribution functions, respectively. The log2 transformed value of each background corrected, perfect-matched probe is obtained and these values are normalised using quantiles normalisation method which makes the array comparable against each other and gives an expression measure for each probe (Irizarry et al., 2003). RMA is then carried out on the expression measures obtained. RMA16 was used for Affymetrix Exon Expression platform data - this involves the addition 16 to expression values prior to log-transformation to stabilise the data (provides the required stabilisation effect without changing or suppressing true signal values as values smaller than 16 are due to noise; Agilent, 2013).

Pre-processing for Agilent single colour platform data was by percentile shift. Percentile shift adjusts the locations of all spot intensities in an array. Each column in an experiment is taken independently and the *n*th percentile (where *n* = 0 to 100) of the expression values for an array is computed across all spots. This value is then subtracted from the expression value of each entity. The percentile is subtracted from the expression value to give the normalised intensity value. A

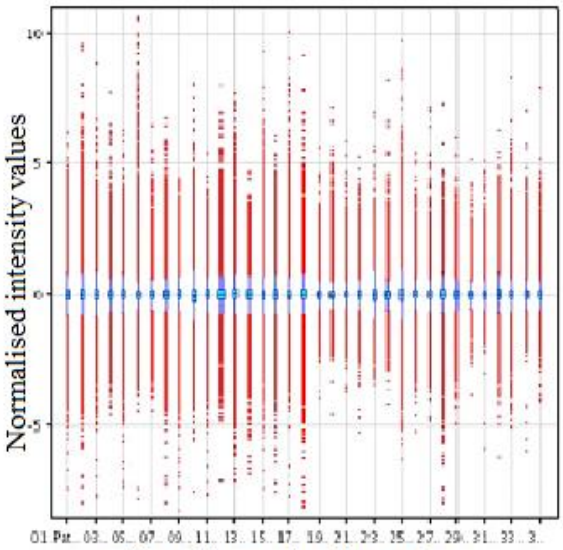
default value of 75 was chosen for normalisation as this value is more robust and makes sure that only genes that are expressed are reported (Agilent, 2013).

3.5.1.2 Quality assessment of datasets

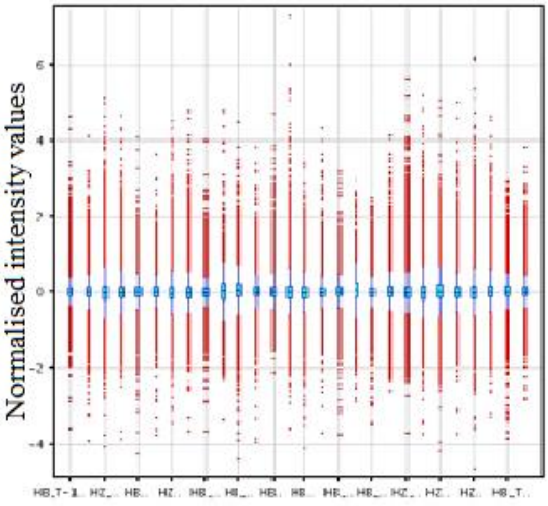
Box plots obtained after pre-processing of individual datasets were assessed in order to evaluate the dataset quality. Box plots were constructed using log2 transformed probe intensity values. Each boxplot from a dataset represents the distribution of probe intensity values for an individual sample, with the middle line representing the median, the whiskers indicating the variability outside the upper and lower quantiles, and the outliers represented by the individual points outside the whiskers (as shown in Fig. 3.4).



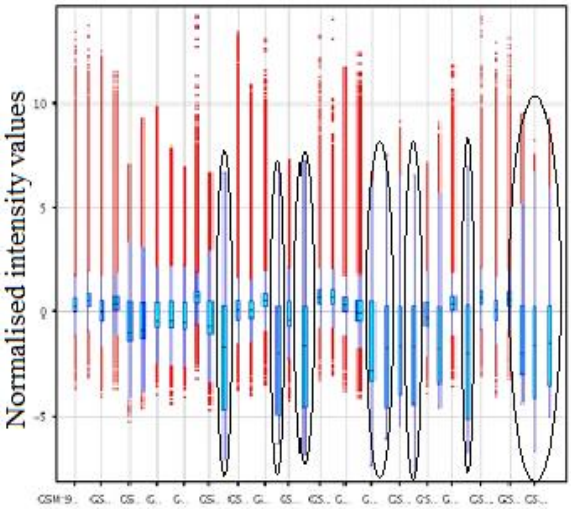
(a) Crispi et al.: All samples



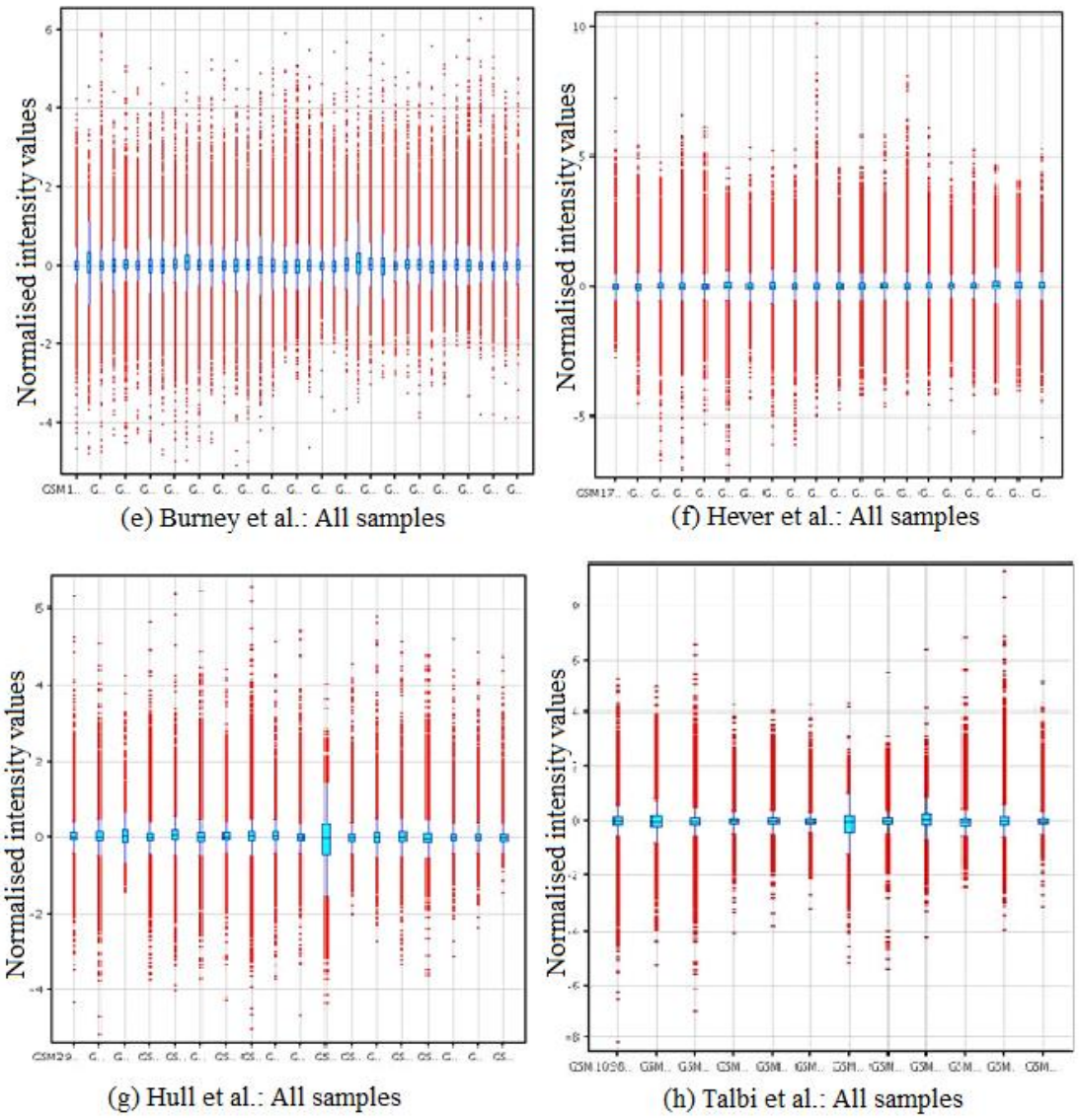
(b) Sohler et al.: All samples



(c) Zevallos: All samples



(d) Khan et al.: All samples



Figs. 3.4 a-h: Box plots illustrating sample-wise log-2 transformed probe intensity values of normalised data from individual participant gene expression studies: (a) Crispi et al. 2013; (b) Sohler et al. 2013; (c) Zevallos 2008; (d) Khan et al. 2012; (e) Burney et al. 2007; (f) Hever et al. 2007; (g) Hull et al. 2008; (h) Talbi et al. 2006. Each boxplot represents the distribution of probe intensity values for an individual sample, the middle line representing the median, the whiskers indicating the variability outside the upper and lower quantiles, and individual points outside the whiskers, the outliers. Encircled box plots in (d) represent problematic array which may be discarded from further analysis.

The box plots with a uniform spread of probe intensity values for individual samples across dataset in each study indicate ideal sample quality. However, Figure 3.4 (d) does not have a uniform spread of normalised log2-transformed intensity values, especially for samples 5, 6, 10, 12, 16 and 18. This indicates that these samples may be of poor quality and should be removed

from further analysis. However, te box plot created after convergence of all the individual participant gene expression datasets shows a uniform spread of probe intensity values for all the samples; therefore all the samples were retained for further analysis (Fig. 3.5).

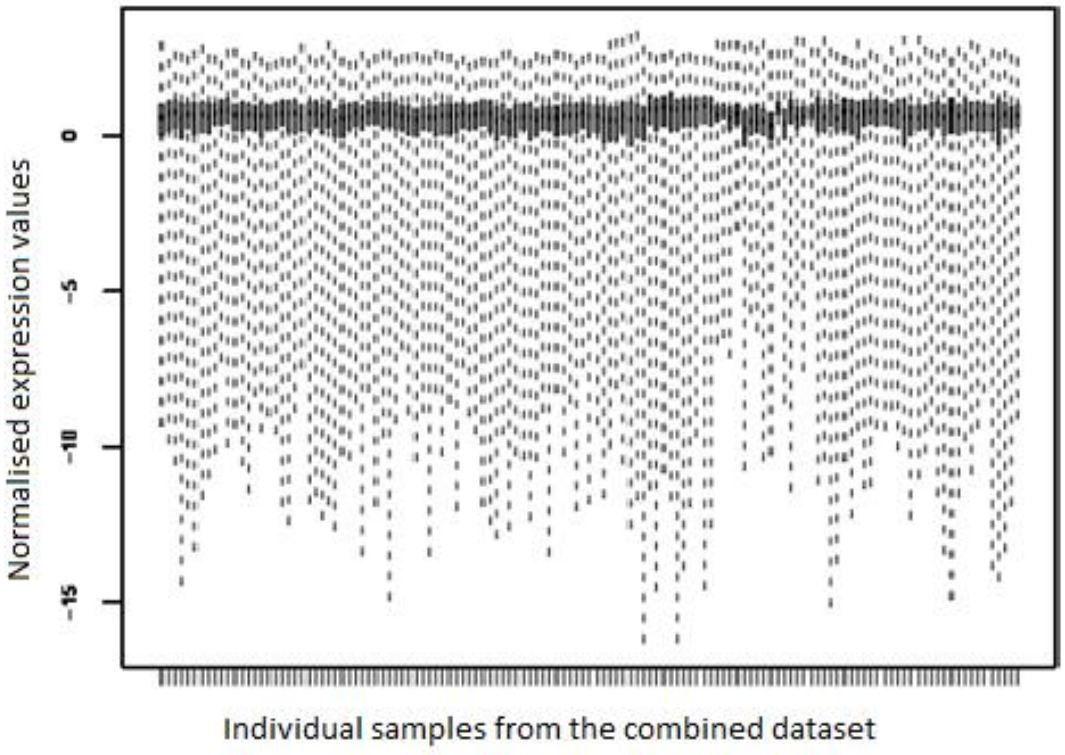


Fig. 3.5: Box plot illustrating uniform probe intensity values for individual participant gene expression data of all datasets obtained after convergence. Each boxplot represents the distribution of probe intensity values for an individual sample, the middle line representing the median, the whiskers indicating the variability outside the upper and lower quantiles, and individual points outside the whiskers, the outliers.

3.5.1.3 Cross-platform integration of datasets

ArrayMining was chosen to conduct individual participant gene expression data meta-analysis as it offers cross-platform integration of data (Glaab et al., 2009). ArrayMining conducts statistical microarray analyses and generates output webpages with downloadable results in the form of plots and tables. Pre-processed data obtained from GeneSpring (in tab-delimited text-file format) were uploaded to ArrayMining as per the programme's instructions (Glaab et al., 2009). ENTREZ gene

IDs were selected as common identifiers across datasets as they are stable and regularly updated (Maglott et al., 2011). Each sample of the dataset was labelled according to the group it belonged to, with '0' for endometrium from women without endometriosis, '1' for endometrium from women with endometriosis, '2' for endometriotic lesions, 'P' for proliferative phase and 'S' for secretory phase. Any missing values in the data files were labelled as 'NA'. Two data files at a time were uploaded in compressed zip formats and integrated by XPN method.

The XPN method for cross-platform integration, devised by Shabalin et al. (2008), integrates gene expression data from different studies by clustering together samples and genes with similar expression characteristics to produce a unified dataset which can be statistically analysed. This is done in two steps. The first step is to find clusters of similar genes and samples across datasets by k-means clustering. In the second step, with in each of these clusters, a combination of weighted averages of the platform parameters is applied to normalise the data across platforms (Deshwar and Morris, 2014, Sirbu et al., 2010, Tsiliki et al., 2011). This procedure runs multiple times in order to account for all possible clustering patterns. The output generated is a unified dataset containing genes/probes that are common across all datasets (Tsiliki et al., 2011, Deshwar and Morris, 2014).

Before starting the method three parameters are required to be set: number of gene clusters, numbers of sample clusters and number of iterations. Although the method is robust to these parameters, however it is recommended that the number of genes clusters should be between 10 and 30, number of sample clusters should be between 5 and 8, and number of iteration should be between 10 and 30. Choosing values that are too low or too high can degrade the performance of the method (Shabalin et al., 2008). In the present meta-analysis, default values of the parameters were chosen.

3.5.1.4 Clustering of samples

After all the individual datasets were integrated into a single dataset, samples were clustered into discrete groups according to their disease status (with or without endometriosis) or menstrual cycle phase (proliferative or secretory phase). This helps in visualising how the samples are grouped together based on similarity of gene expression and provides an integrated understanding of the association between the condition (endometriosis) and the gene expression (Makretsov et al., 2004, Eisen et al., 1998, Alberts et al., 2002). For this, Hierarchical Clustering method (HCL) in ArrayMining was chosen. It joins together the most similar pair of samples, and then identifies and pairs the next most similar samples, repeating the procedure till all the samples in the dataset are merged into one cluster (Makretsov et al., 2004, Alberts et al., 2002). It calculates the similarity between samples by assigning each sample its own cluster and averaging the distance between all the members of the two closest clusters (Eisen et al., 1998). It also increases the robustness and reliability of the statistical tests applied to the dataset (Glaab et al., 2009).

The gene expression values for each sample in the integrated dataset were standardised by choosing the Robust Median Absolute Deviation from the drop down menu (MAD; Gentleman et al., 2005) in order to better distinguish samples into separate groups based on gene expression pattern (Glaab et al., 2009). For each row, Robust MAD subtracts the median gene expression value from the expression value of the particular gene and divides it by the median absolute deviation (Gentleman et al., 2005). A variance filter was also applied to standardised data to retain 2000 genes with the highest variance across samples. This removes all irrelevant genes with low variance across samples as well as improves the interpretability of the results (Tritchler et al., 2009).

3.5.1.5 Detection of dysregulated genes

Gene expression output from the hierarchical clustering of samples was analysed within ArrayMining to identify dysregulated genes in endometriosis. To evaluate gene dysregulation following comparisons were made:

- *Eutopic endometrium from women with and without endometriosis*
    - overall
    - proliferative phase of menstrual cycle
    - secretory phase of the menstrual cycle
    - proliferative phase vs. secretory phase of the menstrual cycle in eutopic endometrium from women with endometriosis
- *Eutopic endometrium and endometriotic lesions from women with endometriosis*
    - overall
    - proliferative phase of menstrual cycle
    - secretory phase of the menstrual cycle
    - proliferative phase vs. secretory phase of the menstrual cycle in endometriotic lesions

This was conducted using moderated t-statistics, which has the same interpretation as an ordinary t-test but is more likely to have a moderate value based on a more reliable variance estimate with higher number of degrees of freedom. This often gives a more significant *p*-value which is adjusted by controlling the false discovery rate (FDR; Smyth, 2004).

The Benjamini and Hochberg (1995) method, which tests thousands of hypotheses simultaneously, was applied for the strong control of false discovery rate (FDR) . The resulting outcome was a list of genes with known gene identifiers (ENTREZ gene IDs). Genes with an

FDR-based significance score (*P* score) < 0.05 and fold-change in expression >1.5 were considered as significant.

3.5.1.6. Interactions amongst dysregulated genes

The expression values of pain related genes obtained from analysing individual participant gene expression data for all the sub-groups were uploaded to Cluster 3.0. The data were imported as a tab-delimited text file with rows representing the genes and columns representing their expression values. This was done in order to determine if the genes involved in neuronal development, sensitisation due to inflammation, signal transduction, conduction and modulation influence expression levels of one another, which may contribute to the enhanced pain generation observed in women with endometriosis. To compute these interactions, Pearson's correlation coefficient was calculated. The correlation coefficient provides a measure of the linear association between two continuous variables, ranging from -1 to +1. A negative value indicates that the expression of one gene decreases with an increase in expression of the other gene. A positive value indicates that the expression of one gene increases with an increase in expression of the other. A value of zero indicates no association.

The most correlated genes were then clustered together by hierarchical clustering. In hierarchical clustering, the distance matrix between gene expression data is calculated. To compute the distance matrix, average linkage clustering was applied in which each gene is assigned its own cluster. Then, the distance between two clusters *x* and *y* is the mean of all pair wise distances between all the items contained in *x* and *y*. The genes closest to each other are clustered together and this process continues until all the genes have been incorporated in a single cluster. The output, a dendogram showing clustered genes (see Fig. 3.6) was visualised using Tree View software (©1998-2000, Stanford University, written by Michael Eisen).

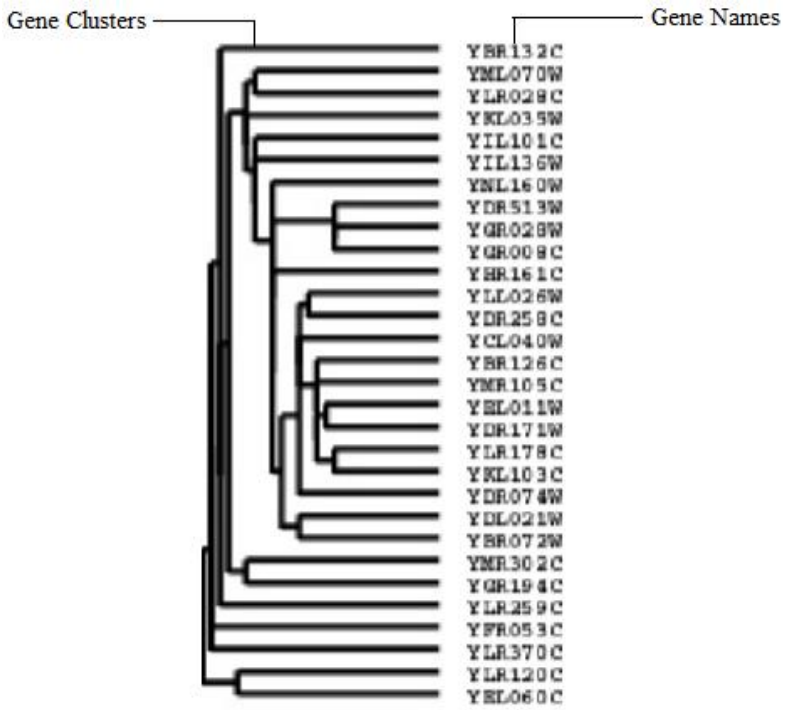


Fig. 3.6. Figure illustrating clustering of genes by hierarchical clustering method with gene clusters on the left and gene names on the right. The smaller the dendograms the more correlated are the genes.

3.5.1.7 Detection of dysregulated pathways

The dysregulated genes were aggregated into functionally related genes to form gene sets using ArrayMining. Within the program, dysregulated pathways were annotated using the Gene Ontology database, which identifies functionally related genes in a dataset. The parametric analysis of gene set enrichment method was chosen to detect dysregulated pathways. It is a robust method which requires less computation and detects dysregulated gene sets across different platforms. It uses a parametric statistical model to define significantly expressed gene sets and employs a fold change between the groups and calculates a *z*-score, the measure of dysregulation and a significance score (*P* value), respectively for a gene set (Kim and Volsky, 2005). Pathways with a *P* value < 0.05 were considered significant.

3.5.2 Meta-analysis of published gene lists

Individual participant gene expression data was unavailable for some gene expression studies. Using published analyses of datasets and integrating the available gene lists provides an alternative approach for meta-analysis of gene expression data (Kolde et al., 2012, Miller and Stamatoyannopoulos, 2010, Cahan et al., 2007, Al-Ejeh et al., 2014, Peri et al., 2013). However, gene expression data usually contains a significant proportion of technical variation, hence a robust method is required to find accurate ranking even if the lists contain only top-most dysregulated genes (Kolde et al., 2012). Rank aggregation based on ordered statistics is a meta-analysis method for published gene lists (Stuart et al., 2003, Aerts et al., 2006).

3.5.2.1 Extraction and standardisation of published gene lists

Published gene lists consist of up or downregulated genes with a measure of significance and fold change showing the difference of expression between disease and control groups (Vosa et al., 2013). For the present meta-analysis, published gene lists from all relevant studies (see Table 3.2) were extracted, and up and downregulated genes listed separately. Gene names across different lists were standardised with the gene annotation tool Database for Annotation, Visualization and Integrated Discovery (DAVID) which systematically combines functionally descriptive data with graphical displays (Huang da et al., 2009). Each gene list was uploaded into DAVID, the type of identifier selected and submitted for mapping to obtain standardised gene names.

3.5.2.2 Gene list integration and detection of dysregulated genes

The robust rank aggregation, proposed by Kolde et al. (2012) integrates published gene lists into a single list of commonly dysregulated genes. It can even be used in cases where the datasets are from different platforms and cover different sets of genes (Ma et al., 2013b). This method assumes that the number of genes in the lists is known and the ranks of the genes are according to their

dysregulation in the disease (endometriosis). Then, the corresponding rank vectors for every gene rank are calculated and assigned a significance score under a null mode. The null model assumes that all the studies produce uncorrelated, irrelevant lists of genes. Since the gene ranks are solely based on the expression measurements, the null model becomes equivalent to a permutation test (Kolde et al., 2012). The significance scores provide a rigorous way of keeping only statistically relevant genes in the final list. This method is implemented as a GNU R package ROBUSTRANKAGGREG (step wise description of the procedure is given in Appendix 5).

3.5.2.3 Detection of dysregulated pathways

The dysregulated genes detected in the published gene lists meta-analysis were further analysed for detection of pathways most affected by them. This was conducted by the Gene Ontology (GO) enrichment analysis tool of the GO consortium (available from http://geneontology.org/). For a group of genes, the enrichment analysis tool finds GO terms that are over- or under-represented. The gene names were pasted, one per row, in the designated area. Then, the name of the species (*H. sapiens*) and the ontology (biological processes) where the enrichment is required to be calculated were chosen from the drop-down menu. The results were displayed as a list of significant GO terms, background frequency (the number of genes annotated to a GO term in the entire background), sample frequency (the number of genes annotated to that GO term in the input list) and the corresponding *p* values. In addition, the criteria used and any unresolved gene names in the analysis were also listed on the top of the table.

\3.6 Convergence of results

The dysregulated genes detected in the meta-analyses of individual participant gene expression as well as the published gene lists comparing gene expression of eutopic endometrium from women with and without endometriosis as well as endometriotic lesions were converged by using Venn

diagrams. Venn diagrams provide multiple circles with overlapping regions which illustrate relations among datasets. This is conducted by calculating all possible logical relations between the given datasets and representing them in the same diagram (Li and Ghosh, 2014, Michael et al., 2011, Granlund et al., 2013).

NetVenn software was applied to converge the results of analysing individual participant gene expression data and published gene lists for this meta-analysis (Wang et al., 2014; freely available from http://probes.pw.usda.gov/NetVenn or http://wheat.pw.usda.gov/NetVenn). It compares and analyses gene expression datasets and provides information regarding the biological function of the genes by interactively annotating each element with their potential biological networks annotation databases such as Gene Ontology (Wang et al., 2014). The lists to be converged were pasted on to the designated columns and submitted for analysis. An output with interactive graphs is the generated which illustrates overlapping circles showing overlapping genes from the provided lists.

Chapter 4

Results

4.1 Individual participant gene expression data

4.1.1 Eutopic endometrium from women with and without endometriosis

Overall, 32 genes involved in neuronal development, sensitisation due to inflammation, signal transduction, conduction and modulation (the pain matrix) were significantly upregulated in the eutopic endometrium of women with endometriosis compared to women without the disease (Table 4.1). The downregulated genes in the eutopic endometrium from women with endometriosis were involved in processes such as, embryogenesis, tumorogenesis, general cell development and cell cycle regulation. A list of the 35 most significantly upregulated and downregulated genes in the eutopic endometrium of women with endometriosis (overall) are provided in Appendices 6 and 7, respectively.

Table 4.1: Upregulated pain related genes in the eutopic endometrium of women with endometriosis compared to endometrium from women without endometriosis.

Entrez Id	Gene symbol	Gene name	Fold change	*P* value
Neuronal development				
1942	EFNA1	Ephrin-A1	2.64	0.4×10^{-22}
1808	DPYSL2	Dihydropyrimidinase-like 2	1.91	0.1×10^{-14}
10397	NDRG1	N-myc downstream regulated 1	2.11	0.1×10^{-14}
8495	PPFIBP2	PTPRF interacting protein, binding protein 2	1.8	0.1×10^{-13}
604	BCL6	B-cell CLL/lymphoma 6	2.86	0.3×10^{-13}
91	ACVR1B	Activin A receptor, type IB	1.69	0.4×10^{-13}
81631	MAP1LC3B	Microtubule-associated protein 1 light chain 3 beta	1.52	0.1×10^{-12}
10677	AVIL	Advillin	1.95	0.1×10^{-12}
Sensitisation due to inflammation				
1052	CEBPD	CCAAT/enhancer binding protein	3.14	0.2×10^{-18}
3600	IL15	Interleukin 15	2.98	0.2×10^{-16}
1438	CSF2RA	Colony stimulating factor 2 receptor, alpha, low-affinity	2.02	0.2×10^{-16}
7132	TNFRSF1A	Tumor necrosis factor receptor superfamily, member 1A	1.55	0.2×10^{-15}
26253	CLEC4E	C-type lectin domain family 4, member E	1.7	0.3×10^{-14}
718	C3	Complement component 3	2.93	0.2×10^{-13}
9252	RPS6KA5	Ribosomal protein S6 kinase, 90kDa, polypeptide 5	2.13	0.2×10^{-13}
7099	TLR4	Toll-like receptor 4	1.75	0.1×10^{-12}
3601	IL15RA	Interleukin 15 receptor, alpha	1.49	0.2×10^{-12}
Signal transduction				
4217	MAP3K5	Mitogen-activated protein kinase kinase 5	3.15	0.3×10^{-17}
347902	AMIGO2	Adhesion molecule with Ig-like domain 2	3.09	0.3×10^{-15}
5597	MAPK6	Mitogen-activated protein kinase 6	1.95	0.8×10^{-13}
6774	STAT3	Signal transducer and activator of transcription 3	1.42	0.2×10^{-12}
Conduction				
2040	STOM	Stomatin	1.73	0.3×10^{-13}
3752	KCND3	Potassium voltage-gated channel, Shal-related subfamily, member 3	1.76	0.2×10^{-12}
Modulation				
6505	SLC1A1	Solute carrier family 1 member 1	4.71	0.5×10^{-21}
6539	SLC6A12	Solute carrier family 6 member 12	2.53	0.6×10^{-20}
54463	FAM134B	Family with sequence similarity 134, member B	1.98	0.3×10^{-16}
3976	LIF	Leukemia inhibitory factor	2.74	0.1×10^{-14}
9846	GAB2	GRB2-associated binding protein 2	1.99	0.3×10^{-14}
5533	PPP3CC	Protein phosphatase 3, catalytic subunit, gamma isozyme	1.49	0.9×10^{-14}
3572	IL6ST	Interleukin 6 signal transducer	2.41	0.4×10^{-13}
80736	SLC44A4	Solute carrier family 44, member 4	2.35	0.5×10^{-13}
81539	SLC38A1	Solute carrier family 38, member 1	2.09	0.2×10^{-12}

Dysregulated pathways. Overall, the most significantly dysregulated pathways were related to inflammatory and immune responses (top-20 most dysregulated pathways in Appendix 8).

Interactions amongst genes. Formation of clusters amongst genes involved in sensitisation due to inflammation, neuronal development and pain generation is illustrated in the figure (see Fig. 4.1). In the figure, the dendograms on the left represent correlations between the gene expression values. The smaller the dendogram, the more correlated are the expression values of the genes. This implies that these genes are functionally related and may regulate each other's expression, thereby contributing to increased pain generation observed in women with endometriosis.

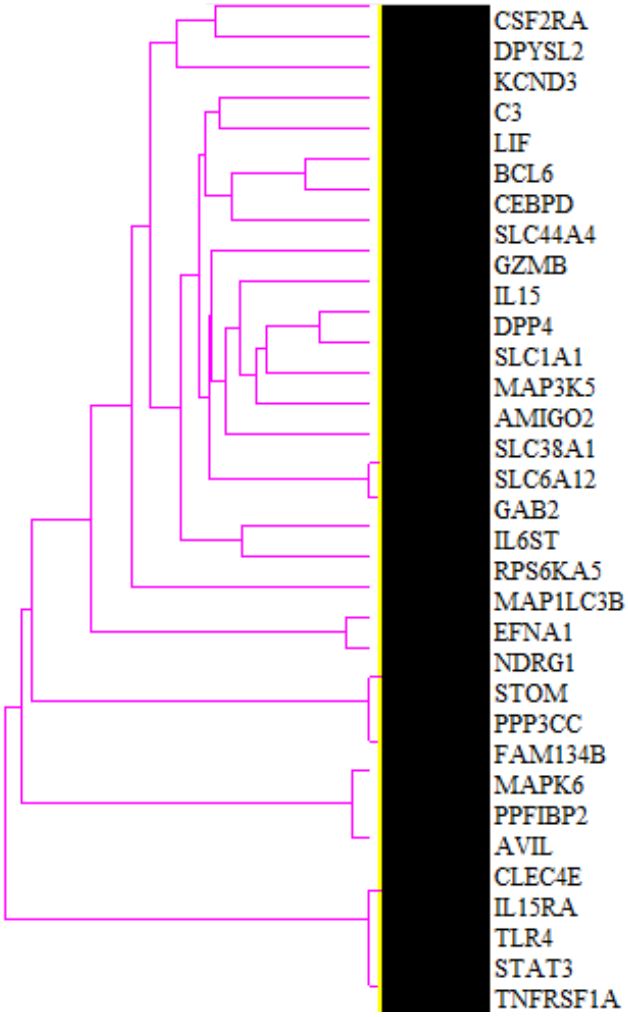


Fig. 4.1: Interactions among upregulated pain related genes in the eutopic endometrium of women with endometriosis. The dendograms on the left illustrate correlation amongst genes expression values. The shorter the dendograms, the more correlated are the genes.

4.1.1.1 Proliferative phase

Twenty genes involved in the pain matrix were significantly upregulated in the eutopic endometrium of women with compared to women without endometriosis (see Table 4.2). The downregulated genes were mostly involved in cell cycle regulation, tumorogenesis, apoptosis and transcription. A list of top-35 upregulated and downregulated genes in the proliferative phase is provided in Appendices 9 and 10, respectively.

Table 4.2: Upregulated pain related genes in the proliferative phase of the eutopic endometrium of women with endometriosis compared to women without endometriosis.

Entrez ID	Gene symbol	Gene name	Fold Change	*P* value
Neuronal development				
1942	EFNA1	Ephrin-A1	1.95	0.0006
604	BCL6	B-cell CLL/lymphoma 6	2.15	0.004
10397	NDRG1	N-myc downstream regulated 1	1.71	0.011
2026	ENO2	Enolase 2 (gamma, neuronal)	1.4	0.023
Sensitisation due to inflammation				
9510	ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	1.92	0.009
6347	CCL2	Chemokine (C-C motif) ligand 2	1.63	0.021
1051	CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	1.37	0.004
1052	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	2.17	0.005
1999	ELF3	E74-like factor 3 (ets domain transcription factor, epithelial-specific)	1.83	0.007
5732	PTGER2	Prostaglandin E receptor 2 (subtype EP2), 53kDa	1.45	0.02
54210	TREM1	Triggering receptor expressed on myeloid cells 1	1.85	0.01
Signal transduction				
4217	MAP3K5	Mitogen-activated protein kinase kinase kinase 5	1.79	0.02
1326	MAP3K8	Mitogen-activated protein kinase kinase kinase 8	1.45	0.02
2872	MKNK2	MAP kinase interacting serine/threonine kinase 2	1.29	0.004
9961	MVP	Major vault protein	1.43	0.02
Conduction				
6533	SLC6A6	Solute carrier family 6 (neurotransmitter transporter, taurine), member 6	1.47	0.004
Modulation				
23529	CLCF1	Cardiotrophin-like cytokine factor 1	1.36	0.008
3659	IRF1	Interferon regulatory factor 1	1.38	0.02
3976	LIF	Leukemia inhibitory factor (cholinergic differentiation factor)	1.87	0.02
80736	SLC44A4	Solute carrier family 44, member 4	1.71	0.02

Dysregulated pathways. Processes involved in immune and inflammatory responses were among the top dysregulated pathways in the proliferative phase of the eutopic endometrium from women with endometriosis (see Appendix 8 for 20-top most dysregulated pathways).

4.1.1.2 Secretory phase

Seventeen genes involved in neuronal development, sensitisation due to inflammation, signal transduction and modulation in the secretory phase eutopic endometrium of women with endometriosis were significantly upregulated when compared to women without endometriosis (see Table 4.3). The downregulated genes in the secretory phase were those involved in embryogenesis, apoptosis, cell growth and differentiation as well as muscle contraction. A list of top-35 upregulated and downregulated genes in the secretory phase is provided in Appendices 11 and 12, respectively.

Table 4.3: Upregulated pain related genes in the secretory phase of the eutopic endometrium of women with endometriosis compared to women without endometriosis.

Entrez ID	Gene Symbol	Gene name	Fold Change	*P* value
Neuronal development				
1942	EFNA1	Ephrin-A1	2.4	0.6×10^{-14}
10397	NDRG1	N-myc downstream regulated 1	1.9	0.4×10^{-12}
8495	PPFIBP2	PTPRF interacting protein, binding protein 2 (liprin beta 2)	2	0.3×10^{-11}
604	BCL6	B-cell CLL/lymphoma 6	2.1	0.7×10^{-10}
Sensitisation due to inflammation				
145741	C2CD4A	C2 calcium-dependent domain containing 4A	7.1	0.1×10^{-14}
9547	CXCL14	Chemokine (C-X-C motif) ligand 14	9	0.3×10^{-11}
718	C3	Complement component 3	3.3	0.1×10^{-10}
1052	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	2.4	0.1×10^{-9}
Signal transduction				
4217	MAP3K5	Mitogen-activated protein kinase kinase kinase 5	3.3	0.9×10^{-14}
347902	AMIGO2	Adhesion molecule with Ig-like domain 2	2.8	0.7×10^{-13}
Conduction				
No. of genes : 0				
Modulation				
6505	SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	7.4	0.1×10^{-14}
54463	FAM134B	Family with sequence similarity 134, member B	2.2	0.4×10^{-11}
9180	OSMR	Oncostatin M receptor	2.2	0.1×10^{-10}
3976	LIF	Leukemia inhibitory factor	2.6	0.2×10^{-10}
80736	SLC44A4	Solute carrier family 44, member 4	2.1	0.3×10^{-10}
81539	SLC38A1	Solute carrier family 38, member 1	2.5	0.1×10^{-9}
3572	IL6ST	Interleukin 6 signal transducer	2.1	0.2×10^{-9}

Dysregulated pathways. The top dysregulated pathways involved processes such as immune and inflammatory responses (see Appendix 8 for 20-top most dysregulated pathways).

4.1.1.3 Eutopic endometrium from women with endometriosis: Secretory vs. proliferative phase

In the eutopic endometrium from women with endometriosis, 30 genes involved in the pain matrix were significantly upregulated in the secretory phase when compared to the proliferative phase of the menstrual cycle (see Table 4.4). Genes involved in processes, such as cellular proliferation and cell cycle regulation were downregulated. A list of top-35 upregulated and downregulated genes in the secretory phase is provided in Appendices 13 and 14, respectively.

Table 4.4: Upregulated pain related genes in the secretory phase of eutopic endometrium of women with endometriosis.

Entrez ID	Gene symbol	Gene name	Fold change	*P* value
Neuronal development				
4684	NCAM1	Neural cell adhesion molecule 1	2.79	$0.7 X10^{-12}$
10397	NDRG1	N-myc downstream regulated 1	2.76	$0.2 X10^{-8}$
1808	DPYSL2	Dihydropyrimidinase-like 2	2.17	$0.1 X10^{-7}$
Sensitisation due to inflammation				
5578	PRKCA	Protein kinase C, alpha	1.8	$0.4 X10^{-9}$
10855	HPSE	Heparanase	3.07	$0.8 X10^{-9}$
1116	CHI3L1	Chitinase 3-like 1 (cartilage glycoprotein-39)	3.46	$0.2 X10^{-8}$
2532	DARC	Duffy blood group, chemokine receptor	2.85	$0.4 X10^{-8}$
1435	CSF1	Colony stimulating factor 1 (macrophage)	2.35	$0.6 X10^{-8}$
2268	FGR	Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog	2.77	$0.3 X10^{-7}$
Signal transduction				
5791	PTPRE	Protein tyrosine phosphatase, receptor type, E	3.01	$0.1 X10^{-10}$
7223	TRPC4	Transient receptor potential cation channel, subfamily C, member 4	3.38	$0.4 X10^{-9}$
916	CD3E	CD3e molecule, epsilon (CD3-TCR complex)	2.41	$0.5 X10^{-8}$
79054	TRPM8	Transient receptor potential cation channel, subfamily M, member 8	2.71	$0.7 X10^{-7}$
3718	JAK3	Janus kinase 3	1.72	$0.1 X10^{-6}$
6777	STAT5B	Signal transducer and activator of transcription 5B	1.56	$0.1 X10^{-6}$
Conduction				
3777	KCNK3	Potassium channel, subfamily K, member 3	2.64	$0.3 X10^{-8}$
3749	KCNC4	Potassium voltage-gated channel, Shaw-related subfamily, member 4	1.83	$0.3 X10^{-7}$
6548	SLC9A1	Solute carrier family 9 (sodium/hydrogen exchanger), member 1	1.92	$0.9 X10^{-7}$
3756	KCNH1	Potassium voltage-gated channel, subfamily H (eag-related), member 1	1.76	$0.1 X10^{-6}$
55117	SLC6A15	Solute carrier family 6 (neutral amino acid transporter), member 15	2.11	$0.1 X10^{-6}$
Modulation				
6539	SLC6A12	Solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	3.02	$0.3 X10^{-8}$
6812	STXBP1	Syntaxin binding protein 1	2.53	$0.9 X10^{-8}$
9180	OSMR	Oncostatin M receptor	2.36	$0.1 X10^{-7}$
6505	SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	4.23	$0.4 X10^{-7}$
27092	CACNG4	Calcium channel, voltage-dependent, gamma subunit 4	2.28	$0.1 X10^{-6}$
3352	HTR1D	5-Hydroxytryptamine (serotonin) receptor 1D	1.95	$0.1 X10^{-6}$

Dysregulated pathways. Pathways involved in cytokine activity as well as potassium ion channel activity were amongst the most upregulated (see Appendix 8 for a list of top-20 dysregulated pathways).

4.1.2 Endometriotic lesions compared to eutopic endometrium from women with endometriosis

Thirty genes involved in the pain matrix were significantly upregulated in the endometriotic lesions when compared to eutopic endometrium from women with endometriosis, overall (see Table 4.5). The downregulated genes were involved in proton conductance, embryonic development, DNA repair and cancer-related processes. A list of top-35 up and downregulated genes is given in Appendices 15 and 16, respectively.

Table 4.5: Upregulated pain related genes in the endometriotic lesions compared to eutopic endometrium from women with endometriosis.

Entrez Id	Gene symbol	Gene name	Fold Change	*P* value
Neuronal development				
1942	EFNA1	Ephrin-A1	1.83	$0.4 X10^{-14}$
10397	NDRG1	N-myc downstream regulated 1	1.79	$0.9 X10^{-9}$
10677	AVIL	Advillin	1.63	$0.5 X10^{-8}$
91	ACVR1B	Activin A receptor, type IB	1.5	$0.1 X10^{-6}$
Sensitisation to inflammation				
9547	CXCL14	Chemokine (C-X-C motif) ligand 14	4.03	$0.9 X10^{-10}$
7099	TLR4	Toll-like receptor 4	1.6	$0.9 X10^{-9}$
3600	IL15	Interleukin 15	2.11	$0.1 X10^{-8}$
9180	OSMR	Oncostatin M receptor	1.86	$0.2 X10^{-8}$
4982	TNFRSF11B	Tumor necrosis factor receptor superfamily, member 11b	1.76	$0.3 X10^{-7}$
10855	HPSE	Heparanase	1.91	$0.3 X10^{-7}$
9252	RPS6KA5	Ribosomal protein S6 kinase, 90kDa, polypeptide 5	1.65	$0.4 X10^{-7}$
2150	F2RL1	Coagulation factor II (thrombin) receptor-like 1	1.83	$0.4 X10^{-7}$
1116	CHI3L1	Chitinase 3-like 1 (cartilage glycoprotein-39)	2.68	$0.5 X10^{-7}$
7127	TNFAIP2	Tumor necrosis factor, alpha-induced protein 2	1.55	$0.6 X10^{-7}$
9173	IL1RL1	Interleukin 1 receptor-like 1	1.75	$0.1 X10^{-6}$
Signal transduction				
55890	GPRC5C	G protein-coupled receptor, family C, group 5, member C	1.56	$0.2 X10^{-9}$
266977	GPR110	G protein-coupled receptor 110	2.02	$0.9 X10^{-9}$
4217	MAP3K5	Mitogen-activated protein kinase kinase kinase 5	1.99	$0.3 X10^{-8}$
302	ANXA2	Annexin A2	1.56	$0.1 X10^{-6}$
6775	STAT4	Signal transducer and activator of transcription 4	1.54	$0.2 X10^{-6}$
Conduction				
6505	SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	3.81	$0.1 X10^{-17}$
6533	SLC6A6	Solute carrier family 6 (neurotransmitter transporter, taurine), member 6	1.76	$0.4 X10^{-8}$
3775	KCNK1	Potassium channel, subfamily K, member 1	1.5	$0.4 X10^{-6}$
Modulation				
6564	SLC15A1	Solute carrier family 15 (oligopeptide transporter), member 1	2.79	$0.2 X10^{-12}$
6539	SLC6A12	Solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	2.05	$0.3 X10^{-12}$
3976	LIF	Leukemia inhibitory factor	2.28	$0.1 X10^{-8}$
80736	SLC44A4	Solute carrier family 44, member 4	2.11	$0.4 X10^{-8}$
2643	GCH1	GTP cyclohydrolase 1	1.71	$0.8 X10^{-7}$
6571	SLC18A2	Solute carrier family 18 (vesicular monoamine), member 2	2.47	$0.1 X10^{-6}$
2555	GABRA2	Gamma-aminobutyric acid (GABA) A receptor, alpha 2	2.15	$0.3 X10^{-6}$

Dysregulated pathways. The pathways involved in both neuron development and pain modulation were found to be significantly upregulated compared to the eutopic endometrium from women with endometriosis (see Appendix A17 for a list of top-20 dysregulated pathways).

Interaction amongst genes. It can be seen from the figure that genes involved in the pain matrix are functionally related and may regulate the expression of one another (see Fig. 4.2). The clustering amongst the genes illustrates that the expression values of the genes are positively correlated with each other. The dendograms on the left show clustering amongst correlated genes. The shorter the dendograms, the more correlated are the expression values of the genes.

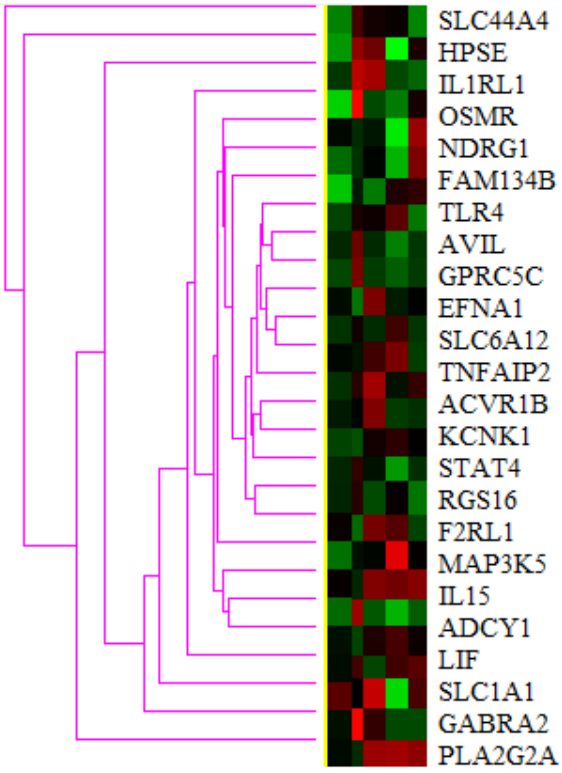


Fig. 4.2: Interactions among upregulated pain related genes in endometriotic lesions. The dendograms on the left illustrate correlation amongst genes expression values. The shorter the dendograms, the more correlated are the genes.

4.1.2.1 Proliferative phase

In the proliferative phase, 28 genes involved in the pain matrix were found to be significantly upregulated in endometriotic lesions compared to the eutopic endometrium from women with endometriosis (Table 4.6). The significantly downregulated genes were involved in immune responses, embryogenesis, tumorogenesis and in encoding proteins for various metabolic processes. For a list of top-35 up and downregulated genes, see Appendices 18 and 19, respectively.

Table 4.6: Upregulated pain related genes in the proliferative phase of the endometriotic lesions compared to eutopic endometrium of women with endometriosis.

Entrez ID	Gene symbol	Gene name	Fold Change	*P* value
Neuronal development				
1729	DIAPH1	Diaphanous homolog 1 (Drosophila)	1.2	$0.6 X10^{-4}$
1906	EDN1	Endothelin 1	1.5	$0.3 X10^{-3}$
10677	AVIL	Advillin	1.3	$0.5 X10^{-3}$
Sensitisation due to inflammation				
728	C5AR1	Complement component 5a receptor 1	2.2	$0.1 X10^{-4}$
1051	CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	1.5	$0.1 X10^{-4}$
3553	IL1B	Interleukin 1, beta	2.3	$0.2 X10^{-4}$
3576	IL8	Interleukin 8	3.9	$0.2 X10^{-4}$
1116	CHI3L1	Chitinase 3-like 1 (cartilage glycoprotein-39)	2.9	$0.1 X10^{-3}$
9173	IL1RL1	Interleukin 1 receptor-like 1	1.6	$0.2 X10^{-3}$
6696	SPP1	Secreted phosphoprotein 1	2.9	$0.2 X10^{-3}$
2921	CXCL3	Chemokine (C-X-C motif) ligand 3	2.2	$0.3 X10^{-3}$
3569	IL6	Interleukin 6 (interferon, beta 2)	1.9	$0.3 X10^{-3}$
3269	HRH1	Histamine receptor H1	1.4	$0.3 X10^{-3}$
3659	IRF1	Interferon regulatory factor 1	1.4	$0.3 X10^{-3}$
4067	LYN	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	1.3	$0.3 X10^{-3}$
9516	LITAF	Lipopolysaccharide-induced TNF factor	1.3	$0.3 X10^{-3}$
10859	LILRB1	Leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 1	1.2	$0.3 X10^{-3}$
834	CASP1	Caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	1.3	$0.4 X10^{-3}$
30817	EMR2	egf-like module containing, mucin-like, hormone receptor-like 2	1.6	$0.4 X10^{-3}$
4982	TNFRSF11B	Tumor necrosis factor receptor superfamily, member 11b	1.5	$0.6 X10^{-3}$
Signal transduction				
5791	PTPRE	Protein tyrosine phosphatase, receptor type, E	1.5	$0.2 X10^{-4}$
1326	MAP3K8	Mitogen-activated protein kinase kinase kinase 8	1.6	$0.3 X10^{-4}$
1366	CLDN7	Claudin 7	1.4	$0.3 X10^{-3}$
5873	RAB27A	RAB27A, member RAS oncogene family	1.3	$0.3 X10^{-3}$
80232	WDR26	WD repeat domain 26	1.2	$0.5 X10^{-3}$
Conduction				
3775	KCNK1	Potassium channel, subfamily K, member 1	1.5	$0.9 X10^{-6}$
Modulation				
3976	LIF	Leukemia inhibitory factor	2.4	$0.4 X10^{-5}$
6539	SLC6A12	Solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	1.7	$0.5 X10^{-4}$

Dysregulated pathways. In endometriotic lesions, pathways involved in inflammatory and immune responses were among the top upregulated pathways (see Appendix 17 for a list of top-20 dysregulated pathways).

4.1.2.2 Secretory phase

In the secretory phase, none of the significantly upregulated genes were involved in the pain matrix , however genes involved in cell adhesion, proliferation and anti-apoptosis were found to be significantly upregulated. A progesterone receptor gene *unc-45 homolog A (C. elegans)* (UNC45A) was significantly downregulated. For a list of top-35 up and down-regulated genes, see Appendix 20, respectively.

Dysregulated pathways. There were no significantly upregulated pathways during the secretory phase in endometriotic lesions.

4.1.2.3 Endometriotic lesions from women with endometriosis: Secretory vs. proliferative phase

Twenty-five genes involved in neuronal development, signal transduction, conduction and pain modulation were significantly upregulated in the secretory phase endometriotic lesions when proliferative and secretory phases of the menstrual cycle were compared (Table 4.7). The dowregulated genes were mostly involved in cytokinesis, antigen presentation, cancer development, apoptosis and immune responses. For a list of top-35 up and downregulated genes, see Appendices 21 and 22, respectively.

Table 4.7: Upregulated pain related genes in the secretory phase of endometriotic lesions.

Entrez Id	Gene symbol	Gene name	Fold Change	*P* value
Neuronal development				
4684	NCAM1	Neural cell adhesion molecule 1	4.8	0.00046
5098	PCDHGA8	Protocadherin gamma subfamily A, 8	2.7	0.00067
157922	CAMSAP1	Calmodulin regulated spectrin-associated protein 1	2.5	0.00069
5354	PLP1	Proteolipid protein 1	4.3	0.00081
4133	MAP2	Microtubule-associated protein 2	2.6	0.00084
2047	EPHB1	EPH receptor B1	3.7	0.00086
9752	PCDHA9	Protocadherin alpha 9	2.7	0.00089
5365	PLXNB3	Plexin B3	2.7	0.00106
63974	NEUROD6	Neurogenic differentiation 6	2.5	0.00107
Sensitisation due to inflammation				
No genes				
Signal transduction				
51208	CLDN18	Claudin 18	2.6	0.00081
607	BCL9	B-cell CLL/lymphoma 9	2.4	0.00082
7275	TUB	Tubby homolog (mouse)	2.3	0.00086
1432	MAPK14	Mitogen-activated protein kinase 14	2.3	0.00089
10178	ODZ1	odz, odd Oz/ten-m homolog 1(Drosophila)	3	0.00102
5567	PRKACB	Protein kinase, cAMP-dependent, catalytic, beta	2.1	0.00106
Conduction				
10479	SLC9A6	Solute carrier family 9 (sodium/hydrogen exchanger), member 6	3.1	0.0008
3778	KCNMA1	Potassium large conductance calcium-activated channel, subfamily M, alpha member 1	2.7	0.00082
6543	SLC8A2	Solute carrier family 8 (sodium/calcium exchanger), member 2	4.3	0.00086
57419	SLC24A3	Solute carrier family 24 (sodium/potassium/calcium exchanger), member 3	3.9	0.00092
3750	KCND1	Potassium voltage-gated channel, Shal-related subfamily, member 1	3.3	0.00098
Modulation				
7166	TPH1	Tryptophan hydroxylase 1	4.3	0.00046
6581	SLC22A3	Solute carrier family 22 (extraneuronal monoamine transporter), member 3	3.4	0.00086
2897	GRIK1	Glutamate receptor, ionotropic, kainate 1	2.3	0.00103
2550	GABBR1	Gamma-aminobutyric acid type B receptor subunit 1	2.7	0.00106
79664	NARG2	NMDA receptor regulated 2	2.2	0.00106

Dysregulated pathways. In the secretory phase endometriotic lesions compared to proliferative phase lesions, pathways involved in ion and neurotransmitter transport were among the top 10 upregulated pathways (see Appendix 17 for a list of top-20 dysregulated pathways).

4. 2 Published gene lists

4.2.1 Eutopic endometrium from women with and without endometriosis

There were 16 significantly upregulated genes involved in the pain matrix (see Table 4.8). In total, there were 45 upregulated genes and 37 downregulated genes across the three datasets (see Appendices 23 and 24).

Table 4.8: Significantly upregulated genes in the eutopic endometrium of women with endometriosis.

Gene Symbol	Gene name	*P* value
Neuronal development		
JUNB	Jun B proto-oncogene	0.0009
ASCL1	Achaete-scute complex homolog 1 (Drosophila)	0.0018
efnb1	Ephrin B1	0.009213
POU3F4	Brain 4 mRNA	0.013459
Sensitisation due to inflammation		
CPE	Carboxypeptidase E	0.002699
CCL21	Chemokine (C–C motif) ligand 21	0.005846
Signal transduction		
PTPRR	Protein tyrosine phosphatase, receptor type, R	0.00045
CASP5	Cysteine protease (ICErel-III)	0.000709
SNCG	Synuclein, gamma	0.002249
PDE9A	Phosphodiesterase 9A	0.002249
TSPAN15	Tetraspanin 15	0.003599
FOS	V-fos FBJ murine osteosarcoma viral oncogene homolog	0.004947
Conduction		
ATP1A2	ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide	0.00045
Modulation		
IL6ST	Interleukin-6 signal transducer	0.003599
GPR56	G-Protein coupled receptor	0.004498
MAP3K1	Mitogen activate protein kinase kinase 1	0.009921

Dysregulated pathways. Pathways related to signal transduction, response to stimuli were significantly upregulated which may contribute to increased signal transduction in the eutopic endometrium from women with endometriosis (for a list of top-20 dysregulated pathways see Appendix 25).

4.2.2 Eutopic endometrium and endometriotic lesions from women with endometriosis

In endometriotic lesions compared to eutopic endometrium from women with endometriosis, there was one gene involved in conduction and two genes involved in inflammation (see Table 4.9). The meta-analysis of published gene lists from seven studies revealed 43 down-regulated and 37 upregulated genes in the endometriotic lesions when compared to the eutopic endometrium from women with endometriosis (see Appendices 26 and 27).

Table 4.9: Significantly upregulated genes in endometriotic lesions

Gene Symbol	Gene Name	*P* value
Neuronal development		
No gene**s**		
Sensitisation due to inflammation		
PLA2G5	Phospholipase A2, group V	0.000068
CPVL	Carboxypeptidase, vitellogenic-like	0.001065
Signal transduction		
No genes		
Conduction		
SCN7A	Sodium channel, voltage-gated, type VII, alpha subunit	0.0000268
Pain modulation		
No genes		

Differentially regulated pathways. No pathways involved in pain generation were significantly dysregulated in endometriotic lesions compared to eutopic endometrium from women with endometriosis. Pathways involved in reproduction and cellular organisation were amongst the top dysregulated pathways in endometriotic lesions compared to eutopic endometrium from women with endometriosis (for a list of top-20 dysregulated pathways see Appendix 25).

4.3 Convergence of gene list results

The converged list of upregulated genes involved in pain generation from both meta-analyses of individual participant gene expression data and published genes lists, comparing eutopic endometrium from women with and without endometriosis revealed only one gene, interleukin 6

signal transducer, *IL6ST* (see Fig. 4.3). No genes involved in pain generation were revealed to be common in the lists comparing gene expression in endometriotic lesions with eutopic endometrium from women with endometriosis.

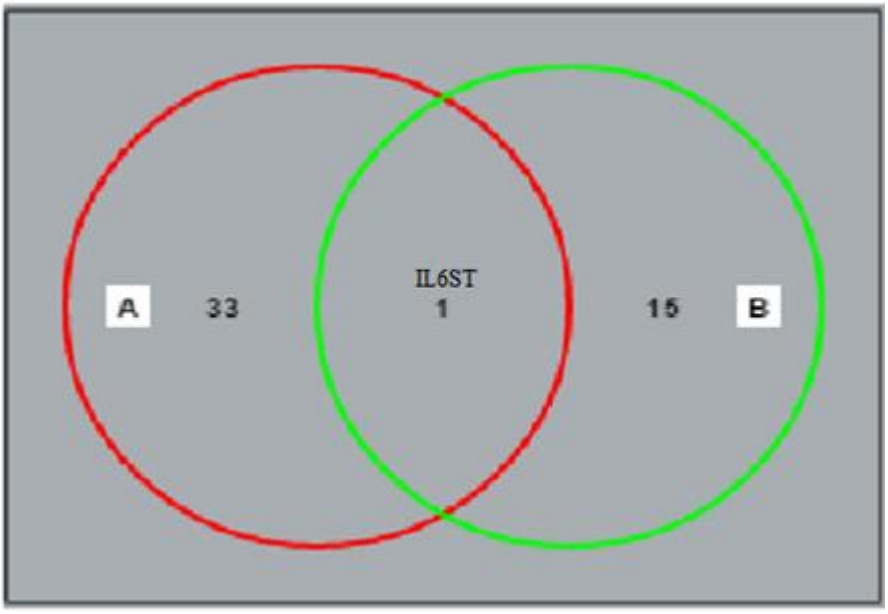


Fig. 4.3: Venn diagram illustrating one upregulated pain related gene common across gene list results obtained from meta-analyses of individual patient gene expression data and published gene list, comparing eutopic endometrium from women with and without endometriosis. A: List of upregulated pain related genes from the meta-analysis of individual participant gene expression data; B: List of upregulated pain genes from meta-analysis of published gene lists. The overlap of the two lists resulted in one common gene: Interleukin 6 signal transducer gene (IL6ST).

Chapter 5

Discussion

5.1 Introduction

This study has demonstrated an upregulation of pain related genes and pathways in both the eutopic endometrium and lesions as well as in the secretory compared to proliferative menstrual cycle phase in women with endometriosis. Genes involved in neuronal development, inflammation and sensitisation, signal transduction, signal conduction and pain modulation were all implicated in endometriosis. An upregulation of pain related genes may enhance peripheral sensitisation thereby leading to increased pain generation observed in women with endometriosis.

5.2 Neuronal development in endometriosis

In both the individual gene expression and published gene list meta-analyses, genes involved in neuronal development were upregulated in the eutopic endometrium from women with endometriosis as well as in endometriotic lesions. Neurogenesis is a well-known phenomenon in endometriosis and has been implicated in the progression of the disease as well as its related pain symptoms (Bokor et al., 2009, Anaf et al., 2002, Arnold et al., 2012, Greaves et al., 2014, Asante and Taylor, 2011, Abu-Asab et al., 2011, Chen et al., 2014, McKinnon et al., 2015, Eyster et al., 2007, Hull et al., 2008).

As an example, in the eutopic endometrium from women with endometriosis, *Jun B proto-oncogene* (*JUNB*) was significantly upregulated. *JUNB* is a member of a family of transcription factors (Jun) and is promoted by growth factors and cytokines such as NGF and IL6 (Ransone and Verma, 1990, Angel and Karin, 1991, Dutta et al., 2011, Lord et al., 1993), which are also found to be at increased levels in the eutopic endometrium, peritoneal fluid and endometriotic lesions of

women with endometriosis (Anaf et al., 2002, Akoum et al., 1996, Barcena de Arellano et al., 2011). *JUNB* functions by decreasing neuronal apoptosis in conjunction with NGF to promote neuronal survival (Lee et al., 2005a). Its mRNA and protein expression levels are high in cancerous cells (Lee et al., 2005a). *JUNB* expression is also known to be increased in neurons which respond to noxious stimuli and contribute to pain (Morgan and Curran, 1991, Naranjo et al., 1991). Recently, Hurst et al. (2014) have demonstrated increased *JUNB* gene expression in the eutopic endometrium of women with endometriosis compared to women without the disease. Furthermore, there is an increase in NGF mRNA and protein expression in the eutopic endometrium (Browne et al., 2012, Tokushige et al., 2007) which may increase JUNB expression in the eutopic endometrium. Together, they may increase sensory innervation in the eutopic endometrium of women with endometriosis (Aghaey Meibody et al., 2011, Kobayashi et al., 2013, Cervero, 1994, Triolo et al., 2013, Tokushige et al., 2007).

In endometriotic lesions, gene encoding for adivilin (*AVIL*) was upregulated compared to the eutopic endometrium. This gene is a member of the Gelsolin superfamily of actin binding proteins and is predominantly expressed in the peripheral somatosensory neurons which innervate peripheral organs and transmit pro-nociceptive painful signals (Hasegawa et al., 2007, Marks et al., 1998, Ravenall et al., 2002). Advillin is involved in axonal remodelling, regrowth of the peripheral sensory neurons and responding to cellular stress (Hasegawa et al., 2007, Zurborg et al., 2011, Marks et al., 1998, Shibata et al., 2004). In endometriotic lesions, upregulation of this gene may lead to the hyper-innervation of the endometriotic lesions and also to increased pro-nociceptive signalling, thereby contributing to increased pain generation in women with endometriosis (Wang et al., 2009, Kobayashi et al., 2013, Anaf et al., 2002, Triolo et al., 2013).
Furthermore, in endometriotic lesions, neuronal development pathways such as those involved in the development of synapses between neurons as well as those involved in formation of the post-

synaptic membrane were also upregulated compared to the eutopic endometrium from women with endometriosis. Upregulation of these genes and the related pathways in endometriotic lesions may contribute to pain by increased lesion innervation which may lead to increased peripheral sensitisation (Asante and Taylor, 2011, Wang et al., 2009, Anaf et al., 2002, Arnold et al., 2012, Stratton and Berkley, 2011).

There was an upregulation of neuronal development genes in the secretory compared to the proliferative phase in both the eutopic endometrium and lesions from women with endometriosis. For example, in the secretory phase compared to the proliferative phases, in both the eutopic endometrium and endometriotic lesions from women with endometriosis, *neural cell adhesion molecule (NCAM)* gene *NCAM-1* was significantly upregulated. *NCAM-1* encodes for a glycoprotein which is involved in intercellular adhesions (Francavilla et al., 2007, Hinsby et al., 2004, Rønn et al., 1998) and mediates neuronal migration, proliferation and survival, as well as synapse formation and plasticity (Delling et al., 2002, Murase and Schuman, 1999, Schachner, 1997). It is also known to be involved in perineural invasion which damages the nerve cells and generates pain (Ben et al., 2010, Bapat et al., 2011). Odagiri et al. (2008) and Yu et al. (2009) have also demonstrated increased *NCAM-1* gene expression in both eutopic endometrium and endometriotic lesions. An upregulation of NCAM-1 may increase innervation of the eutopic endometrium and endometriotic lesions, and may also generate pain by promoting nerve cell damage. Upregulation of neuronal development genes in the secretory phase in endometriosis correlates with increased pain in women during the late secretory phase of the menstrual cycle (Barbosa Mde et al., 2013, de Tommaso, 2011, Hellstrom and Anderberg, 2003).

During chronic pain conditions, there is an upregulation of genes involved in neuronal development (Costigan et al., 2009, Costigan et al., 2002). In endometriosis, upregulation of genes

involved in neuronal development in the eutopic endometrium and endometriotic lesions may contribute to the high density of sensory nerve fibres observed in women with endometriosis and to pain in the disease (Tokushige et al., 2006a, Wang et al., 2009, Tokushige et al., 2007). The importance of this for pain in endometriosis is supported by a correlation between nerve fibre density in lesions with pain intensity in endometriosis (Stratton and Berkley, 2011).

5.3 Sensitisation due to inflammation in endometriosis

Genes involved in inflammation leading to peripheral sensitisation were upregulated in the eutopic endometrium from women with endometriosis as well as in endometriotic lesions in both meta-analyses. Increased expression of these genes is known to be linked to pain (Black et al., 2004, Di Sebastiano et al., 2003, Homma et al., 2013, Yukhananov and Kissin, 2008). Inflammatory mediators sensitise peripheral sensory neurons, lowering their threshold for generating an action potential (Chen et al., 2009, Schaible, 2007, Voscopoulos and Lema, 2010).

Increased expression of genes involved in inflammation in both the eutopic endometrium of women with endometriosis and endometriotic lesions is supported by the included studies (Vouk et al., 2011, Burney et al., 2007, Eyster et al., 2007) as well as the broader literature (Kyama et al., 2006, Chand et al., 2007, Bertschi et al., 2013, Tseng et al., 1996, Abu-Asab et al., 2011, Nikoo et al., 2014, Lin et al., 2014, Li et al., 2013). Genes involved in inflammation have been implicated in the pathogenesis of endometriosis and in related pain symptoms (Scholl et al., 2009). Moreover, this study has found that the most highly dsyregulated pathways in the eutopic endometrium and lesions from women with endometriosis were those involved in inflammatory and immune responses such as acute inflammatory response, activation of cytokines and chemokines as well as promoting a response to stimulus. This correlates with findings of immune dysfunction and an inflammatory microenvironment in endometriosis, leading to disease progression and

development of associated pain symptoms (Braun and Dmowski, 1998, Matarese et al., 2003, Bloski and Pierson, 2008, Herington et al., 2011, Ahn et al., 2015. In press).

In the eutopic endometrium from women with endometriosis compared to endometriotic lesions, upregulated genes involved in inflammation included *interleukin 6 signal transducer* (*IL6ST*). *IL6ST*, also known as glycoprotein 130 (gp130), was the only gene found to be common amongst the converged results of the two meta-analyses. This gene may play an important role in endometriosis-related pain. It is expressed by peripheral sensory neurons and has been implicated in pathological pain (Andratsch et al., 2009, Langeslag et al., 2011). *IL6ST* leads to the sensitisation of peripheral sensory neurons by activating MAPK pathways as well as through the activation of thermal nociceptive receptor transient receptor potential vallinoid (TRPV1; Langeslag et al., 2011, Andratsch et al., 2009, Dominguez et al., 2008). A variety of pro-inflammatory cytokines, such as IL-6, IL-11, leukemia inhibitory factor (LIF), and oncostatin M (OSM) are known to bind to *IL6ST* for activation as well as for signalling the production of mast cells, macrophages and other immune cells (Andratsch et al., 2009). Of these, IL6 is the most notable as it is extremely elevated in chronic inflammatory conditions such as in the peritoneal fluid and eutopic endometrium of women with endometriosis (Tseng et al., 1996, Akoum et al., 1996, Kyama et al., 2006, Velasco et al., 2010, Slater et al., 2006) and causes peripheral sensitisation due to thermal and mechanical stimuli, contributing to pain (Langeslag et al., 2011, Malsch et al., 2014, Punnonen et al., 1996). Increased expression levels of *IL6ST* may increase the cytokine levels secreted by the immune cells which in turn are excessively produced by the eutopic endometrium of women with endometriosis (Schulke et al., 2009, Anaf et al., 2006) and ultimately to sensitisation of peripheral neurons (Howard, 2009, Scholl et al., 2009, Neziri et al., 2014, Cakmak et al., 2009, Bloski and Pierson, 2008).

In both the eutopic endometrium and endometriotic lesions, interleukin-15 (*IL-15*) was significantly upregulated. *IL-15* is a pro-inflammatory cytokine which is important for protective immune responses (Perera et al., 2012, Perera, 2000, Liew and McInnes, 2002). Its levels positively correlate with the severity of pain in chronic pain conditions (Scanzello et al., 2009, Sun et al., 2013). High concentration of IL-15 favours the production of other pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF-α as well as the recruitment of immune cells, thereby amplifying the inflammatory reaction (Alleva et al., 1997, Cassatella and McDonald, 2000, Ren and Dubner, 2010, Sun et al., 2013). In women with endometriosis, IL-15 levels are elevated in endometriotic lesions and peritoneal fluid compared to women without the disease and have been implicated in mediating an early immune response (Arici et al., 2003, Chegini et al., 2003). Upregulation of IL-15 in both the eutopic endometrium and endometriotic lesions may contribute to peripheral sensitisation by increasing local cytokine production and immune cell recruitment (Gomez-Nicola et al., 2008, Chegini et al., 2003).

Genes involved in inflammation were also upregulated in the secretory compared to the proliferative phase in the eutopic endometrium in endometriosis, for example heparanase (*HPSE*). It encodes for a degradation enzyme leading to extracellular matrix remodelling and release of pro-inflammatory mediators such as VEGF and cytokines (Lerner et al., 2011). *HPSE* is upregulated in inflammation and controls many inflammatory and immune responses (Meirovitz et al., 2013, Goldberg et al., 2013). *HPSE* stimulates macrophage activation which in turn induces heparanase production (Lerner et al., 2011, Vlodavsky et al., 2012, Edovitsky et al., 2006). The modulation of macrophage activation and pro-inflammatory cytokine and growth factor production leads to inflammation which may lead to the sensitisation of the peripheral neurons (Vlodavsky et al., 2012, Kidd and Urban, 2001, Meirovitz et al., 2013, Goldberg et al., 2013). Upregulation of *HPSE* expression may promote macrophage recruitment and pro-inflammatory

cytokine production observed in women with endometriosis (Hassa et al., 2009, Scholl et al., 2009, Berbic et al., 2009), thus contributing to peripheral sensitisation and pain generation (Liew and McInnes, 2002, Sun et al., 2013). Significant upregulation of genes involved in inflammation in secretory phase eutopic endometrium from women with endometriosis indicates increased peripheral sensitisation within the uterus in the lead up to menstrual pain (Hellstrom and Anderberg, 2003, de Tommaso, 2011, Tousignant-Laflamme and Marchand, 2009).

5.4 Signal transduction and conduction in endometriosis

Genes involved in signal transduction and conduction were significantly upregulated in both the eutopic endometrium and lesions from women with endometriosis. Studies included in this meta-analysis (Khan et al., 2012, Eyster et al., 2007, Sohler et al., 2013, Hurst et al., 2014) as well as those from the broader literature have reported increased expression of genes involved in signal transduction and conduction in both eutopic endometrium and lesions in women with endometriosis (Liu et al., 2012, Greaves et al., 2014, Abu-Asab et al., 2011, Makker et al., 2012, Poli-Neto et al., 2009, Pelch et al., 2010, Wren et al., 2007). Enhanced expression of these genes increases the excitability of sensory neurons and signal conduction, leading to increased pain signal transfer (Ossipov, 2012, Basbaum et al., 2009, Foulkes and Wood, 2008).

As an example from the current study, in both eutopic endometrium of women with endometriosis and endometriotic lesions, genes encoding for members of the mitogen activated protein kinases (MAPK; involved in signal transduction) family such as *mitogen-activated protein kinase 5* (*MAP3K5*), *mitogen-activated protein kinase 6* (*MAPK6*) and *mitogen-activated protein kinase 8* (*MAP3K8*) were significantly upregulated. MAPK are a family of intracellular signalling molecules expressed by peripheral nociceptive neurons (Ji et al., 2009, Ji and Woolf, 2001). They are activated following intense noxious stimulation (Ji et al., 2009, Adwanikar et al., 2004,

Voscopoulos and Lema, 2010, Imbe et al., 2011, Impey et al., 1999, Gao and Ji, 2008, Kumar et al., 2003, Ji and Woolf, 2001). Their activation leads to impulse generation contributing to pain (Ji et al., 2009). In endometriosis, increased MAPK expression may contribute to increased signal transduction by getting activated following noxious stimuli and generating action potential leading to initiation of painful nerve impulses (Tarek et al., 2001, Bukulmez et al., 2008, Yoshino et al., 2004).

In both the eutopic endometrium of women with endometriosis and endometriotic lesions genes involved in signal transduction were upregulated in the secretory phase of the menstrual cycle when compared to the proliferative phase. In the endometriotic lesions, MAPK family genes were upregulated whereas in the eutopic endometrium, *transient receptor potential M8* (*TRPM8*) was one of the significantly upregulated genes. *TRPM8* is a member of the transient receptor potential channel family that responds to noxious stimuli by initiating transient elevations of intracellular Ca ion concentration (Gees et al., 2010, Nilius and Owsianik, 2011). Its expression levels increase following injury and lower the threshold of peripheral sensory neurons leading to generation of impulses (Proudfoot et al., 2006, McKemy et al., 2002, Levine and Alessandri-Haber, 2007). *TRPM8* is activated by noxious cold or chemical agents as well as modulated by cell stress (Morgan et al., 2014). Increased secretion of pro-inflammatory mediators such as cytokines, during the secretory phase in the eutopic endometrium (Ma et al., 2013a, Wolff et al., 2000) may increase the expression of *TRPM8* leading to enhanced signal transduction thereby contributing to dysmenorrhea.

In both the eutopic endometrium and endometriotic lesions, signal conducting genes encoding for potassium ion gated channels such as *potassium voltage-gated channel, Shal-related subfamily, member 3* (*KCND3*) and *potassium voltage-gated channel, Shaw-related subfamily, member 1*

(*KCNC1*) were upregulated. Electrical impulses generated in excited neurons are conducted along the axons via potential gradients (Schaible, 2007). Potassium ion gated channels generate potential gradient by allowing selective flow of potassium ions across cell membranes (Moldovan et al., 2013, Wulff et al., 2009, Takeda et al., 2011, Hayashi et al., 2014). They conduct currents in order to regulate the sensitisation of the sensory neurons, for example *KCND3* encodes for a channel conducting fast-inactivating currents and *KCNK1* encodes for a channel conducting slow-inactivating current (Tsantoulas and McMahon, 2014, Takeda et al., 2011). In case of intense noxious stimulation, potassium ion channels contribute to enhanced signal conduction by increasing the frequency of impulse firing (Takeda et al., 2011). The intense inflammatory microenvironment in endometriosis (Bloski and Pierson, 2008, Bruner-Tran et al., 2013, Scholl et al., 2009, Neziri et al., 2014) may lead to increased impulse conduction via potassium ion gated channels contributing to pain generation (Sommer and Kress, 2004).

Pathways related to signal transduction and conduction, such as MAPK cascades, activity of ligand gated ion channels and calcium ion homeostasis were among the top upregulated pathways in both eutopic endometrium and endometriotic lesions. The upregulation of genes and pathways involved in signal transduction and conduction in both the eutopic endometrium and endometriotic lesions may be linked to increased sensory innervation and peripheral sensitisation as a result of increased production of pro-inflammatory mediators in the pelvic viscera. Neuronal sensitisation modulates activation of voltage-gated ion channels and thereby excitability, generation and conduction of action potentials (Schaible, 2007, Kitahata, 1993, Binshtok, 2011). Information is then sent from the pelvic viscera to the brain, contributing to perception of pain (Morotti et al., 2014b).

5.5 Pain modulation in endometriosis

In both tissue types included in the meta-analyses, genes involved in pain modulation were upregulated. Certain pain modulating genes are known to be upregulated during chronic pain conditions (Gangadharan and Kuner, 2013, Schaible, 2007, Foulkes and Wood, 2008, Millan, 2002). Pain modulating genes may enhance or inhibit pain generation pathways. They contribute to pain by enhancing the release of neurotransmitters which increase the excitability of sensory neurons and facilitate the transfer of painful signals from the periphery to the CNS (Foulkes and Wood, 2008, Mogil et al., 2000). Included as well as other studies have also shown expression of genes involved in pain modulation is increased in women with endometriosis.

In both the eutopic endometrium of women with endometriosis and endometriotic lesions, *LIF* was one of the significantly upregulated genes involved in pain modulation. *LIF* is a cytokine, the expression levels of which are known to increase following injury (Banner and Patterson, 1994, Banner et al., 1998, Curtis et al., 1994, Oshima et al., 2007, Knight, 2001). It promotes sprouting of cholinergic neurons and modulates pain by enhancing neuropeptide expression (Wang and Lehky, 2012, Banner et al., 1998, Rao et al., 1993, Gadient and Patterson, 1999, Geisterfer and Gauldie, 1996). In endometriosis, increased expression of *LIF* (Tawfeek et al., 2012, Dimitriadis et al., 2006) may contribute to sprouting of sensory neurons that are more sensitive to stimuli. Increased innervation of eutopic endometrium and endometriotic lesions is implicated in pain generation (Tokushige et al., 2006a, Wang et al., 2009, Kobayashi et al., 2013). Moreover, increased *LIF* expression may lead to increased expression of cytokines and neuropeptides, also observed in women with endometriosis (Bokor et al., 2009, Scholl et al., 2009, Tokushige et al., 2006b), thereby contributing to enhancement of peripheral sensitisation.

In endometriotic lesions, the upregulated pain modulating genes included *gamma-aminobutyric acid A receptor, alpha 2* (*GABRA2*). This gene encodes for the member of the GABA family which are major inhibitors of neuronal activity (Rea et al., 2007, Jasmin et al., 2003, Lau and Vaughan, 2014). In chronic pain conditions, GABA receptors ($GABA_A$ and $GABA_B$) actually facilitate pain transmission by increasing the threshold of neurons that inhibit neurotransmission and inactivating them (Enna and McCarson, 2006). Increased expression of GABA encoding genes in endometriotic lesions may enhance pain generation by inactivating the inhibitory neurons.

In the secretory phase, genes involved in pain modulation were upregulated in both endometriotic lesions as well as the eutopic endometrium of women with endometriosis. In the endometriotic lesions, gene encoding for gamma-aminobutyric acid type B (GABBAB) was upregulated which facilitates pain by inactivating inhibitory neurons. In the eutopic endometrium serotonin receptor *5-hydroxytryptamine (serotonin) receptor 1D* (*HTR1D*) was one of the upregulated pain modulating genes. In the periphery, serotonin receptors are present on sensory nerve endings and following noxious stimulation, enhance or inhibit the activation of gated ion channels (Ossipov et al., 2010, Bardin, 2011, Lindstedt et al., 2011, Treister et al., 2011, Sommer, 2004). Serotonin receptors facilitate pain by sensitising peripheral sensory neurons directly (Tegeder and Lötsch, 2009, Wei et al., 2010, Suzuki and Dickenson, 2005, Hooten et al., 2013, Oliveira et al., 2007). *HTR1D* encodes for a serotonin receptor which contributes to inflammatory pain (Ahn and Basbaum, 2006, Manteniotis et al., 2013, Tepper et al., 2002). In endometriosis, increased expression of pain modulating genes in the secretory phase may contribute to dysmenorrhea by modulating neuronal conductance as well as directly sensitising the peripheral sensory neurons.

Pain modulation in endometriosis is complex, as are the other interrelated aspects of the pain matrix in the disease. Indeed, generally speaking, pain generation is a complex process, involving interactions between the peripheral and central nervous systems (Ossipov et al., 2010). In endometriosis, alteration in both the peripheral and central nervous systems may contribute to pain symptoms (Stratton and Berkley, 2011, Triolo et al., 2013). Neuronal development and sensory innervation are locally increased in the eutopic endometrium and endometriotic lesions. The sensory nerve fibres are sensitised by the inflammatory microenvironment which leads to signal transduction and generation of action potential (Morotti et al., 2014b, Berkley et al., 2005, Triolo et al., 2013). The sensitised peripheral sensory neurons conduct action potentials via the DRG of the spinal cord to the CNS (Schaible, 2007, Porpora et al., 1999, Stratton and Berkley, 2011). Once the CNS processes the sent information, descending impulses are sent to the spinal cord to dampen the excitatory impulses (Bolay and Moskowitz, 2002, Kitahata, 1993, Ossipov et al., 2010, Neziri et al., 2014, Triolo et al., 2013). However, in case of chronic pain conditions such as endometriosis, persistent sensitisation may lead to descending impulses to become excitatory and contribute to development of chronic pain (Bolay and Moskowitz, 2002, Kwon et al., 2013, Voscopoulos and Lema, 2010, Morotti et al., 2014b, Triolo et al., 2013, Neziri et al., 2014, Stratton and Berkley, 2011).

5.6 Implications for pain management in endometriosis

There is almost certainly a relationship between variable responses to pain management and complexity of pain mechanisms in endometriosis (Neziri et al., 2014, Evans et al., 2007, Howard, 2009, Kobayashi et al., 2013, Triolo et al., 2013, Bloski and Pierson, 2008). The current pain management techniques are ineffective for a proportion of women with endometriosis and pain symptoms generally have high recurrence rates, in addition to treatments being associated with some unpleasant side effects (Huang, 2008, Bruner-Tran et al., 2013, Kennedy et al., 2005, Nasir

and Bope, 2004, Sutton et al., 1994, Medicine, 2014, Bloski and Pierson, 2008, Culley et al., 2013). Hence, identifying and targeting candidate genes involved in pain generation in endometriosis may aid in better management of pain associated with the disease (Dun et al., 2010).

Gene therapy has been used for managing chronic pain and works by targeting candidate genes known to be involved in pain generation (Goins et al., 2012, Jain, 2008, Wilson and Yeomans, 2000). Delivery of potent bioactive molecules either interrupts nociceptive signalling, or interferes with the plasticity in the nervous system underlying the development or persistence of chronic pain (Jain, 2008, Mata et al., 2008). In gene therapy, genes are delivered through vectors to peripheral tissues from where they are transported through natural mechanisms to the targeted neurons (Goins et al., 2012). A vector is a virus which infects the targeted cells and transports its genome to the nucleus where the candidate gene can be expressed for various desired durations (Wilson and Yeomans, 2000, Tavares and Martins, 2013, Jain, 2008, Goins et al., 2012).

Several gene targets are being tested on animal models for their application to chronic pain management. For example, targeting of primary sensory neurons by modulating signal transducing channels such as TRPV1 alleviates pain symptoms by toxic flood of Ca^{2+} ions. This damages the nociceptive TPRV1 containing axons (Brederson et al., 2013), which has been successfully applied to animal models and is now under Phase I clinical trial on patients with advanced cancer pain (Smith, 2008). Delivering immune modulatory genes have demonstrated a reduction in not only pain, but also in the expression of pro-inflammatory mediators such as TNF-α, IL-6 and IL-1 (Zhou et al., 2008, Ledeboer et al., 2007, Hao et al., 2007). Currently, genes for neuronal growth factors such as NGF and BDNF, modulators of inflammatory cytokines such as IL-2, IL-4 and IL-10, signal transduction such as TRPV1, repolarisation of sensory neurons and inhibitory

neuromodulators such as GABA, opioids are being employed for managing pain (Yao et al., 2002, Yao et al., 2003, Hao et al., 2007, Hao et al., 2006, Milligan et al., 2005).

Gene therapy for managing endometriosis and endometriotic lesions such as delivering negative oestrogen receptors to endometriotic cells for abrogating oestrogen action has been successful in inhibiting angiogenesis, suppressing inflammatory factors and inducing apoptosis (Othman et al., 2007). Similarly in rodent models, the size of endometriotic lesions was significantly reduced along with levels of VEGF in the serum with endostatin gene therapy (Zhang et al., 2012, Ma and He, 2014). Delivery of genes which promote an immunogenic response to endometriotic lesions are being explored for treating endometriosis (Shubina et al., 2013). Application of gene therapy to block NGF by utilising anti-NGF antibodies which will in turn block NGF-dependent neuronal survival is being analysed for treating endometriosis-associated pain (Shubina et al., 2013, Howe et al., 2010). In the future, candidate pain related genes that are dysregulated in endometriosis, may be novel gene therapy targets for treatment of pain symptoms.

Conclusions and Future Directions

Conclusions

Pain related genes were significantly upregulated in the eutopic endometrium of women with endometriosis compared to women without endometriosis, and in endometriotic lesions compared to eutopic endometrium from women with endometriosis. In both eutopic endometrium and endometriotic lesions from women with endometriosis, pain related genes were also significantly upregulated in the secretory compared to the proliferative phase of the menstrual cycle. The expression levels of different pain related genes positively correlated with each other in both the eutopic endometrium and lesions of women with endometriosis.

In conclusion, upregulation of a range of pain related genes may be associated with pain symptoms in endometriosis, particularly in the time leading up to menstruation (secretory phase of the menstrual cycle), specifically, genes involved in neuronal development, sensitisation due to inflammation, signal transduction, conduction and modulation. This, combined with previously described nociceptive, inflammatory and neuropathic pain generation mechanisms in endometriosis indicates the complexity of pain processes in the disease. Improved understanding of the molecular mechanisms underlying generation of pain in endometriosis may in future aid the development of therapeutic approaches.

Future directions

Molecular pain mechanisms associated with endometriosis are very complex and require further in-depth understanding. This study has provided some information about local gene dysregulations which may contribute to pain symptoms in women with endometriosis. However, a variety of possible further studies are of interest which may improve our current understanding of pain

mechanisms in endometriosis. Listed below are some of the investigations which may be considered a priority:

- A range of datasets are required to be explored to identify candidate dysregulated genes involved in pain generation. For example, analysing differential gene expression in blood samples of women with and without endometriosis may provide insights about molecular mechanisms that make women susceptible to endometriosis.
- Identifying differential gene expression between different lesion types (peritoneal, ovarian and deep) may contribute to improved understanding of pain related mechanisms.
- Pain in endometriosis is experienced most during pre-menstrual and menstrual phases, hence profiling endometrial gene expression from women with endometriosis these times in the cycle may shed some light on pain mechanisms.
- Improving understanding of pain in endometriosis may be accomplished by conducting studies focussing on how endometriosis affects the PNS and CNS, and examining these studies in context of mechanisms underlying other chronic pain conditions.
- Understanding mechanisms of nerve fibre stimulation in fibres innervating the eutopic endometrium and endometriotic lesions may further the understanding of mechanisms underlying pain in endometriosis.

Basic studies and clinical trials are required to evaluate treatment options for endometriosis pain. For example, application of immunomodulators and anti-inflammatory mediators in the treatment of endometriosis requires further investigation. Additionally, genes involved in pain generation in other chronic painful conditions as well as those that have been identified in endometriosis should be further explored to for their application in gene therapy for endometriosis-associated pain.

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Appendix 1: Characteristics of included studies.

Hull et al. 2008	
Methods	Cross-sectional study Individual patient gene expression data available
Participants	Women with endometriosis (age 20-46 years) that have regular menstrual cycles and are not using hormonal treatment (N = 9). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies collected using Pipelle suction curettes; RNA extracted from endometrial tissue; Hybridisation with U133A Affymetrix cDNA arrays containing ~23,000 probe sets in total; compared gene expression of eutopic and ectopic endometrial samples.
Outcomes	• Genes found to be significantly up-regulated and down-regulated in ectopic lesions relative to eutopic endometrium were 292 and 390, respectively. • Biological processes significantly over- or under- represented were inflammatory response, response to wounding, cell adhesion, calcium-independent cell adhesion, primary metabolic process, and DNA metabolic process.

Risk of Bias		
Item	***Judgement***	***Description***
Small sample size	Yes	N = 9
Blind assessment of samples by the pathologist	Unclear	Information not provide in the study.
Use of established criteria for assessing menstrual cycle phase	Yes	Noyes criteria were used to confirm the cycle phase from all the biopsies of endometrial tissue.
Quality check of RNA	Yes	RNA integrity was assessed using an Agilent-2100 Bioanalyzer.
Validation of microarray results	Unclear	Method unclear.
Other potential sources	Yes	Clinical characteristics of participants not provided.

Hever et al. 2007	
Methods	Cross-sectional study Individual patient gene expression data available.
Participants	Women with endometriosis (age: missing) that have normal menstrual cycles and are not using hormonal treatment (N = 10). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies; RNA extracted from the endometrial tissue; hybridisation with Affymetrix Human Genome U133 Plus 2.0 gene array; compared gene expression of eutopic and ectopic endometrial samples.
Outcomes	Fifty-three up-regulated genes associated with immune responses, cell-to-cell signaling/interaction, and hematological system development/function; inflammatory diseases, immune responses, and cellular movement were found to be up-regulated.

Risk of Bias		
Item	***Judgement***	***Description***
Small sample size	Yes	*N* = 10
Blind assessment of samples by the pathologist	No	Stage of endometriosis not assessed.
Use of established criteria for assessing menstrual cycle phase	Unclear	Information not provided.
Quality check of RNA	Unclear	Information not provided.
Validation of microarray results	Yes	Quantitative PCR was used to validate the microarray results.
Other potential sources	Yes	Clinical characteristic of patients regarding age not provided.

Burney et al. 2007	
Methods	Case-control study Individual patient gene expression data available.
Participants	Women with endometriosis (age 22-44 years) that have normal menstrual cycles and are not using hormonal treatment (*N* = 21). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies collected from Pipelle catheters or curette from the uterine fundus under sterile conditions; RNA extraction; Hybridisation with Affymetrix Human Genome U133 Plus 2.0 gene array; Compared gene expression of eutopic and normal endometrial samples.
Outcomes	Significantly differentially expressed genes in different phases of the menstrual cycle in endometrium of women with endometriosis compared to women without endometriosis.

Risk of Bias		
Item	***Judgement***	***Description***
Small sample size	No	*N* = 21 (women with endometriosis) *N* = 16 (women without endometriosis)
Blind assessment of samples by the pathologist	Yes	Blind assessment was done by up to four independent histopathologists.
Use of established criteria for assessing menstrual cycle phase	Yes	Noyes criteria were used to confirm the cycle phase from all the biopsies of endometrial tissue.
Quality check of RNA	Yes	RNA quality was confirmed by assessing the A260/A280 ratio and agarose gel electrophoresis.
Validation of microarray results	Yes	Quantitative PCR was used to validate the microarray results.
Other potential sources	No	None.

Khan et al. 2012	
Methods	Cross-sectional study Individual patient gene expression data available.
Participants	Women with endometriosis (age 24-45 years) that have normal

	menstrual cycles and are not using hormonal treatment (N = 26). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies collected from Pipelle suction curette from the uterine fundus; ; RNA extracted from the endometrial tissue; Hybridisation with Agilent Whole Human Genome 60-mer 4X44K; Compared gene expression of eutopic and ectopic endometrial samples.
Outcomes	• Several genes associated with immunological, neuracrine and endocrine functions were found to be differentially expressed. • Twenty-eight genes as potential markers for ovarian endometriosis in fertile women were discovered.

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	No	N = 26
Blind assessment of samples by the pathologist	No	Severity stages were defined at the time of surgery.
Use of established criteria for assessing menstrual cycle phase	Yes	Noyes criteria was used to confirm the cycle phase from all the biopsies of endometrial tissue.
Quality check of RNA	Yes	RNA quality was confirmed by Agilent 2100 Bioanalyzer, RNA 6000 Nano LabChip kit and Agilent 2100 Expert Software.
Validation of microarray results	Yes	Quantitative PCR was used to validate the microarray results.
Other potential sources	No	None.

Crispi et al. 2013

Methods	Case-control study Individual patient gene expression data available.
Participants	Women with endometriosis (age 22-46 years) that have normal menstrual cycles and are not using hormonal treatment (N = 27). Endometriosis was confirmed by laparoscopy. Women without endometriosis that have normal menstrual cycle (N = 6).
Interventions	Endometrial; RNA extraction; Hybridisation with Affymetrix HGU133A 2.0 arrays Arrays; Compared gene expression of eutopic, ectopic and healthy endometrial samples.
Outcomes	Dysregulated genes involved in gonad developmental or wound healing process.

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	N = 9 (women with endometriosis); N = 6 (women without endometriosis)
Blind assessment of samples by the pathologist	No	Diagnosis was made during laparoscopy.
Use of established criteria for assessing menstrual cycle phase	Unclear	Method not mentioned in the paper.

Quality check of RNA	Yes	RNA quality was assessed by Experion RNA StdSens Kit (Bio-Rad Laboratories, Hercules, CA).
Validation of microarray results	Yes	Quantitative PCR was used to validate the microarray results .
Other potential sources	Yes	Limited clinical characteristic information of control participants.

Sohler et al. 2013	
Methods	Cross-sectional study Individual patient gene expression data available.
Participants	Women with endometriosis (age 21-52 years) that have normal menstrual cycles and are not using hormonal treatment (*N* = 27). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsy; RNA extraction; Hybridisation with Affymetrix HGU133Plus2.0 arrays which contain 54 675 probe sets; Compared gene expression of eutopic and ectopic endometrial samples.
Outcomes	• Gene dysregulation in ectopic endometrium compared to eutopic endometrium in women with endometriosis. • Gene expression differed in different menstrual cycle phases in eutopic endometrium but not in ectopic endometrium.

Risk of Bias

Item	***Judgement***	***Description***
Small sample size	No	*N* = 27
Blind assessment of samples by the pathologist	Unclear	Blind assessment by the pathologist was not mentioned.
Use of established criteria for assessing menstrual cycle phase	Yes	Out of the six criteria used to determine the menstrual cycle phase, one was based on published histological criteria to identify menstrual cycle phases.
Quality check of RNA	Yes	RNA quality was assessed by Agilent Bioanalyzer 2100 and the concentration was assessed on a Nanodrop spectrophotometer.
Validation of microarray results	Yes	Quantitative PCR was used to validate the microarray results.
Other potential sources	No	None.

Zevallous et al. 2012	
Methods	Case-control study Individual patient gene expression data available.
Participants	Women with endometriosis (age 25-43 years) that have normal menstrual cycles and are not using hormonal treatment (*N* = 28). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsy; RNA extraction; Hybridisation with Affymetrix HU Gene 1.0 ST arrays; Compared gene expression of eutopic and normal endometrial samples.
Outcomes	Gene dysregulation in eutopic endometrium compared to normal endometrium in women with and without endometriosis.

Risk of Bias

Item	***Judgement***	***Description***

Small sample size	Yes	*N* = 12 (women with endometriosis); *N* = 18 (women without endometriosis)
Blind assessment of samples by the pathologist	Yes	Stage of endometriosis was blind assessed by the pathologist.
Use of established criteria for assessing menstrual cycle phase	Yes	Histological dating was done by haematoxylin staining and eosin staining by an experienced gynaecological pathologist.
Quality check of RNA	Yes	RNA quality was assessed by Agilent Bioanalyzer 2100 and the concentration was assessed on a Nanodrop spectrophotometer.
Validation of microarray results	Yes	Quantitative PCR was used to validate the microarray results.
Other potential sources	No	None.

Talibi et al. 2006	
Methods	Cross-sectional study Individual patient gene expression data available.
Participants	Women without endometriosis (age 23-50 years) that have normal menstrual cycles and are not using hormonal treatment (*N* = 45). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies collected from Pipelle catheter or curetting the endometrium from hysterectomy specimens; RNA extraction; Hybridisation with Affymetrix HG U133 Plus 2.0 Arrays; profiled gene expression of endometrial samples.
Outcomes	Gene expression varies across different phases of the menstrual cycle.

Risk of Bias		
Item	***Judgement***	***Description***
Small sample size	No	*N* = 45
Blind assessment of samples by the pathologist	No	Not required as the women did not have endometriosis.
Use of established criteria for assessing menstrual cycle phase	Yes	Noyes criteria was used to confirm the cycle phase from all the biopsies of endometrial tissue.
Quality check of RNA	Yes	RNA quality was analysed by assessing the 260/280 absorbance ratio and gel electrophoresis.
Validation of microarray results	Yes	Quantitative PCR was used to validate the microarray results.
Other potential sources	No	None.

Sherwin et al. 2008	
Methods	Case-control study Published gene list available
Participants	Women with and without endometriosis that have regular menstrual cycles and are not using hormonal treatment (*N* = 16). Endometriosis presence or absence was confirmed by laparoscopy.
Interventions	Endometrial biopsies collected using Pipelle suction curettes; RNA

	extracted from endometrial tissue; Hybridisation with custom made cDNA arrays containing ~22,000 probe sets in total; compared gene expression of eutopic endometrial samples with and without endometriosis.
Outcomes	• Genes found to be significantly up-regulated and down-regulated in eutopic endometrium from women with and without endometriosis were 8 and 1, respectively.

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	*N* = 16
Blind histological assessment of samples	Unclear	Information not provide in the study.
Use of established criteria for assessing menstrual cycle phase	Yes	Noyes criteria were used to confirm the cycle phase from all the biopsies of endometrial tissue.
Quality check of RNA	Yes	RNA integrity was assessed using an Agilent-2100 Bioanalyzer.
Validation of microarray results	Yes	By RT-PCR
Other potential sources	Yes	Clinical characteristics of participants not provided.

Kao et al. 2003

Methods	Case-control study Published gene list available
Participants	Women with and without endometriosis (age 28-39 years) that have regular menstrual cycles and are not using hormonal treatment (*N* = 20). Endometriosis presence or absence was confirmed by laparoscopy.
Interventions	Endometrial biopsies collected using Pipelle suction curettes; RNA extracted from endometrial tissue; Hybridisation with Affymetrix Genechip Hu95A oligonucleotide microarray containing 12686 probe sets in total; compared gene expression of eutopic endometrial samples with and without endometriosis.
Outcomes	• Genes found to be significantly up-regulated and down-regulated in eutopic endometrium from women with and without endometriosis were 91 and 115, respectively.

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	*N* = 15
Blind histological assessment of samples	Unclear	Information not provided in the study.
Use of established criteria for assessing menstrual cycle phase	Unclear	Information not provided in the study
Quality check of RNA	Unclear	Information not provided in the study
Validation of microarray results	Yes	By RT-PCR and Northern blot analysis

Other potential sources	Yes	Clinical characteristics of participants not provided.

Hurst et al. 2013

Methods	Case-control study Published gene list available
Participants	Women with and without endometriosis (age 18-40 years) that have regular menstrual cycles and are not using hormonal treatment (*N* = 15). Endometriosis present or absent was confirmed by laparoscopy.
Interventions	Endometrial biopsies collected using Pipelle suction curettes; RNA extracted from endometrial tissue; Hybridisation with Affymetrix 8500 oligonucleotide microarray containing 8500 probe sets; compared gene expression of eutopic endometrial samples with and without endometriosis.
Outcomes	• Genes found to be significantly up-regulated and down-regulated in eutopic endometrium from women with and without endometriosis were 26 and 32, respectively.

Risk of Bias

Item	***Judgement***	***Description***
Small sample size	Yes	*N* = 15
Blind histological assessment of samples	No	The surgeon judged the stage of endometriosis at the time of the surgery
Use of established criteria for assessing menstrual cycle phase	Unclear	Information not provided in the study
Quality check of RNA	Unclear	Information not provided in the study
Validation of microarray results	Yes	By RT-PCR
Other potential sources	Yes	Clinical characteristics of participants not provided.

Zafrakas et al. 2008

Methods	Cross-sectional study Published gene list available
Participants	Women with endometriosis that have regular menstrual cycles and are not using hormonal treatment (*N* = 4). Endometriosis was

	confirmed by laparoscopy.
Interventions	Endometrial biopsies as well as endometriotic lesions collected using Pipelle suction curettes; RNA extracted from endometrial tissue; Hybridisation with Affymetrix HG-U133 gene chip containing 40000 probe sets; compared gene expression of eutopic endometrial and endometriotic lesion samples with endometriosis.
Outcomes	Genes found to be significantly up-regulated and down-regulated in the endometriotic lesions compared to eutopic endometrium from women with endometriosis were 26 and 32, respectively.

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	*N* = 4
Blind histological assessment of samples	Unclear	Information not provided in the study
Use of established criteria for assessing menstrual cycle phase	No	Information not provided in the study
Quality check of RNA	Unclear	Information not provided in the study
Validation of microarray results	Yes	By RT-PCR
Other potential sources	Yes	Clinical characteristics of participants not provided.

Gaetje et al. 2007

Methods	Cross-sectional study Published gene list available
Participants	Women with and without endometriosis that have regular menstrual cycles and are not using hormonal treatment (*N* = 3). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies as well as endometriotic lesions collected using Pipelle suction curettes; RNA extracted from endometrial tissue; Hybridisation with Affymetrix HG U133A microarray containing 22283 probe sets; compared gene expression of eutopic endometrial and endometriotic lesion samples with endometriosis.
Outcome	Genes found to be significantly up-regulated and down-regulated in endometriotic lesions as compared to eutopic endometrium from women with endometriosis were 15 and 2, respectively.

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	*N* = 3
Blind histological assessment of samples	Unclear	Information not provided in the study
Use of established criteria for assessing menstrual cycle phase	No	The menstrual cycle phase was not assessed in the study
Quality check of RNA	Unclear	Information not provided in the study
Validation of microarray results	Yes	By RT-PCR and immunofluorescence
Other potential sources	Yes	Clinical characteristics of participants not provided.

Eyster et al. 2007	
Methods	Cross-sectional study Published gene list available
Participants	Women with endometriosis that have regular menstrual cycles and are not using hormonal treatment (*N* = 11). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies as well as endometriotic lesions collected using Hysteroscopy and dilatation and curettage; RNA extracted from endometrial tissue; Hybridisation with CodeLink Whole Human Genome Bioarrays containing 54359 probe sets; compared gene expression of eutopic endometrial and endometriotic lesion samples with endometriosis.
Outcomes	• Genes found to be significantly up-regulated or down-regulated in endometriotic lesions as compared to eutopic endometrium from women with endometriosis were 717 in total. • Genes found to be significantly dysregulated in ovarian compared to peritoneal lesions • Genes found to be significantly dysregulated in mild endometriosis compared to all other patients in the study • Genes found to be significantly dysregulated in peritoneal endometriosis compared to all other patients in the study • Genes found to be significantly dysregulated in proliferative phase of the menstrual cycle compared to all other patients in the study.

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	*N* = 11
Blind histological assessment of samples	Unclear	Information not provided in the study
Use of established criteria for assessing menstrual cycle phase	Unclear	Information not provided in the study
Quality check of RNA	Yes	RNA quality was assessed by RNA 6000 Nano LabChip kit in an Agilent Bioanalyzer
Validation of microarray results	Yes	By RT-PCR
Other potential sources	Yes	Clinical characteristics of participants not provided.

Borghese et al. 2008	
Methods	Cross-sectional study Published gene list available
Participants	Women with endometriosis that have regular menstrual cycles and are not using hormonal treatment (*N* = 12). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies as well as endometriotic lesions collected; RNA extracted from endometrial tissue; Hybridisation with Institut

Outcomes	Cochin HG18 60mer expression array containing 47633 probe sets; compared gene expression of eutopic endometrial and endometriotic lesion samples with endometriosis. • Genes found to be significantly up-regulated or down-regulated in endometriotic lesions as compared to eutopic endometrium from women with endometriosis were 2823 and 2782, respectively. • 27 groups were upregulated and 28 groups were downregulated in the endometriotic lesions compared to the eutopic endometrium from women with endometriosis

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	*N* = 11
Blind histological assessment of samples	Unclear	Information not provided in the study
Use of established criteria for assessing menstrual cycle phase	No	Menstrual cycle phase was not assessed in the study
Quality check of RNA	Yes	RNA quality was assessed by agarose gel electrophoresis and spectrophotometry
Validation of microarray results	Yes	By RT-PCR
Other potential sources	Yes	Clinical characteristics of participants not provided.

Mettler et al. 2006

Methods	Cross-sectional study Published gene list available
Participants	Women with endometriosis (age 22-40) that have regular menstrual cycles and are not using hormonal treatment (*N* = 5). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies as well as endometriotic lesions collected; RNA extracted from endometrial tissue; Hybridisation with Atlas Human 1,2 array containing 1176 probe sets; compared gene expression of eutopic endometrial and endometriotic lesion samples with endometriosis.
Outcome	• Genes found to be significantly up-regulated or down-regulated in endometriotic lesions as compared to eutopic endometrium from women with endometriosis were 9and 4, respectively.

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	*N* = 11
Blind histological assessment of samples	Unclear	Information not provided in the study
Use of established criteria for assessing menstrual cycle phase	No	Menstrual cycle phase was not assessed in the study
Quality check of RNA	Yes	RNA quality was assessed by agarose gel

		electrophoresis
Validation of microarray results	No	Information not provided in the study
Other potential sources	Yes	Clinical characteristics of participants not provided.

Sun et al. 2014	
Methods	Cross-sectional study Published gene list available
Participants	Women with endometriosis (age 24-45) that have regular menstrual cycles and are not using hormonal treatment (*N* = 4). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies as well as endometriotic lesions collected by curettage; RNA extracted from endometrial tissue; Hybridisation with SurePrint G3 Human Gene Expression 8x60K v2 array containing 32776 probe sets; compared gene expression of eutopic endometrial and endometriotic lesion samples with endometriosis.
Outcomes	• Genes found to be significantly up-regulated or down-regulated in endometriotic lesions as compared to eutopic endometrium from women with endometriosis were 527and 421, respectively. • Dysregulated pathways in the endometriotic lesions by Gene Ontology analysis

Risk of Bias

Item	***Judgement***	***Description***
Small sample size	Yes	*N* = 4
Blind histological assessment of samples	Unclear	Information not provided in the study
Use of established criteria for assessing menstrual cycle phase	No	Menstrual cycle phase was not assessed in the study
Quality check of RNA	Yes	RNA yield was assessed by NanoDrop ND-2000 spectrophotometer (Thermo Fisher Scientific) and RNA quality was assessed by Agilent 2100 bioanalyzer and RNA 6000 Nano kit (Agilent Technologies)
Validation of microarray results	Yes	Results verified by RT-PCR
Other potential sources	No	Clinical characteristics of participants provided.

Vouk et al. 2011	
Methods	Cross-sectional study Published gene list available
Participants	Women with endometriosis (age 24-50) that have regular menstrual cycles and are not using hormonal treatment (*N* = 20). Endometriosis was confirmed by laparoscopy.
Interventions	Endometrial biopsies as well as endometriotic lesions collected by hysterectomy or biopsy; RNA extracted from endometrial tissue and endometriotic lesions; Hybridisation with TaqMan low-density array

Outcomes	containing 172 probe sets; compared gene expression of eutopic endometrial and endometriotic lesion samples with endometriosis. • Genes found to be significantly up-regulated or down-regulated in endometriotic lesions as compared to eutopic endometrium from women with endometriosis were 60 and 18, respectively. • Dysregulated pathways in the endometriotic lesions from women with endometriosis

Risk of Bias

Item	*Judgement*	*Description*
Small sample size	Yes	*N* = 20
Blind histological assessment of samples	Unclear	Information not provided in the study
Use of established criteria for assessing menstrual cycle phase	No	Menstrual cycle phase was not assessed in the study
Quality check of RNA	Yes	RNA quality was assessed by Agilent bioanalyzer
Validation of microarray results	Yes	Results verified by RT-PCR
Other potential sources	No	Clinical characteristics of participants provided.

Appendix 2: Characteristics of excluded studies.

Study	Reason for exclusion
Sha et al. (2007)	Endometrial endothelial cells from eutopic endometrium from women with and without endometriosis used
Wu et al. (2006)	Epithelial cells from eutopic endometrium and endometriotic lesions from women with endometriosis were used
Matsuzaki et al. (2005)	Epithelial and stromal cells from eutopic endometrium and deep rectovaginal endometriotic lesions from women with endometriosis
Matsuzaki et al. (2004)	Epithelial and stromal cells from eutopic endometrium and rectovaginal endometriotic lesions from women with endometriosis by laser capture micro-dissection
Arimoto et al. (2003)	Epithelial cells isolated from eutopic endometrium and ovarian lesions from women with endometriosis
Fassbender et al. (2012)	Published gene lists with menstrual cycle phase adjusted data for women with endometriosis and for women without endometriosis
Roth et al. (2007)	Study has not been peer-reviewed as yet. Only individual patient gene expression data was available

Appendix 3: Participant characteristics for studies included in the meta-analysis with individual patient gene expression data available.

Patient ID	Age	Menstrual phase	Diagnosed endometriosis (E/NE)$^{++}$	Hormone treatment (Y/N)
Hull et al. 2008: Unavailable participant characteristics				
Hever et al.2007				
01-M	Missing	Proliferative	E	N
02-M	Missing	Proliferative	E	N
04-M	Missing	Secretory	E	N
05-M	Missing	Secretory	E	N
06-M	Missing	Secretory	E	N
02-G	Missing	Secretory	E	N
03-G	Missing	Secretory	E	N
05-G	Missing	Secretory	E	N
06-G	Missing	Secretory	E	N
08-G	Missing	Secretory	E	N
Khan et al. 2012				
E17	29	Proliferative	E	N
E20	40	Proliferative	E	N
E23	33	Proliferative	E	N
E26	45	Proliferative	E	N
E31	24	Proliferative	E	N
E32	28	Proliferative	E	N
E33	28	Secretory	E	N
E40	25	Proliferative	E	N
E43	40	Proliferative	E	N
E48	31	Proliferative	E	N
E49	37	Secretory	E	N
E52	30	Proliferative	E	N
E56	30	Proliferative	E	N
E57	37	Secretory	E	N
E68	31	Secretory	E	N
E70	34	Secretory	E	N
E73	25	Proliferative	E	N
E75	40	Proliferative	E	N
Talbi et al. 2006				
598	33	Proliferative	NE	N
M182	34	Proliferative	NE	N
M165	31	Proliferative	NE	N
M169	32	Proliferative	NE	N
455*	39	Proliferative	NE	N
562	50	Proliferative	NE	N
629	46	Secretory	NE	N
650	48	Secretory	NE	N
664	44	Secretory	NE	N
610	49	Secretory	NE	N
617	42	Secretory	NE	N

Patient ID	Age	Menstrual phase	Diagnosed endometriosis (E/NE)$^{++}$	Hormone treatment (Y/N)
626	42	Secretory	NE	N
M153	34	Secretory	NE	N
659	46	Secretory	NE	N
G98A	30	Secretory	NE	N
M158	23	Secretory	NE	N
M163	33	Secretory	NE	N
442	43	Secretory	NE	N
449	39	Secretory	NE	N
462	39	Secretory	NE	N
614	43	Secretory	NE	N
576	41	Secretory	NE	N
619	44	Secretory	NE	N
Burney et al. 2007				
26A	31	Proliferative	E	N
587	37	Proliferative	E	N
647	39	Proliferative	E	N
594	38	Proliferative	E	N
651	37	Proliferative	E	N
508	25	Proliferative	E	N
489	39	Secretory	E	N
496	37	Secretory	E	N
599	35	Secretory	E	N
27A	22	Secretory	E	N
517	35	Secretory	E	N
575	26	Secretory	E	N
33A	27	Secretory	E	N
7A/97A	35	Secretory	E	N
73A	26	Secretory	E	N
516	34	Secretory	E	N
540	37	Secretory	E	N
543	38	Secretory	E	N
678	44	Secretory	E	N
72A	31	Secretory	E	N
645	39	Secretory	E	N
Zevallos 2012				
PECN T-047	25	Secretory	E	N
PECN T-061	29	Secretory	E	N
PECN T-126	29	Proliferative	E	N
PECN T-145	43	Proliferative	E	N
PECN T-147	38	Proliferative	E	N
PECN T-148	36	Proliferative	E	N
PECN T-169	34	Secretory	E	N
PECN T-174	39	Secretory	E	N
PECN T-186	38	Secretory	E	N
PECN T-215	37	Secretory	E	N
PECN T-244	31	Secretory	E	N

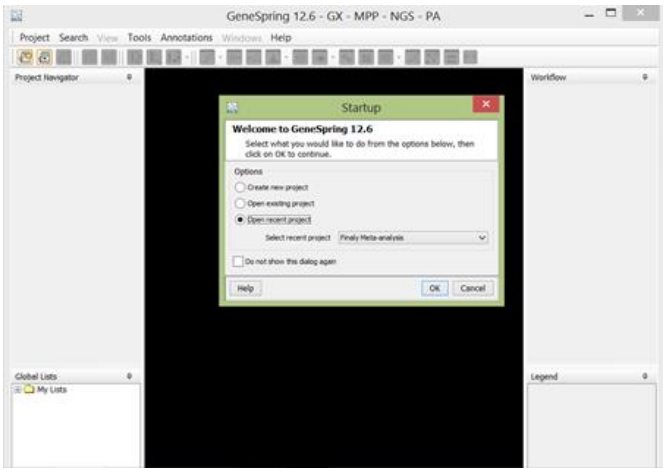
Patient ID	Age	Menstrual phase	Diagnosed endometriosis (E/NE)$^{++}$	Hormone treatment (Y/N)
PECN T-271	34	Secretory	E	N
PECN T-013	34	Secretory	NE	N
PECN T-078	32	Secretory	NE	N
PECN T-089	34	Secretory	NE	N
PECN T-124	32	Proliferative	NE	N
PECN T-136	33	Secretory	NE	N
PECN T-139	28	Proliferative	NE	N
PECN T-156	25	Proliferative	NE	N
PECN T-160	34	Proliferative	NE	N
PECN T-164	35	Secretory	NE	N
PECN T-167	37	Secretory	NE	N
PECN T-184	29	Secretory	NE	N
PECN T-192	42	Proliferative	NE	N
PECN T-223	40	Secretory	NE	N
PECN T-231	32	Proliferative	NE	N
PECN T-224	39	Secretory	NE	N
PECN T-257	43	Secretory	NE	N
Crispi et al. 2013: Unavailable no endometriosis participant characteristics				
1	31	Proliferative	E	N
2	30	Proliferative	E	N
3	32	Proliferative	E	N
4	35	Proliferative	E	N
5	30	Proliferative	E	N
6	30	Proliferative	E	N
7	22	Proliferative	E	N
8	42	Proliferative	E	N
Sohler et al. 2013				
1	40	Proliferative	E	N
2	43	Secretory	E	N
3	33	Proliferative	E	N
4	23	Secretory	E	N
5	29	Proliferative	E	N
6	25	Secretory	E	N
7	36	Secretory	E	N
8	52	Secretory	E	N
9	30	Proliferative	E	N
10	30	Proliferative	E	N
11	37	Secretory	E	N
12	35	Proliferative	E	N
13	35	Secretory	E	N
14	38	Secretory	E	N
15	29	Proliferative	E	N
16	33	Secretory	E	N
17	21	Proliferative	E	N
18	47	Proliferative	E	N
22	38	Proliferative	E	N

Patient ID	Age	Menstrual phase	Diagnosed endometriosis (E/NE)$^{++}$	Hormone treatment (Y/N)
25	36	Secretory	E	N
27	33	Not known	E	N
31	34	Not known	E	N
32	22	Secretory	E	N
35	36	Not known	E	N
36	29	Proliferative	E	N
37	26	Mid-cycle	E	N
38	46	Secretory	E	N

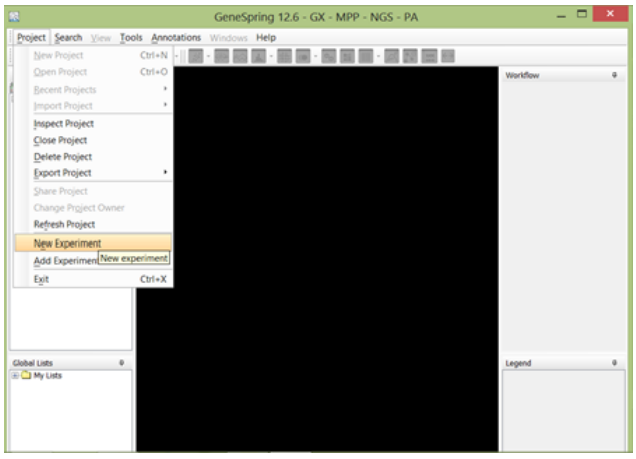
E: Endometriosis; **NE:** No endometriosis

Appendix 4: Steps for normalisation of individual patient gene expression data by GeneSpring.

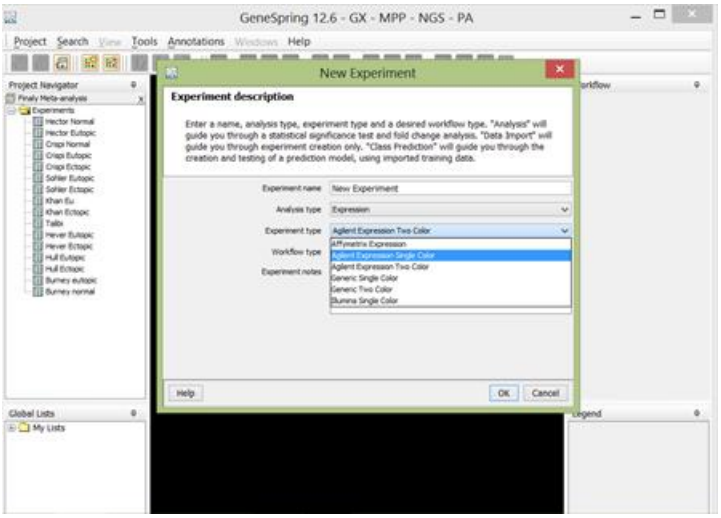
1. A new project was created in the start-up dialogue box.



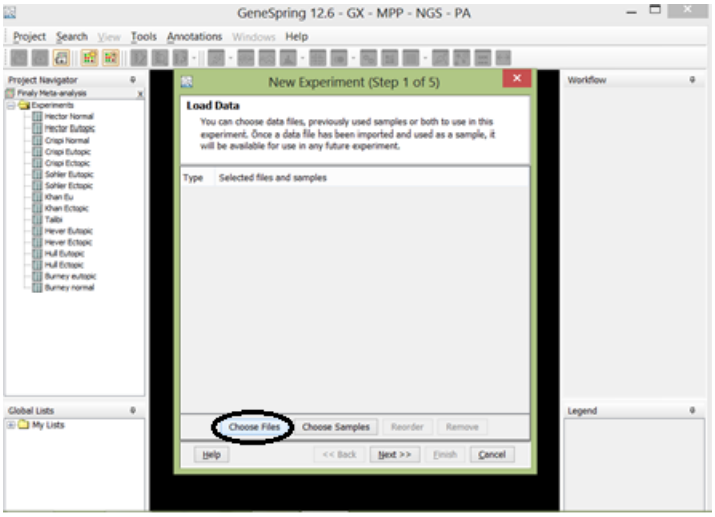
2. From under the “Project” option, “New Experiment” option was chosen to create a new experiment.



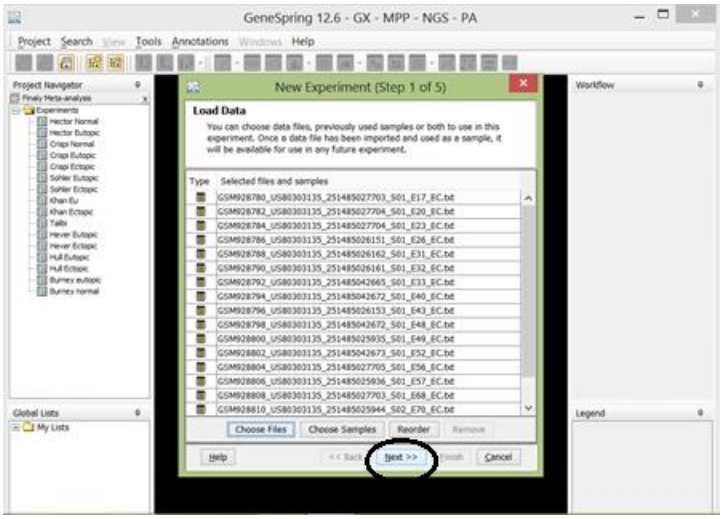
3. The experiment was named accordingly and analysis chosen depending on the type of platform used. *Data Import* work flow was chosen.



4. Once the experiment was set up, the data was loaded on to the programme.

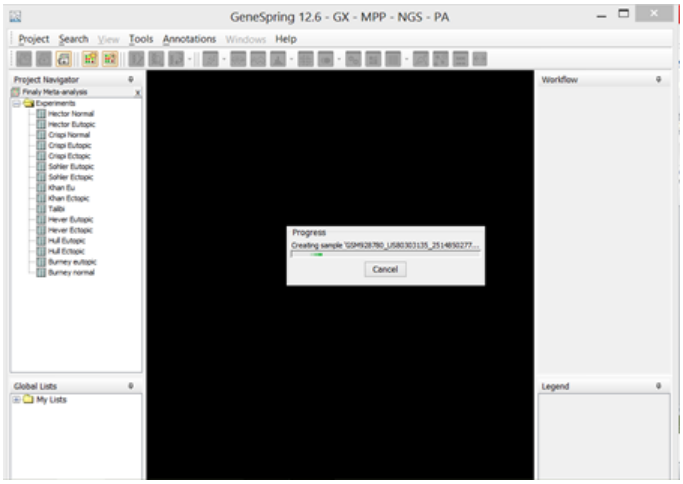


5. Proceed on to the next step once data has been loaded.

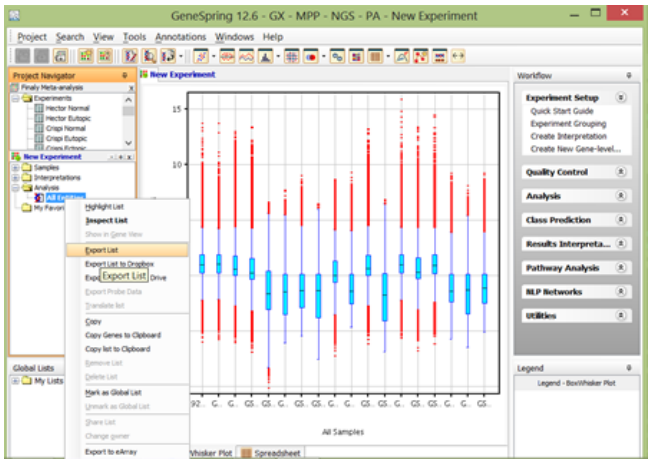


6. For preproceesing, “baseline to median of all samples” was chosen.

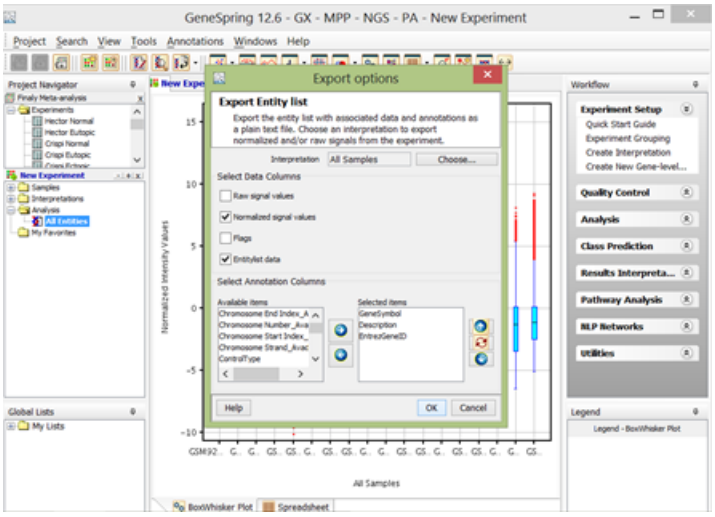
7. The programme then runs the pre-processing and normalisation.



8. Once normalisation is finished the programme gives the boxplots and the entity list of the normalised data. The normalised entity list can be exported to another drive for further analysis by right clicking on the "entity list" option under the experiment and then choosing "export list" option.



9. The information that is required to be included in the list, such as Entrez gene ID, Gene name, etc., can be chosen.



Appendix 5: Steps for the meta-analysis and analysis of dysregulated genes for published gene lists.

1. Install R version 3.1.2 using standard installation procedures.
2. Create an analysis folder in your hard drive to store the input and output files as well as the R analysis script.
3. Install the RobustRankAggreg package by going to “Packages” and then to “Install packages”. The package containing functions for RRA analysis is downloaded from CRAN website and installed the system.
4. Load the previously installed RobustRankAggreg package to use the functions defined by it by running the command in the R console:
   library(RobustRankAggreg)
5. Define the working directory for the analysis.
   setwd("C:/Name of the Working Directory/")
6. To read the data from the constructed file into R, use the command
   meta <- read.delim("up_regulated.txt", na = "")
   This command reads in the aforementioned file and assigns it to the data frame named “meta”. The argument na = "" defines that empty cells in the table are recognized as “not available” in the data frame “meta”.
7. Convert the data to a list format as required by RobustRankAggreg
   meta <- as.list(meta)
8. To get rid of the “not available” positions in the list, we use custom helper function:
   for (i in 1: length(meta)){meta[[i]] <- meta[[i]] [!is.na(meta[[i]])]
   meta[[i]] <- as.character(meta[[i]])}
9. Define the vector count , which stores the data about how many genes each study was able to detect:
   count <- c(x, y, z,)
   where x,y and Z denote the total number of a genes detectable by the study or the microarray platform being used.
10. Construct the matrix of normalized ranks using rankMatrix command:
    rankmat <- rankMatrix(meta, N = count)
    This command uses the list consisting of dysregulated genes as an input (previously constructed list meta). The argument N is used to define the number of genes each study was able to profile (previously defined vector count)
11. Run RRA analysis using the “aggregateRanks” command to obtain a significance score ρ-score
    ranks<- aggregateRanks(rmat=rankmat)
12. Apply a multiple testing correction. Conservative Bonferroni correction is used by multiplying all the ρ-scores with the number of studies or the number of gene lists
    ranks$adjustedPval <- apply(cbind(ranks$Score * max(count), 1), 1, min)
13. Filter the results by significance
    results <- ranks[ranks$adjustedPval < 0.05,]
    Results can be displayed by running the command results, which displays the outcome of the analysis
14. Export the results table out of R with the following command:
    write.table(results, "results.txt", sep = "\t")
    This command creates a tab-delimited results file into the analysis folder.

Appendix 6: Top-35 upregulated genes in eutopic endometrium from women with endometriosis compared to from women without endometriosis.

Entrez ID	Gene Symbol	Gene name	Fold Change	P value
384	ARG2	Arginase, type II	2.65	$1.8X10^{-24}$
4837	NNMT	Nicotinamide N-methyltransferase	4.48	$3X10^{-23}$
23710	GABARAPL1	GABA(A) receptor-associated protein like 1	2.51	$8.5X10^{-23}$
9547	CXCL14	Chemokine (C-X-C motif) ligand 14	10.7	$1X10^{-22}$
1612	DAPK1	Death-associated protein kinase 1	2.61	$1.2X10^{-22}$
1942	EFNA1	Ephrin-A1	2.64	$3.9X10^{-22}$
6564	SLC15A1	Solute carrier family 15 member 1	4.38	$7.2X10^{-22}$
1910	EDNRB	Endothelin receptor type B	3.22	$1.6X10^{-21}$
6505	SLC1A1	Solute carrier family 1 member 1	4.71	$4.9X10^{-21}$
53630	BCMO1	Beta-carotene 15,15'-monooxygenase 1	2.45	$6.8X10^{-21}$
1604	CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	3.73	$6.8X10^{-21}$
7042	TGFB2	Transforming growth factor, beta 2	2.64	$6.8X10^{-21}$
347	APOD	Apolipoprotein D	3.32	$8.6X10^{-21}$
79838	TMC5	Transmembrane channel-like 5	3.31	$1.8X10^{-20}$
54762	GRAMD1C	GRAM domain containing 1C	3.71	$6.1X10^{-20}$
6539	SLC6A12	Solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	2.53	$6.2X10^{-20}$
8531	CSDA	Cold shock domain protein A	1.78	$9.7X10^{-20}$
6696	SPP1	Secreted phosphoprotein 1	5.35	$2.1X10^{-19}$
1356	CP	Ceruloplasmin (ferroxidase)	4.89	$8.8X10^{-19}$
10370	CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	2.57	$9.8X10^{-19}$
3914	LAMB3	Laminin, beta 3	3.49	$1.2X10^{-18}$
1052	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	3.14	$2\ X10^{-18}$
7849	PAX8	Paired box 8	2.33	$2.1X10^{-18}$
1647	GADD45A	Growth arrest and DNA-damage-inducible α	3.21	$2.2X10^{-18}$
5047	PAEP	Progestagen-associated endometrial protein	10	$2.3X10^{-18}$
1803	DPP4	Dipeptidyl-peptidase 4	3.32	$3X10^{-18}$
79722	ANKRD55	Ankyrin repeat domain 55	2.49	$4.8X10^{-18}$
22996	TTC39A	Tetratricopeptide repeat domain 39A	2.56	$5.2X10^{-18}$
1311	COMP	Cartilage oligomeric matrix protein	4.58	$6.9X10^{-18}$
107	ADCY1	Adenylate cyclase 1 (brain)	2.59	$1X10^{-17}$
3026	HABP2	Hyaluronan binding protein 2	3	$2.5X10^{-17}$
4217	MAP3K5	Mitogen-activated protein kinase kinase kinase 5	3.15	$2.9X10^{-17}$
9829	DNAJC6	DnaJ (Hsp40) homolog, subfamily C, member 6	3.2	$3.3X10^{-17}$
6947	TCN1	Transcobalamin I	4.86	$3.3X10^{-17}$
1824	DSC2	Desmocollin 2	2.09	$4.1X10^{-17}$

Appendix 7: Top-35 downregulated genes in eutopic endometrium from women with endometriosis compared to from women without endometriosis.

Entrez ID	Gene Symbol	Gene name	Fold Change	P value
6424	SFRP4	Secreted frizzled-related protein 4	0.2	$3X10^{-23}$
1307	COL16A1	Collagen, type XVI, alpha 1	0.4	$3.9X10^{-22}$
2735	GLI1	GLI family zinc finger 1	0.6	$8.3X10^{-20}$
9770	RASSF2	Ras association (RalGDS/AF-6) domain family member 2	0.4	$2.1X10^{-19}$
891	CCNB1	Cyclin B1	0.4	$4.10X10^{19}$
1908	EDN3	Endothelin 3	0.3	$4.8X10^{-19}$
10857	PGRMC1	Progesterone receptor membrane component 1	0.4	$4.8X10^{-19}$
9493	KIF23	Kinesin family member 23	0.4	$6.6X10^{-19}$
9315	C5orf13	Chromosome 5 open reading frame 13	0.3	$7.2X10^{-18}$
11065	UBE2C	Ubiquitin-conjugating enzyme E2C	0.4	$9.2X10^{-18}$
55244	SLC47A1	Solute carrier family 47, member 1	0.3	$1.2X10^{-17}$
10234	LRRC17	Leucine rich repeat containing 17	0.4	$1.3X10^{-17}$
332	BIRC5	Baculoviral IAP repeat-containing 5	0.5	$1.9X10^{-17}$
9133	CCNB2	Cyclin B2	0.4	$2.2X10^{-17}$
7298	TYMS	Thymidylate synthetase	0.4	$2.8X10^{-17}$
5241	PGR	Progesterone receptor	0.4	$3.1X10^{-17}$
6240	RRM1	Ribonucleotide reductase M1	0.6	$4.5X10^{-17}$
26227	PHGDH	Phosphoglycerate dehydrogenase	0.5	$4.5X10^{-17}$
701	BUB1B	Budding uninhibited by benzimidazoles 1 homolog beta (yeast)	0.4	$4.7X10^{-17}$
4675	NAP1L3	Nucleosome assembly protein 1-like 3	0.4	$4.9X10^{-17}$
5111	PCNA	Proliferating cell nuclear antigen	0.5	$5.4X10^{-17}$
58189	WFDC1	WAP four-disulfide core domain 1	0.4	$7.1X10^{-17}$
140465	MYL6B	Myosin, light chain 6B, alkali, smooth muscle and non-muscle	0.6	$1.6X10^{-16}$
55872	PBK	PDZ binding kinase	0.3	$2.7X10^{-16}$
64388	GREM2	Gremlin 2	0.3	$3.3X10^{-16}$
8395	PIP5K1B	Phosphatidylinositol-4-phosphate 5-kinase, type I, beta	0.4	$3.7X10^{-16}$
7083	TK1	Thymidine kinase 1, soluble	0.5	$4.6X10^{-16}$
10112	KIF20A	Kinesin family member 20A	0.4	$5.3X10^{-16}$
4678	NASP	Nuclear autoantigenic sperm protein (histone-binding)	0.6	$6.6X10^{-16}$
3479	IGF1	Insulin-like growth factor 1 (somatomedin C)	0.4	$9.9X10^{-16}$
24141	C20orf103	Chromosome 20 open reading frame 103	0.5	$1X10^{-15}$
3033	HADH	Hydroxyacyl-CoA dehydrogenase	0.6	$1.2X10^{-15}$
991	CDC20	Cell division cycle 20 homolog (S. cerevisiae)	0.5	$1.4X10^{-15}$
7153	TOP2A	Topoisomerase (DNA) II alpha 170kDa	0.3	$1.4X10^{-15}$
9833	MELK	Maternal embryonic leucine zipper kinase	0.4	$1.6X10^{-15}$

Appendix 8: Top 20 dysregulated pathways in the eutopic endometrium from women with endometriosis as compared to from women without endometriosis.

Pathway ID	Pathway name	P value	F score
Overall			
GO:0045087	Innate immune response	$1.9X10^{-6}$	16.53
GO:0005275	Amine transmembrane transporter activity	$5.7X10^{-6}$	14.92
GO:0002526	Acute inflammatory response	$7.4X10^{-6}$	14.08
GO:0019724	B cell mediated immunity	$1X10^{-5}$	13.44
GO:0016064	Immunoglobulin mediated immune response	$1X10^{-5}$	13.43
GO:0004896	Hematopoietin/interferon-class (D200-domain) cytokine receptor activity	$1.2X10^{-5}$	13.03
GO:0050817	Coagulation		
GO:0007596	Blood coagulation	$1.3X10^{-5}$	12.59
GO:0006935	Chemotaxis	$1.3X10^{-5}$	12.54
GO:0042330	Taxis	$1.3X10^{-5}$	12.54
GO:0002253	Activation of immune response	$2X10^{-5}$	12.12
GO:0002460	Adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	$2.1X10^{-5}$	11.99
GO:0002250	Adaptive immune response	$2.3X10^{-5}$	11.83
GO:0007204	Elevation of cytosolic calcium ion concentration	$2.3X10^{-5}$	11.76
GO:0051480	Cytosolic calcium ion homeostasis	$2.3X10^{-5}$	11.76
GO:0050776	Regulation of immune response	$2.4X10^{-5}$	11.49
GO:0015171	Amino acid transmembrane transporter activity	$2.9X10^{-5}$	11.29
GO:0007599	Hemostasis	$2.9X10^{-5}$	11.25
GO:0046943	Carboxylic acid transmembrane transporter activity	$3.8X10^{-5}$	11.01
GO:0006959	Humoral immune response	$4.4X10^{-5}$	10.76
Proliferative phase			
GO:0006935	Chemotaxis	$5.6X10^{-4}$	563.24
GO:0042330	Taxis	$5.6X10^{-4}$	563.24
GO:0002684	Positive regulation of immune system process	$5.6X10^{-4}$	472.76
GO:0009617	Response to bacterium	$5.6X10^{-4}$	465.51
GO:0042379	Chemokine receptor binding	$7.5X10^{-4}$	460.02
GO:0046649	Lymphocyte activation	$8.5X10^{-4}$	457.74
GO:0008009	Chemokine activity	$7.5X10^{-4}$	455.66
GO:0001664	G-Protein-coupled receptor binding	$1X10^{-3}$	438.23
GO:0000165	MAPKKK cascade	$5.6X10^{-4}$	438.17
GO:0030097	Hemopoiesis	$5.6X10^{-4}$	416.35
GO:0048534	Hemopoietic or lymphoid organ development	$5.6X10^{-4}$	391.78
GO:0007626	Locomotory behaviour	$1.2X10^{-3}$	382.76
GO:0002521	Leukocyte differentiation	$5.3X10^{-5}$	373.21
GO:0042110	T cell activation	$8.2X10^{-4}$	369.29
GO:0045595	Regulation of cell differentiation	$5.6X10^{-4}$	348.41
GO:0048584	Positive regulation of response to stimulus	$2.9X10^{-3}$	346.79
GO:0002252	Immune effector process	$3.2X10^{-3}$	341.76

Pathway ID	Pathway name	P value	F score
GO:0048583	Regulation of response to stimulus	$1.1X10^{-3}$	332.09
GO:0019882	Antigen processing and presentation	$5.4X10^{-3}$	330.89
GO:0051347	Positive regulation of transferase activity	$2.6X10^{-3}$	327.04
Secretory phase			
GO:0045087	Innate immune response	$3.9X10^{-12}$	800.29
GO:0002253	Activation of immune response	$1.9X10^{-11}$	731.01
GO:0048583	Regulation of response to stimulus	$1X10^{-9}$	727.45
GO:0050776	Regulation of immune response	$1.6X10^{-11}$	727.08
GO:0002684	Positive regulation of immune system process	$9.8X10^{-10}$	718.7
GO:0048584	Positive regulation of response to stimulus	$4.2X10^{-10}$	703.8
GO:0002526	Acute inflammatory response	$2.5X10^{-10}$	702.86
GO:0050778	Positive regulation of immune response	$1.4X10^{-10}$	676.53
GO:0019724	B cell mediated immunity	$1.5X10^{-10}$	668.52
GO:0006959	Humoral immune response	$2.5X10^{-10}$	646.26
GO:0016064	Immunoglobulin mediated immune response	$2.2X10^{-10}$	645.13
GO:0006935	Chemotaxis	$1.3X10^{-4}$	617.04
GO:0042330	Taxis	$1.3X10^{-4}$	617.04
GO:0002460	Adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	$1X10^{-9}$	607.88
GO:0002250	Adaptive immune response	$1X10^{-9}$	600.73
GO:0002252	Immune effector process	$2X10^{-8}$	599.32
GO:0002449	Lymphocyte mediated immunity	$3.1X10^{-10}$	529.1
GO:0002443	Leukocyte mediated immunity	$9.2X10^{-10}$	514.51
GO:0030155	Regulation of cell adhesion	$4.9X10^{-7}$	502.69
GO:0006916	Anti-apoptosis	$3.8X10^{-5}$	449.56
Eutopic endometrium: Proliferative Vs Secretory phase			
GO:0042035	Regulation of cytokine biosynthetic process	$9.7X10^{-8}$	21.65
GO:0005249	Voltage-gated potassium channel activity	$9.7X10^{-8}$	21.2
GO:0042107	Cytokine metabolic process	$1.6X10^{-7}$	20.03
GO:0030955	Potassium ion binding	$1.6X10^{-7}$	19.78
GO:0042089	Cytokine biosynthetic process	$1.7X10^{-7}$	19.34
GO:0022843	Voltage-gated cation channel activity	$1.7X10^{-7}$	19.29
GO:0008227	Amine receptor activity	$2.7X10^{-7}$	18.56
GO:0009897	External side of plasma membrane	$3.5X10^{-7}$	18.11
GO:0001816	Cytokine production	$3.5X10^{-7}$	18
GO:0001653	Peptide receptor activity	$3.6X10^{-7}$	17.73
GO:0008528	Peptide receptor activity, G-protein coupled	$3.6X10^{-7}$	17.73
GO:0031225	Anchored to membrane	$4.7X10^{-7}$	17.33
GO:0006968	Cellular defense response	$4.7X10^{-7}$	17.25
GO:0003015	Heart process	$5.4X10^{-7}$	16.95
GO:0060047	Heart contraction	$5.4X10^{-7}$	16.95
GO:0006874	Cellular calcium ion homeostasis	$5.7X10^{-7}$	16.82
GO:0055074	Calcium ion homeostasis	$5.8X10^{-7}$	16.7
GO:0016459	Myosin complex	$5.8X10^{-7}$	16.66
GO:0005819	Spindle	$6X10^{-7}$	16.56
GO:0015370	Solute:sodium symporter activity	$6.1X10^{-7}$	16.49

Appendix 9: Top-35 upregulated genes in eutopic endometrium from women with endometriosis compared to from women without endometriosis in the proliferative phase of the menstrual cycle.

Entrez Id	Gene symbol	Gene name	Fold change	P value
1942	EFNA1	Ephrin-A1	1.95	0.00058
50486	G0S2	G0/G1switch 2	2.78	0.00058
9052	GPRC5A	G protein-coupled receptor, family C, group 5, member A	1.88	0.00058
3034	HAL	Histidine ammonia-lyase	2.66	0.00058
3557	IL1RN	Interleukin 1 receptor antagonist	2.75	0.00058
10221	TRIB1	Tribbles homolog 1 (Drosophila)	2.24	0.00058
23764	MAFF	v-Maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	2.08	0.00065
6696	SPP1	Secreted phosphoprotein 1	3.61	0.00086
1356	CP	Ceruloplasmin (ferroxidase)	3.58	0.00116
4791	NFKB2	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	1.24	0.00117
1890	TYMP	Thymidine phosphorylase	1.67	0.00135
1364	CLDN4	Claudin 4	2.21	0.0017
1647	GADD45A	Growth arrest and DNA-damage-inducible, alpha	1.86	0.00187
56649	TMPRSS4	Transmembrane protease, serine 4	2.06	0.00209
1316	KLF6	Kruppel-like factor 6	2.14	0.00219
9258	MFHAS1	Malignant fibrous histiocytoma amplified sequence 1	1.35	0.00238
5801	PTPRR	Protein tyrosine phosphatase, receptor type, R	2	0.00242
2114	ETS2	v-Ets erythroblastosis virus E26 oncogene homolog 2 (avian)	1.4	0.00247
8714	ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	2	0.00248
7849	PAX8	Paired box 8	1.54	0.00259
3914	LAMB3	Laminin, beta 3	2.62	0.00274
124044	SPATA2L	Spermatogenesis associated 2-like	1.34	0.00319
8553	BHLHE40	Basic helix-loop-helix family, member e40	1.9	0.00329
6928	HNF1B	HNF1 homeobox B	1.54	0.00338
2634	GBP2	Guanylate binding protein 2, interferon-inducible	1.9	0.00348
1051	CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	1.37	0.00356
6533	SLC6A6	Solute carrier family 6 (neurotransmitter transporter, taurine), member 6	1.47	0.00395
604	BCL6	B-cell CLL/lymphoma 6	2.15	0.00396
2872	MKNK2	MAP kinase interacting serine/threonine kinase 2	1.29	0.00396
3400	ID4	Inhibitor of DNA binding 4, dominant negative helix-loop-helix protein	1.48	0.00415
8878	SQSTM1	Sequestosome 1	1.31	0.00424
10158	PDZK1IP1	PDZK1 interacting protein 1	2.39	0.00425
2810	SFN	Stratifin	1.59	0.00455
79838	TMC5	Transmembrane channel-like 5	1.98	0.00466
1604	CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	2.57	0.00489

Appendix 10: Top-35 downregulated genes in eutopic endometrium from women with endometriosis compared to from women without endometriosis in the proliferative phase of the menstrual cycle.

Entrez Id	Gene symbol	Gene name	Fold change	P value
2200	FBN1	Fibrillin 1	0.69	0.00065
4628	MYH10	Myosin, heavy chain 10, non-muscle	0.69	0.00219
539	ATP5O	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	0.77	0.00263
79712	GTDC1	Glycosyltransferase-like domain containing 1	0.79	0.00263
5213	PFKM	Phosphofructokinase, muscle	0.83	0.00343
1289	COL5A1	Collagen, type V, alpha 1	0.62	0.00396
56945	MRPS22	Mitochondrial ribosomal protein S22	0.86	0.00455
6424	SFRP4	Secreted frizzled-related protein 4	0.38	0.00497
273	AMPH	Amphiphysin	0.69	0.00521
64943	NT5DC2	5'-Nucleotidase domain containing 2	0.58	0.0059
1036	CDO1	Cysteine dioxygenase, type I	0.71	0.00603
54875	CNTLN	Centlein, centrosomal protein	0.74	0.0064
4052	LTBP1	Latent transforming growth factor beta binding protein 1	0.54	0.00667
292	SLC25A5	Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5	0.8	0.00702
2184	FAH	Fumarylacetoacetate hydrolase (fumarylacetoacetase)	0.78	0.00708
1009	CDH11	Cadherin 11, type 2, OB-cadherin (osteoblast)	0.69	0.00729
10763	NES	Nestin	0.69	0.00735
3151	HMGN2	High-mobility group nucleosomal binding domain 2	0.74	0.00749
1307	COL16A1	Collagen, type XVI, alpha 1	0.63	0.00782
8270	LAGE3	L antigen family, member 3	0.79	0.00782
5125	PCSK5	Proprotein convertase subtilisin/kexin type 5	0.51	0.00786
9	NAT1	N-Acetyltransferase 1 (arylamine N-acetyltransferase)	0.62	0.0079
8975	USP13	Ubiquitin specific peptidase 13 (isopeptidase T-3)	0.76	0.0079
2735	GLI1	GLI family zinc finger 1	0.7	0.00859
4192	MDK	Midkine (neurite growth-promoting factor 2)	0.64	0.00859
3232	HOXD3	Homeobox D3	0.74	0.00867
26227	PHGDH	Phosphoglycerate dehydrogenase	0.64	0.00867
5001	ORC5	Origin recognition complex, subunit 5	0.82	0.00904
991	CDC20	Cell division cycle 20 homolog (S. cerevisiae)	0.52	0.00911
3202	HOXA5	Homeobox A5	0.54	0.00916
7372	UMPS	Uridine monophosphate synthetase	0.81	0.01031
2201	FBN2	Fibrillin 2	0.46	0.01061
10962	MLLT11	Myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11	0.65	0.01082
8507	ENC1	Ectodermal-neural cortex 1 (with BTB-like domain)	0.55	0.0112
23085	ERC1	ELKS/RAB6-interacting/CAST family member 1	0.78	0.0112

Appendix 11: Top-35 upregulated genes in eutopic endometrium from women with endometriosis compared to from women without endometriosis in the secretory phase of the menstrual cycle.

Entrez Id	Gene symbol	Gene name	Fold Change	P value
5047	PAEP	Progestagen-associated endometrial protein	16.23	$6.3X10^{-15}$
145741	C2CD4A	C2 calcium-dependent domain containing 4A	7.07	$1.1X10^{-14}$
6505	SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	7.43	$1.1X10^{-14}$
1942	EFNA1	Ephrin-A1	2.43	$6.1X10^{-14}$
307	ANXA4	Annexin A4	2.85	$8.6X10^{-14}$
1356	CP	Ceruloplasmin (ferroxidase)	5.43	$8.6X10^{-14}$
2886	GRB7	Growth factor receptor-bound protein 7	2.08	$8.6X10^{-14}$
4217	MAP3K5	Mitogen-activated protein kinase kinase kinase 5	3.26	$8.6X10^{-14}$
3321	IGSF3	Immunoglobulin superfamily, member 3	1.71	$9.7X10^{-14}$
84159	ARID5B	AT rich interactive domain 5B (MRF1-like)	2.24	$1.3X10^{-13}$
710	SERPING1	Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1	3.21	$1.4X10^{-13}$
2634	GBP2	Guanylate binding protein 2, interferon-inducible	3.07	$2.1X10^{-13}$
4233	MET	Met proto-oncogene	3.36	$2.9X10^{-13}$
6564	SLC15A1	Solute carrier family 15 (oligopeptide transporter), member 1	4.49	$2.9X10^{-13}$
91404	SESTD1	SEC14 and spectrin domains 1	2.49	$3.7X10^{-13}$
120224	TMEM45B	Transmembrane protein 45B	2.59	$3.7X10^{-13}$
10451	VAV3	vav 3 guanine nucleotide exchange factor	2.15	$3.7X10^{-13}$
8714	ABCC3	ATP-binding cassette, sub-family C, member 3	2.66	$3.9X10^{-13}$
85415	RHPN2	Rhophilin, Rho GTPase binding protein 2	3.6	$4.1X10^{-13}$
3026	HABP2	Hyaluronan binding protein 2	3.31	$6.2X10^{-13}$
79838	TMC5	Transmembrane channel-like 5	3.75	$6.2X10^{-13}$
23555	TSPAN15	Tetraspanin 15	2.26	$6.2X10^{-13}$
347902	AMIGO2	Adhesion molecule with Ig-like domain 2	2.77	$6.8X10^{-13}$
3914	LAMB3	Laminin, beta 3	3.48	$6.8X10^{-13}$
1604	CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	5	$6.9X10^{-13}$
28231	SLCO4A1	Solute carrier organic anion transporter family, member 4A1	2.51	$6.9X10^{-13}$
722	C4BPA	Complement component 4 binding protein, alpha	5.7	$8.8X10^{-13}$
3620	IDO1	Indoleamine 2,3-dioxygenase 1	3.26	$8.8X10^{-13}$
2308	FOXO1	Forkhead box O1	1.98	$1.1X10^{-12}$
6990	DYNLT3	Dynein, light chain, Tctex-type 3	2.34	$1.4X10^{-12}$
1910	EDNRB	Endothelin receptor type B	3.21	$1.8X10^{-12}$
121260	SLC15A4	Solute carrier family 15, member 4	2.63	$1.8X10^{-12}$
64114	TMBIM1	Transmembrane BAX inhibitor motif containing 1	1.77	$1.8X10^{-12}$
9249	DHRS3	Dehydrogenase/reductase (SDR family) member 3	2.5	$2X10^{-12}$
10509	SEMA4B	Sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B	1.63	$2.3X10^{-12}$

Appendix 12: Top-35 downregulated genes in eutopic endometrium from women with endometriosis compared to from women without endometriosis in the secretory phase of the menstrual cycle.

Entrez Id	Gene symbol	Gene name	Fold change	P value
8395	PIP5K1B	Phosphatidylinositol-4-phosphate 5-kinase, type I,β	0.4	$1.1X10^{-14}$
1908	EDN3	Endothelin 3	0.28	$5.9X10^{-14}$
10439	OLFM1	Olfactomedin 1	0.46	$8.6X10^{-14}$
10234	LRRC17	Leucine rich repeat containing 17	0.34	$2.7X10^{-13}$
744	MPPED2	Metallophosphoesterase domain containing 2	0.34	$6.2X10^{-13}$
79695	GALNT12	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase	0.39	$6.8X10^{-13}$
25803	SPDEF	SAM pointed domain containing ets transcription factor	0.41	$1.4X10^{-12}$
79695	GALNT12	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase	0.42	$4.6X10^{-12}$
6565	SLC15A2	Solute carrier family 15 member 2	0.19	$5.4X10^{-12}$
3112	HLA-DOB	Major histocompatibility complex, class II, DOβ	0.39	$7.4X10^{-12}$
9770	RASSF2	Ras association (RalGDS/AF-6) domain family member 2	0.42	$9.3X10^{-12}$
249	ALPL	Alkaline phosphatase, liver/bone/kidney	0.36	$1X10^{-11}$
9493	KIF23	Kinesin family member 23	0.58	$1.1X10^{-11}$
64388	GREM2	Gremlin 2	0.39	$1.7X10^{-11}$
80010	RMI1	RMI1, RecQ mediated genome instability 1, homolog (S. cerevisiae)	0.61	$1.7X10^{-11}$
29091	STXBP6	Syntaxin binding protein 6 (amisyn)	0.47	$1.8X10^{-11}$
201164	PLD6	Phospholipase D family, member 6	0.66	$2.1X10^{-11}$
580	BARD1	BRCA1 associated RING domain 1	0.63	$2.2X10^{-11}$
6424	SFRP4	Secreted frizzled-related protein 4	0.23	$2.2X10^{-11}$
9687	GREB1	Growth regulation by estrogen in breast cancer 1	0.47	$2.6X10^{-11}$
148327	CREB3L4	cAMP responsive element binding protein 3-like 4	0.51	$3X10^{-11}$
83690	CRISPLD1	Cysteine-rich secretory protein LCCL domain containing 1	0.43	$3.1X10^{-11}$
3248	HPGD	Hydroxyprostaglandin dehydrogenase 15-(NAD)	0.34	$3.2X10^{-11}$
146456	TMED6	Transmembrane emp24 protein transport domain containing 6	0.38	$3.6X10^{-11}$
10512	SEMA3C	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C	0.47	$4.1X10^{-11}$
10346	TRIM22	Tripartite motif-containing 22	0.57	$4.4X10^{-11}$
79366	HMGN5	High-mobility group nucleosome binding domain 5	0.62	$5X10^{-11}$
25878	MXRA5	Matrix-remodelling associated 5	0.5	$5.1X10^{-11}$
155066	ATP6V0E2	ATPase, H+ transporting V0 subunit e2	0.53	$6.1X10^{-11}$
128239	IQGAP3	IQ motif containing GTPase activating protein 3	0.7	$6.1X10^{-11}$
55283	MCOLN3	Mucolipin 3	0.52	$7.2X10^{-11}$
57447	NDRG2	NDRG family member 2	0.53	$7.4X10^{-11}$
359845	FAM101B	Family with sequence similarity 101, member B	0.62	$8.3X10^{-11}$
8654	PDE5A	Phosphodiesterase 5A, cGMP-specific	0.58	$9X10^{-11}$
84189	SLITRK6	SLIT and NTRK-like family, member 6	0.4	$9.7X10^{-11}$

Appendix 13: Top-35 upregulated genes in eutopic endometrium from women with endometriosis in the proliferative vs. secretory phase of the menstrual cycle.

Entrez Id	Gene symbol	Gene name	Fold change	P value
4684	NCAM1	Neural cell adhesion molecule 1	2.79	$6.5X10^{-12}$
5627	PROS1	Protein S (alpha)	3.09	$2.5X10^{-11}$
5791	PTPRE	Protein tyrosine phosphatase, receptor type, E	3.01	$1.6X10^{-10}$
54438	GFOD1	Glucose-fructose oxidoreductase domain containing 1	3.07	$2.6X10^{-10}$
5271	SERPINB8	Serpin peptidase inhibitor, clade B (ovalbumin), member 8	2.43	$3.5X10^{-10}$
81855	SFXN3	Sideroflexin 3	2.35	$4X10^{-10}$
80303	EFHD1	EF-hand domain family, member D1	3.02	$5X10^{-10}$
4862	NPAS2	Neuronal PAS domain protein 2	2.32	$9.2X10^{-10}$
1890	TYMP	Thymidine phosphorylase	3.28	$1.8X10^{-9}$
7035	TFPI	Tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)	2.35	$2.2X10^{-9}$
5918	RARRES1	Retinoic acid receptor responder (tazarotene induced) 1	2.98	$2.4X10^{-9}$
57214	KIAA1199	KIAA1199	4.15	$2.8X10^{-9}$
23476	BRD4	Bromodomain containing 4	1.97	$3.9X10^{-9}$
1803	DPP4	Dipeptidyl-peptidase 4	4.47	$3.9X10^{-9}$
3690	ITGB3	Integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	2.15	$3.9X10^{-9}$
8714	ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	3.81	$4.1X10^{-9}$
9846	GAB2	GRB2-associated binding protein 2	2.45	$4.1X10^{-9}$
5578	PRKCA	Protein kinase C, alpha	1.8	$4.1X10^{-9}$
710	SERPING1	Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1	3.06	$4.1X10^{-9}$
3855	KRT7	Keratin 7	4.52	$4.2X10^{-9}$
7223	TRPC4	Transient receptor potential cation channel, subfamily C, member 4	3.38	$4.4X10^{-9}$
415	ARSE	Arylsulfatase E (chondrodysplasia punctata 1)	2.87	$5.4X10^{-9}$
11030	RBPMS	RNA binding protein with multiple splicing	1.93	$5.7X10^{-9}$
1521	CTSW	Cathepsin W	3.19	$5.9X10^{-9}$
3026	HABP2	Hyaluronan binding protein 2	4	$6.2X10^{-9}$
978	CDA	Cytidine deaminase	2.59	$6.5X10^{-9}$
7378	UPP1	Uridine phosphorylase 1	2.48	$6.8X10^{-9}$
579	NKX3-2	NK3 homeobox 2	2.37	$7.3X10^{-9}$
10855	HPSE	Heparanase	3.07	$8.9X10^{-9}$
113146	AHNAK2	AHNAK nucleoprotein 2	3.26	$1X10^{-8}$
8534	CHST1	Carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	2.36	$1X10^{-8}$
1824	DSC2	Desmocollin 2	2.63	$1X10^{-8}$
4524	MTHFR	Methylenetetrahydrofolate reductase (NAD(P)H)	2.67	$1.3X10^{-8}$
11067	C10orf10	Chromosome 10 open reading frame 10	2.97	$1.6X10^{-8}$
3034	HAL	Histidine ammonia-lyase	3.97	$1X10^{-8}$

Appendix 14: Top-35 downregulated genes in eutopic endometrium from women with endometriosis in the proliferative vs. secretory phase of the menstrual cycle.

Entrez Id	Gene symbol	Gene name	Fold change	P value
53407	STX18	Syntaxin 18	0.32	$2X10^{-12}$
26275	HIBCH	3-Hydroxyisobutyryl-CoA hydrolase	0.37	$4X10^{-10}$
983	CDK1	Cyclin-dependent kinase 1	0.39	$8.7X10^{-10}$
9232	PTTG1	Pituitary tumor-transforming 1	0.37	$1.3X10^{-9}$
10455	PECI	Peroxisomal D3,D2-enoyl-CoA isomerase	0.33	$1.8X10^{-9}$
5241	PGR	Progesterone receptor	0.3	$1.9X10^{-9}$
8836	GGH	Gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)	0.41	$2.1X10^{-9}$
3251	HPRT1	Hypoxanthine phosphoribosyltransferase 1	0.51	$2.2X10^{-9}$
29127	RACGAP1	Rac GTPase activating protein 1	0.48	$3.6X10^{-9}$
2146	EZH2	Enhancer of zeste homolog 2 (Drosophila)	0.44	$3.9X10^{-9}$
3655	ITGA6	Integrin, alpha 6	0.46	$3.9X10^{-9}$
5111	PCNA	Proliferating cell nuclear antigen	0.46	$3.9X10^{-9}$
3838	KPNA2	Karyopherin alpha 2 (RAG cohort 1, importin alpha 1)	0.44	$4.4X10^{-9}$
6240	RRM1	Ribonucleotide reductase M1	0.45	$5.5X10^{-9}$
3148	HMGB2	High-mobility group box 2	0.35	$7.7X10^{-9}$
7514	XPO1	Exportin 1 (CRM1 homolog, yeast)	0.49	$8.2X10^{-9}$
9133	CCNB2	Cyclin B2	0.37	$1.2X10^{-8}$
57535	KIAA1324	KIAA1324	0.34	$1.3X10^{-8}$
29880	ALG5	Asparagine-linked glycosylation 5, dolichyl-phosphate beta-glucosyltransferase	0.53	$1.4X10^{-8}$
7298	TYMS	Thymidylate synthetase	0.34	$1.4X10^{-8}$
3161	HMMR	Hyaluronan-mediated motility receptor (RHAMM)	0.42	$1.7X10^{-8}$
54431	DNAJC10	DnaJ (Hsp40) homolog, subfamily C, member 10	0.34	$1.8X10^{-8}$
3479	IGF1	Insulin-like growth factor 1 (somatomedin C)	0.42	$1.8X10^{-8}$
4487	MSX1	Msh homeobox 1	0.39	$1.8X10^{-8}$
9493	KIF23	Kinesin family member 23	0.39	$1.9X10^{-8}$
56547	MMP26	Matrix metallopeptidase 26	0.15	$1.9X10^{-8}$
5955	RCN2	Reticulocalbin 2, EF-hand calcium binding domain	0.41	$1.9X10^{-8}$
79084	WDR77	WD repeat domain 77	0.38	$2.4X10^{-8}$
9709	HERPUD1	Homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	0.39	$2.6X10^{-8}$
4678	NASP	Nuclear autoantigenic sperm protein (histone-binding)	0.51	$2.8X10^{-8}$
8395	PIP5K1B	Phosphatidylinositol-4-phosphate 5-kinase, type I, beta	0.39	$2.8X10^{-8}$
9055	PRC1	Protein regulator of cytokinesis 1	0.35	$3.2X10^{-8}$
3015	H2AFZ	H2A histone family, member Z	0.49	$3.6X10^{-8}$
6430	SRSF5	Serine/arginine-rich splicing factor 5	0.46	$3.7X10^{-8}$
515	ATP5F1	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1	0.52	$4.6X10^{-8}$

Appendix 15: Top-35 upregulated genes in endometriotic lesions compared to eutopic endometrium from women with endometriosis.

Entrez Id	Gene symbol	Gene name	Fold change	P value
6505	SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter system Xag) member1	3.81	$1.1X10^{-17}$
7042	TGFB2	Transforming growth factor, beta 2	2.28	$1.1X10^{-16}$
3026	HABP2	Hyaluronan binding protein 2	3.04	$1.8X10^{-16}$
79838	TMC5	Transmembrane channel-like 5	2.38	$2.3X10^{-14}$
79820	CATSPERB	Cation channel, sperm-associated, beta	2.11	$2.4X10^{-14}$
1604	CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	2.87	$2.7X10^{-14}$
54762	GRAMD1C	GRAM domain containing 1C	2.98	$5.8X10^{-14}$
6947	TCN1	Transcobalamin I (vitamin B12 binding protein)	4.93	$1.8X10^{-13}$
1803	DPP4	Dipeptidyl-peptidase 4	2.95	$3.4X10^{-13}$
3034	HAL	Histidine ammonia-lyase	3.11	$5.3X10^{-13}$
1591	CYP24A1	Cytochrome P450, family 24, subfamily A, polypeptide 1	3.28	$5.3X10^{-13}$
486	FXYD2	FXYD domain containing ion transport regulator 2	2	$1.3X10^{-12}$
6564	SLC15A1	Solute carrier family 15 (oligopeptide transporter), member 1	2.79	$1.5X10^{-12}$
79722	ANKRD55	Ankyrin repeat domain 55	2.1	$1.7X10^{-12}$
6539	SLC6A12	Solute carrier family 6 member 12	2.05	$2.9X10^{-12}$
28231	SLCO4A1	Solute carrier organic anion transporter family, member 4A1	2.49	$4X10^{-12}$
1311	COMP	Cartilage oligomeric matrix protein	3.73	$4.6X10^{-12}$
53630	BCMO1	Beta-carotene 15,15'-monooxygenase 1	1.89	$5.2X10^{-12}$
5271	SERPINB8	Serpin peptidase inhibitor, clade B (ovalbumin), member 8	1.77	$6.2X10^{-12}$
1577	CYP3A5	Cytochrome P450, family 3, subfamily A, polypeptide 5	2.27	$7.7X10^{-12}$
9829	DNAJC6	DnaJ (Hsp40) homolog, subfamily C, member 6	2.51	$2.9X10^{-11}$
10045	SH2D3A	SH2 domain containing 3A	1.63	$3.4X10^{-11}$
6097	RORC	RAR-related orphan receptor C	1.6	$3.8X10^{-11}$
6542	SLC7A2	Solute carrier family 7 member 2	2.07	$3.9X10^{-11}$
1942	EFNA1	Ephrin-A1	1.83	$3.9X10^{-11}$
22996	TTC39A	Tetratricopeptide repeat domain 39A	2.19	$4.6X10^{-11}$
54463	FAM134B	Family with sequence similarity 134, member B	1.88	$4.7X10^{-11}$
722	C4BPA	Complement component 4 binding protein, alpha	3.57	$4.8X10^{-11}$
22904	SBNO2	Strawberry notch homolog 2 (Drosophila)	1.93	$4.9X10^{-11}$
8714	ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	2.38	$5.3X10^{-11}$
9001	HAP1	Huntingtin-associated protein 1	1.65	$6.6X10^{-11}$
1910	EDNRB	Endothelin receptor type B	2.05	$7X10^{-11}$
6690	SPINK1	Serine peptidase inhibitor, Kazal type 1	2.17	$1.7X10^{-10}$
1824	DSC2	Desmocollin 2	1.79	$2.6X10^{-10}$
11138	TBC1D8	TBC1 domain family, member 8	1.63	$2.8X10^{-10}$

Appendix 16: Top-35 downregulated genes in endometriotic lesions compared to eutopic endometrium from women with endometriosis.

Entrez Id	Gene symbol	Gene name	Fold change	P value
3151	HMGN2	High-mobility group nucleosomal binding domain 2	0.61	$1.8X10^{-13}$
51596	CUTA	CutA divalent cation tolerance homolog (E. coli)	0.53	$1.6X10^{-11}$
27018	NGFRAP1	Nerve growth factor receptor (TNFRSF16) associated protein 1	0.6	$1.4X10^{-10}$
9791	PTDSS1	Phosphatidylserine synthase 1	0.6	$1.6X10^{-10}$
9770	RASSF2	Ras association (RalGDS/AF-6) domain family member 2	0.52	$2.1X10^{-10}$
9500	MAGED1	Melanoma antigen family D, 1	0.45	$2.7X10^{-10}$
26227	PHGDH	Phosphoglycerate dehydrogenase	0.65	$5.2X10^{-10}$
10857	PGRMC1	Progesterone receptor membrane component 1	0.59	$9.2X10^{-10}$
57570	TRMT5	TRM5 tRNA methyltransferase 5 homolog	0.64	$1.9X10^{-9}$
140465	MYL6B	Myosin, light chain 6B, alkali, smooth muscle and non-muscle	0.67	$4.2X10^{-9}$
1628	DBP	D site of albumin promoter (albumin D-box) binding protein	0.63	$6.3X10^{-9}$
5955	RCN2	Reticulocalbin 2, EF-hand calcium binding domain	0.6	$7.2X10^{-9}$
9324	HMGN3	High mobility group nucleosomal binding domain 3	0.63	$1.1X10^{-8}$
23475	QPRT	Quinolinate phosphoribosyltransferase	0.59	$1.3X10^{-8}$
5501	PPP1CC	Protein phosphatase 1, catalytic subunit, gamma isozyme	0.64	$1.7X10^{-8}$
64710	NUCKS1	Nuclear casein kinase and cyclin-dependent kinase substrate 1	0.63	$5.3X10^{-8}$
201254	STRA13	Stimulated by retinoic acid 13 homolog (mouse)	0.76	$6.3X10^{-8}$
10234	LRRC17	Leucine rich repeat containing 17	0.5	$7X10^{-8}$
1278	COL1A2	Collagen, type I, alpha 2	0.62	$7.5X10^{-8}$
64110	MAGEF1	Melanoma antigen family F, 1	0.78	$8.1X10^{-8}$
6424	SFRP4	Secreted frizzled-related protein 4	0.41	$1.1X10^{-7}$
3945	LDHB	Lactate dehydrogenase B	0.56	$1.2X10^{-7}$
1163	CKS1B	CDC28 protein kinase regulatory subunit 1B	0.72	$1.4X10^{-7}$
9315	C5orf13	Chromosome 5 open reading frame 13	0.54	$1.6X10^{-7}$
55830	GLT8D1	Glycosyltransferase 8 domain containing 1	0.69	$1.8X10^{-7}$
8270	LAGE3	L antigen family, member 3	0.62	$1.9X10^{-7}$
4192	MDK	Midkine (neurite growth-promoting factor 2)	0.63	$2X10^{-7}$
3033	HADH	Hydroxyacyl-CoA dehydrogenase	0.65	$2.2X10^{-7}$
6297	SALL2	Sal-like 2 (Drosophila)	0.71	$2.2X10^{-7}$
11331	PHB2	Prohibitin 2	0.71	$2.4X10^{-7}$
5985	RFC5	Replication factor C (activator 1) 5, 36.5kDa	0.75	$2.4X10^{-7}$
6117	RPA1	Replication protein A1, 70kDa	0.62	$2.5X10^{-7}$
10575	CCT4	Chaperonin containing TCP1, subunit 4 (delta)	0.72	$2.7X10^{-7}$
10455	PECI	Peroxisomal D3,D2-enoyl-CoA isomerase	0.63	$2.7X10^{-7}$
79017	GGCT	Gamma-glutamylcyclotransferase	0.59	$3X10^{-7}$

Appendix 17: Top 20 dysregulated pathways in the endometriotic lesions compared eutopic endometrium from women with endometriosis.

Pathway ID	Pathway name	P value	F score
Overall			
GO:0045087	Innate immune response	$1.9X10^{-6}$	16.53
GO:0005275	Amine transmembrane transporter activity	$5.7X10^{-6}$	14.92
GO:0002526	Acute inflammatory response	$7.4X10^{-6}$	14.08
GO:0019724	B cell mediated immunity	$1X10^{-5}$	13.44
GO:0016064	Immunoglobulin mediated immune response	$1X10^{-5}$	13.43
GO:0004896	Hematopoietin/interferon-class (D200-domain) cytokine receptor activity	$1.2X10^{-5}$	13.03
GO:0050817	Coagulation	$1.3X10^{-5}$	12.6
GO:0007596	Blood coagulation	$1.3X10^{-5}$	12.59
GO:0006935	Chemotaxis	$1.3X10^{-5}$	12.54
GO:0042330	Taxis	$1.3X10^{-5}$	12.54
GO:0002253	Activation of immune response	$2X10^{-5}$	12.12
GO:0002460	Adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domain	$2.1X10^{-5}$	11.99
GO:0002250	Adaptive immune response	$2.3X10^{-5}$	11.83
GO:0007204	Elevation of cytosolic calcium ion concentration	$2.3X10^{-5}$	11.76
GO:0051480	Cytosolic calcium ion homeostasis	$2.3X10^{-5}$	11.76
GO:0050776	Regulation of immune response	$2.4X10^{-5}$	11.49
GO:0015171	Amino acid transmembrane transporter activity	$2.9X10^{-5}$	11.29
GO:0007599	Hemostasis	$2.9X10^{-5}$	11.25
GO:0046943	Carboxylic acid transmembrane transporter activity	$3.8X10^{-5}$	11.01
GO:0006959	Humoral immune response	$4.4X10^{-5}$	10.76
Proliferative phase			
GO:0009617	Response to bacterium	$1.4X10^{-5}$	11.05
GO:0002521	Leukocyte differentiation	$1.4X10^{-5}$	11.06
GO:0019955	Cytokine binding	$1.4X10^{-5}$	10.43
GO:0006935	Chemotaxis	$2X10^{-5}$	9.85
GO:0042330	Taxis	$2X10^{-5}$	9.23
GO:0030098	Lymphocyte differentiation	$2.8X10^{-5}$	9.37
GO:0006968	Cellular defence response	$4.1X10^{-5}$	8.58
GO:0042742	Defence response to bacterium	$4.1X10^{-5}$	7.67
GO:0019882	Antigen processing and presentation	$5.5X10^{-5}$	7.23
GO:0002696	Positive regulation of leukocyte activation	$5.5X10^{-5}$	6.64
GO:0050867	Positive regulation of cell activation	$5.5X10^{-5}$	6.02
GO:0004896	Hematopoietin/interferon-class (D200-domain) cytokine receptor activity	$5.5X10^{-5}$	5.92
GO:0007626	Locomotory behaviour	$7.3X10^{-5}$	5.06
GO:0045087	Innate immune response	$8X10^{-5}$	4.82
GO:0042110	T cell activation	$8X10^{-5}$	4.32
GO:0051251	Positive regulation of lymphocyte activation	$1.1X10^{-4}$	3.89

Pathway ID	Pathway name	P value	F score
GO:0002684	Positive regulation of immune system process	$1.2X10^{-4}$	3.53
GO:0030155	Regulation of cell adhesion	$1.2X10^{-4}$	3.32
GO:0042035	Regulation of cytokine biosynthetic process	$1.9X10^{-4}$	2.89
GO:0031401	Positive regulation of protein modification process	$3X10^{-4}$	2.5
Secretory phase: No significant pathways			
Endometriotic lesions: Proliferative Vs Secretory phase			
GO:0006816	Calcium ion transport	$1.5X10^{-7}$	26.05
GO:0044456	Synapse part	$1.5X10^{-7}$	25.41
GO:0045211	Postsynaptic membrane	$1.7X10^{-7}$	24.57
GO:0015276	Ligand-gated ion channel activity	$2X10^{-7}$	23.45
GO:0022834	Ligand-gated channel activity	$2X10^{-7}$	23.45
GO:0006836	Neurotransmitter transport	$2.7X10^{-7}$	22.64
GO:0015674	Di-, tri-valent inorganic cation transport	$8.1X10^{-7}$	20.52
GO:0005230	Extracellular ligand-gated ion channel activity	$8.1X10^{-7}$	20.48
GO:0005262	Calcium channel activity	$1.1X10^{-6}$	19.82
GO:0001505	Regulation of neurotransmitter levels	$1.4X10^{-6}$	19.32
GO:0030594	Neurotransmitter receptor activity	$2X10^{-6}$	18.6
GO:0042165	Neurotransmitter binding	$2X10^{-6}$	18.52
GO:0030136	Clathrin-coated vesicle	$2.4X10^{-6}$	18.19
GO:0007187	G-Protein signaling, coupled to cyclic nucleotide second messenger	$2.9X10^{-6}$	17.79
GO:0008509	Anion transmembrane transporter activity	$3.6X10^{-6}$	17.37
GO:0022843	Voltage-gated cation channel activity	$3.6X10^{-6}$	17.26
GO:0006813	Potassium ion transport	$3.6X10^{-6}$	17.22
GO:0030135	Coated vesicle	$3.9X10^{-6}$	17.03
GO:0005267	Potassium channel activity	$4X10^{-6}$	16.85
GO:0060249	Anatomical structure homeostasis	$4X10^{-6}$	16.85

Appendix 18: Top-35 upregulated genes in the proliferative phase endometriotic lesions compared to eutopic endometrium from women with endometriosis.

Entrez ID	Gene symbol	Gene name	Fold change	P value
4783	NFIL3	Nuclear factor, interleukin 3 regulated	1.95	$3.9X10^{-6}$
3775	KCNK1	Potassium channel, subfamily K, member 1	1.5	$9.4X10^{-6}$
23764	MAFF	v-Maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	2.11	$1.1X10^{-5}$
9473	C1orf38	Chromosome 1 open reading frame 38	1.58	$1.3X10^{-5}$
10221	TRIB1	Tribbles homolog 1 (Drosophila)	1.91	$1.7X10^{-5}$
7127	TNFAIP2	Tumor necrosis factor, alpha-induced protein 2	1.39	$3X10^{-5}$
3976	LIF	Leukemia inhibitory factor (cholinergic differentiation factor)	2.35	$3.8X10^{-5}$
28984	C13orf15	Chromosome 13 open reading frame 15	1.81	$4.1X10^{-5}$
4973	OLR1	Oxidized low density lipoprotein (lectin-like) receptor 1	1.71	$4.3X10^{-5}$
64092	SAMSN1	SAM domain, SH3 domain and nuclear localization signals 1	1.68	$6.7X10^{-5}$
728	C5AR1	Complement component 5a receptor 1	2.18	$1.1X10^{-4}$
1051	CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	1.46	$1.2X10^{-4}$
3914	LAMB3	Laminin, beta 3	2.31	$1.2X10^{-4}$
79838	TMC5	Transmembrane channel-like 5	2.12	$1.4X10^{-4}$
597	BCL2A1	BCL2-related protein A1	2.59	$1.5X10^{-4}$
9766	KIAA0247	KIAA0247	1.34	$1.5X10^{-4}$
1316	KLF6	Kruppel-like factor 6	1.87	$1.5X10^{-4}$
5791	PTPRE	Protein tyrosine phosphatase, receptor type, E	1.51	$1.5X10^{-4}$
6781	STC1	Stanniocalcin 1	2.05	$1.5X10^{-4}$
10123	ARL4C	ADP-ribosylation factor-like 4C	1.84	$1.6X10^{-4}$
55765	C1orf106	Chromosome 1 open reading frame 106	1.85	$1.6X10^{-4}$
3553	IL1B	Interleukin 1, beta	2.31	$1.7X10^{-4}$
6774	STAT3	Signal transducer and activator of transcription 3 (acute-phase response factor)	1.29	$1.7X10^{-4}$
3576	IL8	Interleukin 8	3.92	$2X10^{-4}$
5055	SERPINB2	Serpin peptidase inhibitor, clade B (ovalbumin), member 2	1.63	$2.1X10^{-4}$
1992	SERPINB1	Serpin peptidase inhibitor, clade B (ovalbumin), member 1	1.37	$2.6X10^{-4}$
6692	SPINT1	Serine peptidase inhibitor, Kunitz type 1	1.76	$2.6X10^{-4}$
9123	SLC16A3	Solute carrier family 16, member 3 (monocarboxylic acid transporter 4)	1.48	$3.1X10^{-4}$
2114	ETS2	v-Ets erythroblastosis virus E26 oncogene homolog 2 (avian)	1.43	$3.2X10^{-4}$
1326	MAP3K8	Mitogen-activated protein kinase kinase kinase 8	1.64	$3.2X10^{-4}$
6364	CCL20	Chemokine (C-C motif) ligand 20	3.3	$3.3X10^{-4}$
9518	GDF15	Growth differentiation factor 15	2.41	$3.4X10^{-4}$
29909	GPR171	G protein-coupled receptor 171	1.34	$3.4X10^{-4}$
3383	ICAM1	Intercellular adhesion molecule 1	1.68	$3.5X10^{-4}$
10135	NAMPT	Nicotinamide phosphoribosyltransferase	1.57	$3.5X10^{-4}$

Appendix 19: Top-35 downregulated genes in the proliferative phase endometriotic lesions compared to eutopic endometrium from women with endometriosis.

Entrez Id	Gene symbol	Gene name	Fold change	P value
40	ACCN1	Amiloride-sensitive cation channel 1, neuronal	0.68	$2.1X10^{-3}$
8309	ACOX2	Acyl-CoA oxidase 2, branched chain	0.71	$2.8X10^{-4}$
118	ADD1	Adducin 1 (alpha)	0.84	$2.7X10^{-3}$
501	ALDH7A1	Aldehyde dehydrogenase 7 family, member A1	0.83	$3.6X10^{-3}$
11041	B3GNT1	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1	0.71	$5.4X10^{-5}$
576	BAI2	Brain-specific angiogenesis inhibitor 2	0.76	$3.6X10^{-3}$
8815	BANF1	Barrier to autointegration factor 1	0.82	$6.1X10^{-3}$
54987	C1orf123	Chromosome 1 open reading frame 123	0.83	$2.7X10^{-3}$
79000	C1orf135	Chromosome 1 open reading frame 135	0.77	$2.1X10^{-3}$
92342	C1orf156	Chromosome 1 open reading frame 156	0.74	$1.7X10^{-3}$
51161	C3orf18	Chromosome 3 open reading frame 18	0.79	$5.6X10^{-3}$
55319	C4orf43	Chromosome 4 open reading frame 43	0.77	$2.2X10^{-3}$
63920	C5orf54	Chromosome 5 open reading frame 54	0.7	$1.6X10^{-3}$
729515	C6orf35	Chromosome 6 open reading frame 35	0.84	$1.3X10^{-4}$
65265	C8orf33	Chromosome 8 open reading frame 33	0.82	$5.9X10^{-3}$
23066	CAND2	Cullin-associated and neddylation-dissociated 2 (putative)	0.69	$2.1X10^{-3}$
9994	CASP8AP2	Caspase 8 associated protein 2	0.73	$6.8X10^{-3}$
869	CBLN1	Cerebellin 1 precursor	0.55	$3.7X10^{-3}$
10574	CCT7	Chaperonin containing TCP1, subunit 7 (eta)	0.84	$5.5X10^{-3}$
51293	CD320	CD320 molecule	0.76	$3.4X10^{-4}$
1031	CDKN2C	Cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)	0.67	$2X10^{-3}$
1307	COL16A1	Collagen, type XVI, alpha 1	0.62	$1.2X10^{-3}$
22894	DIS3	DIS3 mitotic control homolog (S. cerevisiae)	0.84	$7X10^{-3}$
56986	DTWD1	DTW domain containing 1	0.78	$5.5X10^{-3}$
8665	EIF3F	Eukaryotic translation initiation factor 3, subunit F	0.9	$7X10^{-3}$
2135	EXTL2	Exostoses (multiple)-like 2	0.73	$3.1X10^{-3}$
83989	FAM172A	Family with sequence similarity 172, member A	0.82	$2.7X10^{-3}$
91775	FAM55C	Family with sequence similarity 55, member C	0.74	$6.5X10^{-3}$
80204	FBXO11	F-box protein 11	0.82	$6.8X10^{-3}$
2318	FLNC	Filamin C, gamma	0.73	$6.7X10^{-4}$
79068	FTO	Fat mass and obesity associated	0.85	$6.2X10^{-4}$
5348	FXYD1	FXYD domain containing ion transport regulator 1	0.64	$6.7X10^{-5}$
51659	GINS2	GINS complex subunit 2 (Psf2 homolog)	0.71	$6.8X10^{-3}$
2736	GLI2	GLI family zinc finger 2	0.7	$5.9X10^{-3}$
9737	GPRASP1	G protein-coupled receptor associated sorting protein 1	0.68	$3.2X10^{-3}$

Appendix 20: Significantly dysregulated genes in the secretory phase endometriotic lesions compared to eutopic endometrium from women with endometriosis.

Entrez ID	Gene symbol	Gene name	Fold change	P value
		Upregulated genes		
71	JUND	Jun D proto-oncogene	1.7	0.00078
165	SRSF3	Serine/arginine-rich splicing factor 3	1.37	0.00078
83692	CYB5R3	Cytochrome b5 reductase 3	1.41	0.00132
1307	UBC	Ubiquitin C	1.51	0.00557
1277	CD99L2	CD99 molecule-like 2	1.28	0.00931
1291	PTRF	Polymerase I and transcript release factor	1.57	0.01020
1293	HNRNPM	Heterogeneous nuclear ribonucleoprotein M	1.35	0.01231
1385	LAMP1	Lysosomal-associated membrane protein 1	1.47	0.02249
1434	COL1A1	Collagen, type I, alpha 1	1.69	0.02337
6387	RPS12	Ribosomal protein S12	1.46	0.02580
1727	EEF1D	Eukaryotic translation elongation factor 1 delta (guanine nucleotide exchange protein)	1.34	0.03132
1634	COL16A1	Collagen, type XVI, alpha 1	2	0.03189
10395	FMOD	Fibromodulin	1.65	0.03240
3301	SRSF3	Serine/arginine-rich splicing factor 3	1.34	0.03281
29940	U2AF1	U2 small nuclear RNA auxiliary factor 1	1.3	0.03322
1843	FBLN1	Fibulin 1	1.87	0.03614
1936	AEBP1	AE binding protein 1	1.57	0.03614
1938	NR4A1	Nuclear receptor subfamily 4, group A, member 1	2.35	0.03746
30845	NDUFAF3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 3	1.25	0.04246
10209	COL6A1	Collagen, type VI, alpha 1	2.01	0.04956
		Downregulated genes		
55898	UNC45A	Unc-45 homolog A (C. elegans)	0.82	0.00572

Appendix 21: Top-35 upregulated genes in the secretory phase endometriotic lesions compared to proliferative phase endometriotic lesions from women with endometriosis.

Entrez Id	Gene symbol	Gene name	Fold change	P value
7705	ZNF146	Zinc finger protein 146	2.57	0.0004
22794	CASC3	Cancer susceptibility candidate 3	2.77	0.00046
1387	CREBBP	CREB binding protein	2.77	0.00046
342096	GOLGA6A	Golgin A6 family, member A	4.65	0.00046
7166	TPH1	Tryptophan hydroxylase 1	4.33	0.00046
253959	RALGAPA1	Ral GTPase activating protein, alpha subunit 1 (catalytic)	2.78	0.00046
84162	KIAA1109	KIAA1109	4.11	0.00046
23230	VPS13A	Vacuolar protein sorting 13 homolog A (S. cerevisiae)	2.89	0.00046
55888	ZNF167	Zinc finger protein 167	3	0.00046
4684	NCAM1	Neural cell adhesion molecule 1	4.77	0.00046
9825	SPATA2	Spermatogenesis associated 2	2.64	0.00046
9668	ZNF615	Zinc finger protein 615	3.55	0.00046
56154	TEX15	Testis expressed 15	4.22	0.00046
54806	AHI1	Abelson helper integration site 1	2.37	0.00064
1859	DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	4.47	0.00064
374354	NHLRC2	NHL repeat containing 2	2.92	0.00064
23648	SSBP3	Single stranded DNA binding protein 3	2.4	0.00064
4598	MVK	Mevalonate kinase	2.06	0.00064
55291	PPP6R3	Protein phosphatase 6, regulatory subunit 3	3.03	0.00064
9373	PLAA	Phospholipase A2-activating protein	2.31	0.00064
254394	MCM9	Minichromosome maintenance complex component 9	2.19	0.00064
10472	ZNF238	Zinc finger protein 238	2.77	0.00067
5098	PCDHGA8	Protocadherin gamma subfamily A, 8	2.67	0.00067
157922	CAMSAP1	Calmodulin regulated spectrin-associated protein 1	2.48	0.00069
9611	NCOR1	Nuclear receptor corepressor 1	2.46	0.00069
3980	LIG3	Ligase III, DNA, ATP-dependent	3.39	0.00069
9831	ZNF623	Zinc finger protein 623	2.69	0.00069
8675	STX16	Syntaxin 16	2.49	0.0007
8708	B3GALT1	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 1	2.89	0.00073
80184	CEP290	Centrosomal protein 290kDa	2.56	0.00073
9362	CPNE6	Copine VI (neuronal)	2.51	0.00073
27332	ZNF638	Zinc finger protein 638	2.64	0.00073
152006	RNF38	Ring finger protein 38	2.69	0.00073
9569	GTF2IRD1	GTF2I repeat domain containing 1	2.33	0.00073
23390	ZDHHC17	Zinc finger, DHHC-type containing 17	3.25	0.00073

Appendix 22: Top-35 downregulated genes in the secretory phase endometriotic lesions compared to proliferative phase endometriotic lesions from women with endometriosis.

Entrez Id	Gene symbol	Gene name	Fold change	P value
397	ARHGDIB	Rho GDP dissociation inhibitor (GDI) beta	0.38	0.0005
1622	DBI	Diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)	0.28	0.0005
2512	FTL	Ferritin, light polypeptide	0.26	0.0005
4792	NFKBIA	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	0.23	0.0005
9144	SYNGR2	Synaptogyrin 2	0.24	0.0005
301	ANXA1	Annexin A1	0.31	0.0006
55615	PRR5	Proline rich 5 (renal)	0.29	0.0006
7905	REEP5	Receptor accessory protein 5	0.32	0.0006
8407	TAGLN2	Transgelin 2	0.37	0.0006
837	CASP4	Caspase 4, apoptosis-related cysteine peptidase	0.28	0.0007
1729	DIAPH1	Diaphanous homolog 1 (Drosophila)	0.34	0.0007
50848	F11R	F11 receptor	0.37	0.0007
4836	NMT1	N-myristoyltransferase 1	0.33	0.0007
8673	VAMP8	Vesicle-associated membrane protein 8 (endobrevin)	0.25	0.0007
6574	SLC20A1	Solute carrier family 20 (phosphate transporter), member 1	0.33	0.0008
6720	SREBF1	Sterol regulatory element binding transcription factor 1	0.33	0.0008
6890	TAP1	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	0.37	0.0008
26472	PPP1R14B	Protein phosphatase 1, regulatory (inhibitor) subunit 14B	0.41	0.0008
9709	HERPUD1	Homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	0.32	0.0008
9592	IER2	Immediate early response 2	0.18	0.0008
3936	LCP1	Lymphocyte cytosolic protein 1 (L-plastin)	0.37	0.0008
10899	JTB	Jumping translocation breakpoint	0.4	0.0008
10490	VTI1B	Vesicle transport through interaction with t-SNAREs homolog 1B (yeast)	0.41	0.0008
10577	NPC2	Niemann-Pick disease, type C2	0.26	0.0009
527	ATP6V0C	ATPase, H+ transporting, lysosomal 16kDa, V0 subunit c	0.31	0.0009
2896	GRN	Granulin	0.24	0.0009
3059	HCLS1	Hematopoietic cell-specific Lyn substrate 1	0.32	0.0009
3106	HLA-B	Major histocompatibility complex, class I, B	0.35	0.0009
8519	IFITM1	Interferon induced transmembrane protein 1 (9-27)	0.26	0.0009
10410	IFITM3	Interferon induced transmembrane protein 3 (1-8U)	0.32	0.0009
6888	TALDO1	Transaldolase 1	0.32	0.0009
23585	TMEM50A	Transmembrane protein 50A	0.4	0.0009
840	CASP7	Caspase 7, apoptosis-related cysteine peptidase	0.49	0.0009
7184	HSP90B1	Heat shock protein 90kDa beta (Grp94), member 1	0.25	0.0009
57136	C20orf3	Chromosome 20 open reading frame 3	0.36	0.0009

Appendix 23: Upregulated genes in the eutopic endometrium from women with compared to women without endometriosis.

Entrez ID	Gene name	P value
TGFB3	Transforming growth factor β-3	0.000018
PTPRR	Protein tyrosine phosphatase, receptor type, R	0.00045
CASP5	Cysteine protease	0.000709
PCDH17	Protocadherin 17	0.0009
ATP1A2	ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide	0.001059
BAIAP2	BAI1-associated protein 2	0.00135
ART3	Putative mono-ADP-ribosyltransferase	0.001419
FN1	Fibronectin 1	0.0018
JUNB	Jun B proto-oncogene	0.002117
CELF1	RNA-binding protein CUG-BP/hNab50 (NAB50)	0.002128
SNCG	Synuclein, gamma	0.002249
CPE	Carboxypeptidase E	0.002699
abcb11	Bile salt export pump	0.002837
CYP2J2	Cytochrome P450, Family 2, Subfamily J, polypeptide 2	0.003149
DPT	Dermatopontin	0.003175
ZIC2	ZIC2 protein	0.003546
IL6ST	Interleukin-6 signal transducer	0.003599
ASCL1	Achaete-scute complex homolog 1 (Drosophila)	0.004233
CA1	Carbonic anhydrase XII	0.004255
PMS2L2	PMS7 mRNA (yeast mismatch repair gene PMS1 homologue)	0.004963
PDE9A	Phosphodiesterase 9A	0.005291
PRIM2	DNA primase (subunit p58)	0.005672
DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	0.006348
IFNA21	Leukocyte (α) interferon	0.00638
SCQ2	Secretogranin II gene	0.007797
TSPAN15	Tetraspanin 15	0.008463
Vhl	von Hippel-Lindau tumor suppressor (VHL) gene	0.008505
efnb1	ELK receptor tyrosine kinase ligand	0.009213
PLEKHB1	Pleckstrin homology domain containing, family B (evectins) member 1	0.009519
MEKK1	MEK kinase 1	0.009921
GPR56	G-protein-coupled receptor 56	0.010576
MG2	Mucin	0.010629
CD1E	CD1 R2 gene for MHC-related antigen	0.011337
FOS	V-fos FBJ murine osteosarcoma viral oncogene homolog	0.011632
ANK2	Ankyrin, Brank-2 protein	0.012044
ITGA2	Integrin α-2 subunit	0.012752
POU3F4	Brain 4 mRNA	0.013459
CCL21	Chemokine (C–C motif) ligand 21	0.013744
ATF6B	G13 protein	0.014167
PGF	Placental growth factor, vascular endothelial growth factor-related protein	0.014799
DNAJB4	Heat shock protein hsp40 homolog	0.014874
KLK1	Kallikrein	0.015581
C11orf9	Chromosome 11 open reading frame 9	0.015854

Appendix 24: Downregulated genes in the eutopic endometrium from women with compared to women without endometriosis.

Entrez ID	Gene name	P value
OGN	Osteoglycin	0.00045
APC2	APCL protein	0.000709
HSPBP1	Hsp70 binding protein HspBP1	0.001419
LGTN	Ligatin	0.002117
NPHP1	Nephrocystin	0.002128
LAT	36-kDa Phosphothyrosine protein	0.002837
KIT	V-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog	0.003175
IFP35	Interferon-induced leucine zipper protein	0.003546
CALR	Calreticulin	0.004233
IER3	IEX-1: radiation-inducible immediate-early gene	0.004255
ICAM2	Cell adhesion ligand for LFA-1	0.004963
SNUPN	Snurportin 1	0.005291
SOD2	Manganese superoxide dismutase	0.005672
PDCD4	Programmed cell death 4 (neoplastic transformation inhibitor)	0.006348
WASP	Wiskott-Aldrich syndrome protein	0.00638
IL15	IL-15 precursor	0.007089
AP2	Cytoplasmic antiproteinase 2	0.007406
GABBR2	GABA-B receptor mRNA	0.007797
ALDH7A1	Aldehyde dehydrogenase 7 family, member A1	0.008463
PP14	Human placental protein 14	0.008505
FBLN2	Fibulin-2	0.009213
DMD	Dystrophin (muscular dystrophy, Duchenne and Becker types)	0.009519
VCAN	Chondroitin sulphate proteoglycan versican, V1 splice-variant	0.009921
EPHX2	Epoxide hydrolase 2, cytoplasmic	0.010576
PLA2G16	HREV107-like protein	0.010629
PNP	Purine nucleoside phosphorylase	0.011337
LOC388796	Small nucleolar RNA, H/ACA box 71C	0.011632
DHRS3	Retinal short-chain dehydrogenase/reductase retSDR1 mRNA	0.012044
PFN2	Profilin 2	0.012688
CLDN10	Claudin-10	0.012752
PIM1	pim-1 Oncogene	0.013459
GPSM2	G-protein signaling modulator 2 (AGS3-like, C. elegans)	0.013744
G0S2	G0S2 protein	0.014167
RAD17	Rad17-like protein	0.014874
PAEP	Pregnancy-associated endometrial α2-globulin	0.015581
FGF13	Fibroblast growth factor 13	0.015854
MITF	A-type microphthalmia associated transcription factor	0.016288

Appendix 25: Top 20 up- and down-regulated pathways in endometriosis.

Pathway ID	Pathway name	P value
Eutopic endometrium from women with and without endometriosis		
GO:0042221	Response to chemical	$6.8X10^{-6}$
GO:0010033	Response to organic substance	$9.9X10^{-6}$
GO:0050896	Response to stimulus	$1.2X10^{-5}$
GO:0009605	Response to external stimulus	$1.2X10^{-5}$
GO:0048856	Anatomical structure development	$3.8X10^{-5}$
GO:0051716	Cellular response to stimulus	$5.7X10^{-5}$
GO:0044767	Single-organism developmental process	$5.8X10^{-5}$
GO:0032502	Developmental process	$7.1X10^{-5}$
GO:0009612	Response to mechanical stimulus	$7.4X10^{-5}$
GO:0044763	Single-organism cellular process	$8.6X10^{-5}$
GO:0007275	Multicellular organismal development	$1.6X10^{-4}$
GO:0048869	Cellular developmental process	$1.8X10^{-4}$
GO:0014070	Response to organic cyclic compound	$2.7X10^{-4}$
GO:0007165	Signal transduction	$3.7X10^{-4}$
GO:0044700	Single organism signaling	$3.9X10^{-4}$
GO:0023052	Signaling	$3.9X10^{-4}$
GO:0044707	Single-multicellular organism process	$3.9X10^{-4}$
GO:0008150	Biological process	4.610^{-4}
GO:0030154	Cell differentiation	$4.7X10^{-4}$
Endometriotic lesions vs. Eutopic endometrium from women with endometriosis		
GO:0008584	Male gonad development	$4.1X10^{-8}$
GO:0046546	Development of primary male sexual characteristics	$4.1X10^{-8}$
GO:0046661	Male sex differentiation	$1.7X10^{-7}$
GO:0008406	Gonad development	$1.1X10^{-6}$
GO:0045137	Development of primary sexual characteristics	$1.2X10^{-6}$
GO:0007548	Sex differentiation	$6.5X10^{-6}$
GO:0048608	Reproductive structure development	$1.6X10^{-4}$
GO:0061458	Reproductive system development	$1.7X10^{-4}$
GO:0060008	Sertoli cell differentiation	$2.8X10^{-4}$
GO:0007530	Sex determination	$4.3X10^{-4}$
GO:0030325	Adrenal gland development	$6.3X10^{-4}$
GO:0048856	Anatomical structure development	$9.7X10^{-4}$
GO:0030154	Cell differentiation	$1.2X10^{-3}$
GO:0044707	Single-multicellular organism process	$1.2X10^{-3}$
GO:0044767	Single-organism developmental process	$1.2X10^{-3}$
GO:0032502	Developmental process	$1.4X10^{-3}$
GO:0003006	Developmental process involved in reproduction	$1.7X10^{-3}$
GO:0048869	Cellular developmental process	$1.9X10^{-3}$
GO:0032501	Multicellular organismal process	$2.1X10^{-3}$
GO:0048731	System development	$3.3X10^{-3}$

Appendix 26: Upregulated genes in the endometriotic lesions compared to eutopic endometrium from women with endometriosis.

Entrez ID	Gene name	P value
C7	Complement factor 7	$5.1X10^{-9}$
CLDN11	Claudin 11	$2.4X10^{-8}$
VIT	Vitirin	$4.5X10^{-8}$
MYH11	Myosin heavy chain 11, smooth muscle	$5.5X10^{-8}$
PNOC	Prepronociceptin	$3.1X10^{-6}$
RARRES1	Retinoic acid receptor responder 1	$4.5X10^{-6}$
DLK1	Delta-like 1 homolog (Drosophila)	$6.5X10^{-6}$
PLA2G2A	Phospholipase A2, group IIA (platelets, synovial fluid)	$1.1X10^{-5}$
IGKC	Immunoglobulin κ constant	$1.6X10^{-5}$
KLHDC8A	Kelch domain containing 8A	$2X10^{-5}$
GATA4	GATA binding protein 4	$2.3X10^{-5}$
SCN7A	Sodium channel, voltage-gated, type VII, alpha subunit	$2.7X10^{-5}$
TCF21	Transcription factor 21	$3.1X10^{-5}$
SPRR2A	Small proline-rich protein 2A	$5.6X10^{-5}$
GSTA1	Glutathione S-transferase A1	$5.8X10^{-5}$
WISP2	WNT1 inducible signaling pathway protein 2	$6.1X10^{-5}$
PLA2G5	Phospholipase A2, group V	$6.8X10^{-5}$
HSD11B1	Hydroxysteroid (11-beta) dehydrogenase 1	$8.7X10^{-5}$
IGJ	Immunoglobulin J polypeptide, linker for alpha and mu	$9.2X10^{-5}$
HOXC9	Homeobox C9 (HOXC9)	0.000301
SYNPO2	Synaptopodin 2	0.000514
LTBP2	Latent transforming growth factor beta binding protein 2	0.000676
CYP17A1	Cytochrome P450, family 17, subfamily A, polypeptide 1	0.001029
CPVL	Carboxypeptidase, vitellogenic-like	0.001065
SFRP2	Secreted frizzled-related protein 2	0.001803
INSL3	Insulin-like 3 (Leydig cell)	0.002057
SMR3B	Submaxillary gland androgen regulated protein 3B	0.002199
MGC27165	Hypothetical protein MGC27165	0.00245
FABP4	Fatty acid-binding protein 4	0.002704
ITLN1	Intelectin 1 (galactofuranose binding)	0.002989
FLJ38894	FLJ38894	0.003086
TAGLN	Transgelin	0.003674
NELL1	NEL-like 1 (chicken)	0.004397
THBS1	Thrombospondin 1	0.004506
NR0B1	Nuclear receptor subfamily 0, group B, member 1	0.005978
NR5A1	Nuclear receptor subfamily 5, group A, member 1	0.00617
HP	Haptoglobin	0.006307

Appendix 27: Downregulated genes in the endometriotic lesions compared to eutopic endometrium from women with endometriosis.

Entrez ID	Gene name	P value
MMP26	Matrix metalloproteinase 26	$2.8X10^{-7}$
C9orf152	Chromosome 9 open reading frame 152	$7.8X10^{-6}$
SCGB2A1	Secretoglobin, family 2A, member 1	$1.1X10^{-5}$
FOXA2	Forkhead box A2	$1.3X10^{-5}$
DLX6	Distal-less homeobox 6	$3.6X10^{-5}$
KIAA1324	KIAA1324	$5.8X10^{-5}$
SCGB1D4	Secretoglobin, family 1D, member 4	$6.2X10^{-5}$
SCGB1D2	Secretoglobin, family 1D, member 2	$6.6X10^{-5}$
CKS2	CDC28 protein kinase regulatory subunit 2	0.000197
FEN1	Flap structure-specific endonuclease 1	0.000446
TYMS	Thymidylate synthetase	0.000494
CCNB1	Cyclin B1	0.000847
MCCC2	Methylcrotonoyl-coenzyme A carboxylase 2 (beta)	0.000901
MSX1	Msh homeobox homolog 1	0.000926
TOP2A	Topoisomerase (DNA) II alpha	0.001124
ASPM	Asp (abnormal spindle)-like, microcephaly associated (Drosophila)	0.001225
CDC2	Cell division cycle 2, G1 to S and G2 to M	0.00149
MSX2	Msh homeobox homolog 2	0.001559
SPDEF	SAM pointed domain containing ets transcription factor	0.001577
ENPP3	Ectonucleotide pyrophosphatase/phosphodiesterase 3	0.001665
UGT8	UDP glycosyltransferase 8	0.001757
CRB3	Crumbs homolog 3 (CRB3)	0.001803
CLDN3	Claudin 3	0.001869
PRSS8	Protease, serine, 8 (prostasin)	0.001927
IHH	Indian hedgehog homolog	0.001946
GABRP	Gamma-aminobutyric acid (GABA) A receptor, pi	0.001966
TRH	Thyrotropin releasing hormone	0.001985
PKHD1L1	Polycystic kidney and hepatic disease 1 (autosomal recessive)-like 1	0.002057
EHF	ets homologous factor	0.002065
AIPL1	Aryl hydrocarbon receptor interacting protein-like 1	0.002199
GJD3	Gap junction protein, chi 1(connexin 31.9)	0.002704
RBM35A	RNA binding motif protein 35A	0.003086
PCDH19	Protocadherin 19	0.003605
DLG7	Discs, large homolog 7 (Drosophila)	0.003674
FLJ21511	FLJ21511	0.004114
RPL12L2	Ribosomal protein L12 pseudogene 11	0.004397
TPD52	Tumor protein D52	0.004506
HSD17B2	Hydroxysteroid (17-beta) dehydrogenase 2	0.005142
ELMO3	Engulfment and cell motility 3 (ced-12 homolog)	0.005407
SCGB1D1	Secretoglobin, family 1D, member 1	0.005978
KIAA0101	KIAA0101	0.006123
SH3YL1	SH3 domain containing, Ysc84-like 1	0.006307

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