Neuroscience 338 (2016) 36–62

REVIEW

GENETIC PREDICTORS OF HUMAN CHRONIC PAIN CONDITIONS

KATERINA ZORINA-LICHTENWALTER,* C. B. MELOTO S. KHOURY AND L. DIATCHENKO

The Alan Edwards Centre for Research on Pain, McGill University, 740 Docteur Penfield, Suite 2300, Montreal, Quebec H3A 0G1, Canada

Abstract—Chronic pain conditions are multifactorial disorders with a high frequency in the population. Their pathophysiology is often unclear, and treatment is inefficient. During the last 20 years, genetic linkage analysis and association studies have made considerable strides toward identifying key molecular contributors to the onset and maintenance of chronic pain. Here, we review the genetic variants that have been implicated in chronic pain conditions, divided into the following etiologically-grouped categories: migraine, musculoskeletal pain disorders, neuropathic pain disorders, and visceral pain disorders. In rare familial monogenic pain conditions several strong-effect mutations have been identified. In contrast, the genetic landscape of common chronic pain conditions suggests minor contributions from a large number of single nucleotide polymorphisms representing different functional pathways. A comprehensive survey of up-to-date genetic association results reveals migraine and musculoskeletal pain to be the most investigated chronic pain disorders, in which nearly half of identified genetic variability alters neurotransmission pathways.

Key words: chronic pain conditions, genetic association studies, GWAS, pain genetics, single nucleotide polymorphisms.

Contents

INTRODUCTION

Chronic pain is a persistent maladaptive condition, estimated to affect up to 30% of the world's population (Elzahaf et al., 2012). Given the reported heritability of 16–50% (Hocking et al., 2012; Nielsen et al., 2012), a substantial proportion of the risk of developing a chronic pain condition is driven by genetic background. To date the search for contributing genetic variants has yielded an outline of a centralized pain-processing system, spearheaded by neurotransmitters and their receptors and modulated by myriad other factors, ranging from inflammatory cytokines to growth factors. Although a gestalt understanding is important for conceptualizing chronic pain, genetic studies have shown a cosegregation of distinct pathologies with their putative causal factors at the gene/protein level. Therefore, it will be helpful to present an overview of the current knowledge about genetics of chronic pain separated by etiology, known or hypothesized.

Numerous genetic risk factors have been identified for musculoskeletal, neuropathic, and visceral conditions, as well as migraine. Among these, migraine and musculoskeletal pain disorders have undergone the most extensive investigation in association studies and

*Corresponding author.
E-mail address: katerina.lichtenwalter@mail.mcgill.ca (K. Zorina-Lichtenwalter).

Abbreviations: CWP, chronic widespread pain; FHM, familial hemiplegic migraine; GWAS, genome-wide association studies; OA, osteoarthritis; SNPs, single nucleotide polymorphisms; TMD, temporomandibular disorder; TMJ, temporomandibular joint; VNTR, variable number of tandem repeats.

http://dx.doi.org/10.1016/j.neuroscience.2016.04.041
0306-4522/

have accumulated the highest number of implicated genetic variants (Fig. 1), although many of them await replication (Fig. 2). The list of chronic pain genes (Table 1) is a snapshot of the incredible complexity of the suspected network of molecular interactions. This list includes genes from catecholaminergic, serotonergic, estrogenic, glutamatergic, GABAergic, purinergic and orexinergic pathways; cytokines; growth factors; and proteinases.

The purpose of this review is threefold: (1) provide an overview of the current state of knowledge in human chronic pain genetics, (2) highlight relevant genetic studies and their outcomes for each pathology category, and (3) summarize the genomically-derived mechanisms of molecular pathophysiology for each category.

Genetic variability

The human genome is replete with genetic variants. The majority are germline mutations, passed from parents to offspring. Less common *de novo* mutations are not inherited from parents and occur in offspring only. Examples of *de novo* mutations in sodium channels, Nav1.7, *SCN9A*, and Nav1.9, *SCN11A*, have been described in post-trauma pain perception, congenital insensitivity to pain, and primary erythromelalgia (Klein et al., 2012; Leipold et al., 2013). Somatic mutations acquired during one's lifetime are not passed on to offspring. These mutations have been implicated in cancer but so far have not been associated with chronic pain conditions.

Rare but drastic mutations have been identified as causal in several monogenic familial disorders, in which mutations in a single gene locus result in the onset of the condition. For example, a frameshift mutation, which severely compromises the function of the encoded protein, has been discovered in the TWIK-related spinal cord potassium channel (TRESK) gene, *KCNK18*, and is responsible for familial migraine with aura (Lafrenière et al., 2010). A more common type of causal mutation in rare familial disorders is a nonsynonymous mutation in one nucleotide that leads to an amino acid change of substantial functional effect in the resulting protein. Sodium channels are the best-known example, extensively studied for their role in monogenic conditions such as erythromelalgia, caused by mutations in *SCN9A* (Yang et al., 2004).

Unlike the rare, high-impact mutations described above, common single nucleotide polymorphisms (SNPs), found in >1% of the population, comprise the vast majority of human genetic association studies. These mutations usually have a very minor phenotypic effect and often exert their effect in concert with specific environmental pressures. Rather than directly causing a chronic pain disease, these SNPs modulate susceptibility to it. The minor allele contributes either risk or protection by increasing (conferring gain-of-function on) or decreasing (conferring loss-of-function on) the activity of the resultant protein. Approximately 90% of SNPs are found in introns or intergenic regions, outside of the protein-coding segments of the gene, outlining their regulatory role. SNPs that fall in the exonic, or protein-coding, region may be either non-synonymous, resulting in a different amino acid, or synonymous, not

Condition	# of associations
Migraine	194
Temporomandibular disorder	36
Fibromyalgia	29
Low back pain	20
Visceral pain	11
Cancer pain	11
Postoperative pain	9
Stress-induced chronic pain	7
Diabetic neuropathic pain	2
Trigeminal neuralgia	1

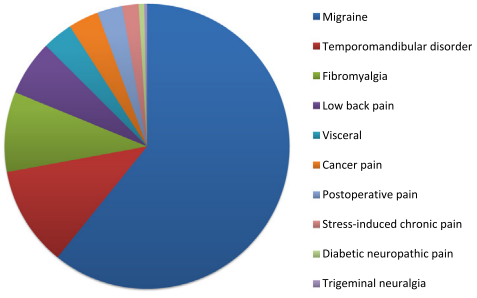

Fig. 1. Chronic pain conditions quantified by the number of genetic association studies. For each condition, the number of published genetic associations is given, including both positive and negative results. Rare Mendelian disorder variants from linkage studies are not included.

Condition	# of citations
Migraine	32
Low back pain	5
Temporomandibular disorder	4
Stress-induced chronic pain	2
Visceral pain	2
Fibromyalgia	2
Postoperative pain	2
Cancer pain	1

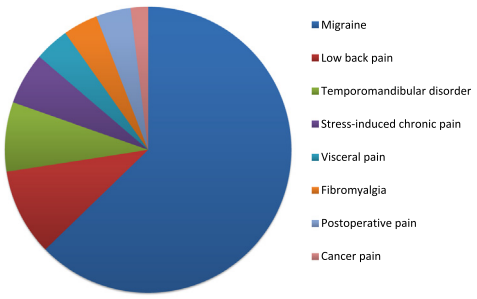

Fig. 2. Chronic pain conditions quantified by the number of genetic loci. Only genes with positive association in a given disorder or group of disorders reported in at least two studies are included, and rare Mendelian disorder variants from linkage studies are not included.

Table 1. Genes reported in genetic association studies of chronic pain conditions

Gene	Function/Pathway	Condition(s)	Citation
ACAN	Structural protein	Low back pain	Solovieva et al. (2007)
ACE	Other	Migraine	Paterna et al. (2000), Kowa et al. (2005), Lea et al. (2005), Lin et al. (2005), Kara et al. (2007), Joshi et al. (2009), Alicakmak et al. (2003), Tronvik et al. (2008), Schürks et al. (2009), Tietjen et al. (2009)
ADAMTSL4	Protein degradation	Migraine	Gormley et al. (2015)
ADARB2	Neurotransmission	Migraine	Cox et al. (2012)
ADRA1D	Neurotransmission	TMD	Smith et al. (2011)
ADRA2C	Neurotransmission	TMD	Smith et al. (2011)
ADRB2	Neurotransmission	TMD	Diatchenko et al. (2006)
		Low back pain	Skouen et al. (2012)
		Fibromyalgia	Vargas-Alarcón et al. (2009)
AJAP1	Other	Migraine	Anttila et al. (2013), Esserlind et al. (2015), Lin et al. (2015), Gormley et al. (2015)
ANKK1	Other	Migraine	Ghosh et al. (2013)
APOA1BP	Metabolism	Migraine	Anttila et al. (2013)
APOE	Metabolism	Fibromyalgia	Reeser et al. (2011)
AR	Other	Visceral	Pontari (2013)
ARMS2	Other	Migraine	Gormley et al. (2015)
ASTN2	Other	Migraine	Freilinger et al. (2012), Esserlind et al. (2015), Gormley et al. (2015)
ATP1A2	Neurotransmission	FHM2	Moskowitz et al. (2004)
ATP5B	Other	Migraine	Anttila et al. (2013)
BDNF	Cellular growth	Migraine	Lemos et al. (2010), Sutherland et al. (2014), Marziniak et al. (2008)
C7orf10	Metabolism	Migraine	Anttila et al. (2013), Esserlind et al. (2015), Lin et al. (2015), Gormley et al. (2015)
CACNA1A	Neurotransmission	FHM1	Ophoff et al. (1996)
CAMK4	Other	TMD	Smith et al. (2011)
CARF	Other	Migraine	Gormley et al. (2015)
CASP9	Apoptosis	Low back pain	Guo et al. (2011), Mu et al. (2013)
CCM2L	Other	Migraine	Gormley et al. (2015)
CCR2	Immune response	Migraine	Schürks et al. (2009)
CCT5	Structural protein	Fibromyalgia	Peters et al. (2013)
CFDP1	Other	Migraine	Gormley et al. (2015)
CFTR	Immune response	Visceral	Sharer et al. (1998), Cohn et al. (1997), Noone et al. (2001)
CGRP	Neurotransmission	Migraine	Lemos et al. (2010)
CHRM2	Neurotransmission	TMD	Smith et al. (2011)
COMT	Neurotransmission	Fibromyalgia	Vargas-Alarcón et al. (2007), Fernández-de-las Peñas et al. (2012), Martínez-Jauand et al. (2013), Barbosa et al. (2012), Cohen et al. (2009), Finan et al. (2011), Matsuda et al. (2010)
		Low back pain	Rut et al. (2014), Jacobsen et al. (2012), Omair et al. (2012, 2015)
		Postoperative pain	Rut et al. (2014)
		Migraine	Cargnin et al. (2013)
		Stress-induced chronic pain	McLean et al. (2011), Bortsov et al. (2014)
		TMD	Erdal et al. (2003), Diatchenko et al. (2005), Smith et al. (2011), Michelotti et al. (2014), Meloto et al. (2015)
CPQ	Neurotransmission	Migraine	I.H.G. Consortium et al. (2010)
CRHBP	Neurotransmission	Stress-induced chronic pain	Linnstaedt et al. (2016)
		Fibromyalgia	Holliday et al. (2010)
CXCL8	Immune response	TMD	Slade et al. (2011)
		Cancer pain	Reyes-Gibby et al. (2007)
DAO	Neurotransmission	Migraine	García-Martín et al. (2015)
DBH	Neurotransmission	Migraine	Lea et al. (2000), Fernandez et al. (2006, 2009), Ghosh et al. (2013)
DOCK4	Other	Migraine	Gormley et al. (2015)
DRD2	Neurotransmission	Migraine	Peroutka et al. (1998), Del Zompo et al. (1998), Ghosh et al. (2013)
DRD4	Neurotransmission	Migraine	Del Zompo et al. (1998), Mochi et al. (2003), de Sousa et al. (2007)
		TMD	Aneiros-Guerrero et al. (2011)
		Fibromyalgia	Buskila et al. (2004)
EDNRA	Other	Migraine	Tzourio et al. (2001), Tikka-Kleemola et al. (2009)
ESR1	Other	TMD	Kang et al. (2007), Ribeiro-Dasilva et al. (2009), Kim et al. (2010), Stemig et al. (2015)
		Migraine	Colson et al. (2004), Oterino et al. (2006), Kaunisto et al. (2006), Oterino et al.

Table 1 (*continued*)

Gene	Function/Pathway	Condition(s)	Citation
			(2008), Corominas et al. (2009), Ghosh et al. (2012), Rodriguez-Acevedo et al. (2013)
		Low back pain	Roh et al. (2013)
ESR2	Other	Migraine	Oterino et al. (2008), Ghosh et al. (2012)
FAM183B	Other	Fibromyalgia	Peters et al. (2013)
FGF6	Immune response	Migraine	Gormley et al. (2015)
FHL5	Other	Migraine	Anttila et al. (2013), Esserlind et al. (2015), Lin et al. (2015), Gormley et al. (2015)
FKBP5	Immune response	Stress-induced chronic pain	Bortsov et al. (2013)
FSHR	Other	Migraine	Oterino et al. (2008)
FUT9	Metabolism	Migraine	Anttila et al. (2013)
GABRB3	Neurotransmission	Migraine	Russo et al. (2005), Netzer et al. (2008)
		Fibromyalgia	Oswell et al. (2008), Smith et al. (2012)
GBP1	Immune response	Fibromyalgia	Smith et al. (2012)
GCH1	Metabolism	Fibromyalgia	Kim et al. (2013)
		Peripheral neuropathy	Hendry et al. (2013)
		Postoperative pain	Tegeder et al. (2006), Kim et al. (2010)
GDF5	Cellular growth	Low back pain	Mu et al. (2013)
		TMD	Xiao et al. (2015)
GJA1	Other	Migraine	Gormley et al. (2015)
GPR149	Other	Migraine	Gormley et al. (2015)
GRIA1	Neurotransmission	Migraine	Formicola et al. (2010), Maher et al. (2013), Cargnin et al. (2014)
GRIA3	Neurotransmission	Migraine	Formicola et al. (2010), Maher et al. (2013)
GRK5	Other	TMD	Smith et al. (2011)
GSTM1	Metabolism	TMD	Aneiros-Guerrero et al. (2011)
HCRTR1	Other	Migraine	Rainero et al. (2011)
HEY2	Other	Migraine	Gormley et al. (2015)
HLA-DRB1	Immune response	Migraine	Rainero et al. (2005)
HPSE2	Metabolism	Migraine	Gormley et al. (2015)
HTR2A	Neurotransmission	TMD	Mutlu et al. (2004), Ojima et al. (2007) ,Smith et al. (2011), de Freitas et al. (2013), Slade et al. (2013)
		Fibromyalgia	Mergener et al. (2011), Holliday et al. (2010), Gürsoy et al. (2001), Bondy et al. (1999)
HTR7	Neurotransmission	Migraine	Cox et al. (2012)
IFRD1	Immune response	TMD	Smith et al. (2011)
IGSF9B	Neurotransmission	Migraine	Gormley et al. (2015)
IL10	Immune response	Postoperative pain	Stephens et al. (2014)
		TMD	Smith et al. (2011)
		Visceral	Shoskes et al. (2002)
IL10RB	Immune response	Cancer pain	Reyes-Gibby et al. (2013)
IL13	Immune response	Cancer pain	McCann et al. (2012)
IL18R1	Immune response	Low back pain	Omair et al. (2013)
IL18RAP	Immune response	Low back pain	Omair et al. (2013)
IL1A	Immune response	Low back pain	Schistad et al. (2014), Omair et al. (2013)
IL1B	Immune response	Migraine	Ylmaz et al. (2010)
		Cancer pain	Reyes-Gibby et al. (2013)
IL1R1	Immune response	Cancer pain	McCann et al. (2012)
IL1R2	Immune response	Postoperative pain	Stephens et al. (2014)
IL1RN	Immune response	Low back pain	Lončar et al. (2013)
IL9	Immune response	Migraine	Schürks et al. (2009)
INSR	Metabolism	Migraine	McCarthy et al. (2001)
ITPK1	Metabolism	Migraine	Gormley et al. (2015)
JAG1	Metabolism	Migraine	Gormley et al. (2015)
KCNAB3	Neurotransmission	Migraine	Lafrenière and Rouleau (2012)
KCNG4	Neurotransmission	Migraine	Lafrenière and Rouleau (2012)
KCNK18	Neurotransmission	Migraine	Lafrenière et al. (2010), Lafrenière and Rouleau (2011)
KCNS1	Neurotransmission	Sensory neuropathy	Hendry et al. (2013)
		Postoperative pain	Costigan et al. (2010), Hendry et al. (2013)
LDLR	Metabolism	Migraine	Mochi et al. (2003), Curtain et al. (2004)
LRP1	Neurotransmission	Migraine	Chasman et al. (2011), Esserlind et al. (2015), Gormley et al. (2015), Ghosh et al. (2013)

(*continued on next page*)

Table 1 (*continued*)

Gene	Function/Pathway	Condition(s)	Citation
LRRIQ3	Other	Migraine	Gormley et al. (2015)
LTA	Immune response	Migraine	Trabace et al. (2002), Asuni et al. (2009), Ghosh et al. (2010), Ishii et al. (2012)
MAOA	Neurotransmission	Fibromyalgia	Gürsoy et al. (2008)
		TMD	Mutlu et al. (2005)
MC2R	Neurotransmission	Fibromyalgia	Holliday et al. (2010)
MED14	Metabolism	Migraine	Gormley et al. (2015)
MEF2D	Apoptosis	Migraine	Freilinger et al. (2012), Esserlind et al. (2015), Gormley et al. (2015)
MMP1	Protein degradation	Low back pain	Song et al. (2008), Jacobsen et al. (2013)
MMP2	Protein degradation	Low back pain	Dong et al. (2007)
MMP3	Protein degradation	Low back pain	Takahashi et al. (2001)
MMP16	Protein degradation	Migraine	Anttila et al. (2013), Esserlind et al. (2015), Gormley et al. (2015)
MNSOD	Other	Visceral	Arisan et al. (2006)
MPPED2	Other	Migraine	Gormley et al. (2015)
MRVI1	Other	Migraine	Gormley et al. (2015)
MTDH	Other	Migraine	I.H.G. Consortium et al. (2010), Freilinger et al. (2012), Gormley et al. (2015)
MTHFD1	Other	TMD	Aneiros-Guerrero et al. (2011)
MTHFR	Metabolism	Migraine	Kowa et al. (2000), Bassi et al. (2003), Kara et al. (2003), Lea et al. (2004), Lea et al. (2005), Oterino et al. (2005), Bottini et al. (2006), Kaunisto et al. (2006), Scher et al. (2006), Todt et al. (2006), Pezzini et al. (2007), Ferro et al. (2008), Schürks et al. (2008), Joshi et al. (2009), Schürks et al. (2009), Tietjen et al. (2009), Liu et al. (2010), An et al. (2013), Azimova et al. (2013)
MTRR	Other	TMD	Aneiros-Guerrero et al. (2011)
MYT1L	Other	Fibromyalgia	Docampo et al. (2014)
NFKBIA	Immune response	Cancer pain	Reyes-Gibby et al. (2009)
NGFR	Cellular growth	Migraine	Ligthart et al. (2011)
NOS3	Neurotransmission	Migraine	Borroni et al. (2006), Schürks et al. (2009)
		Cancer pain	Reyes-Gibby et al. (2013)
NOTCH3	Other	Migraine	Iso et al. (2003), Alva and Iruela-Arispe (2004)
NOTCH4	Other	Migraine	Rubino et al. (2013), Gormley et al. (2015)
NR3C1	Immune response	TMD	Smith et al. (2011)
NRP1	Apoptosis	Migraine	Gormley et al. (2015)
NRXN3	Neurotransmission	Fibromyalgia	Docampo et al. (2014)
NTRK1	Other	Congenital insensitivity to pain	Shatzky et al. (2000), Miura et al. (2000), Indo (2001), Indo et al. (2001), Bodzioch et al. (2001), Bonkowsky et al. (2003), Huehne et al. (2008), Li et al. (2012), Gao et al. (2013), Liu et al. (2014), Yis et al. (2015), Tang et al. (2014), Wang et al. (2015)
OPRM1	Neurotransmission	Stress-induced chronic pain	Ballina et al. (2013), Linnstaedt et al. (2015)
		Low back pain	Hasvik et al. (2014), Omair et al. (2015)
		Postoperative pain	Kolesnikov et al. (2013), Olsen et al. (2012)
		Diabethic neuropathic pain	Cheng et al. (2010)
P2RX7	Neurotransmission	Postoperative pain	Sorge et al. (2012)
		Diabethic neuropathic pain	Ursu et al. (2014)
PGK1	Metabolism	Visceral	Riley and Krieger (2002)
PGR	Other	Migraine	Colson et al. (2005)
PHACTR1	Metabolism	Migraine	Freilinger et al. (2012), Esserlind et al. (2015), Gormley et al. (2015)
PLCE1	Other	Migraine	Gormley et al. (2015)
POMC	Neurotransmission	Fibromyalgia	Holliday et al. (2010)
PRDM16	Other	Migraine	Chasman et al. (2011), An et al. (2013), Fan et al. (2014), Esserlind et al. (2015), Gormley et al. (2015), Ghosh et al. (2013)
PRRT2	Other	FHM	Riant et al. (2012), Dale et al. (2012)
PRSS1	Protein degradation	Visceral	Whitcomb et al. (1996), Gorry et al. (1997), Noone et al. (2001), Simon et al. (2002), Le Marechal et al. (2004), Le Maréchal et al. (2006)
PTGS2	Immune response	Migraine	Dasdemir et al. (2013), Mozaffari et al. (2015)
		Cancer pain	Reyes-Gibby et al. (2009), Reyes-Gibby et al. (2013)
RAMP1	Other	Migraine	Sutherland et al. (2013), Cargnin et al. (2015)
REST	Other	Migraine	Gormley et al. (2015)

Table 1 (*continued*)

Gene	Function/Pathway	Condition(s)	Citation
RNF213	Other	Migraine	Gormley et al. (2015)
RUNX2	Other	TMD	Xiao et al. (2015)
SCN1A	Neurotransmission	FHM3	Dichgans et al. (2005), Persico et al. (2015)
SCN9A	Neurotransmission	Erythromelalgia	Yang et al. (2004), Cummins et al. (2004), Dib-Hajj et al. (2005), Drenth et al. (2005), Li et al. (2005), Michiels et al. (2005), Han et al. (2006), Zhang et al. (2006), Lee et al. (2007), Drenth et al. (2008), Lin et al. (2008), Samuels et al. (2008), Estacion et al. (2009), Han et al. (2009)
		Paroxysmal estreme pain disorder	Fertleman et al. (2006), Dib-Hajj et al. (2008), Estacion et al. (2008)
		Congenital insensitivity to pain	Cox et al. (2006, 2010), Kurban et al. (2010), Klein et al. (2012), Peddareddygari et al. (2014), Mansouri et al. (2014), Shorer et al. (2014)
		Peripheral neuropathy	Dabby et al. (2011), Faber et al. (2012a), Han et al. (2012)
		Fibromyalgia	Vargas-Alarcon et al. (2012)
		Visceral	Reeder et al. (2013)
SCN10A	Neurotransmission	Peripheral neuropathy	Faber et al. (2012b), Huang et al. (2013), Dabby et al. (2016)
SCN11A	Neurotransmission	Congenital insensitivity to pain	Leipold et al. (2013), Phatarakyijnirund et al. (2015)
		Peripheral neuropathy	Huang et al. (2014), Han et al. (2015)
SERPINA6	Immune response	Fibromyalgia	Holliday et al. (2010)
SHMT1	Metabolism	TMD	Aneiros-Guerrero et al. (2011)
SLC24A3	Neurotransmission	Migraine	Gormley et al. (2015)
SLC6A4	Neurotransmission	Fibromyalgia	Offenbaecher et al. (1999)
		Migraine	Ylmaz et al. (2001), Kotani et al. (2002), Gonda et al. (2007), Todt et al. (2006)
		TMD	Herken et al. (2001), Ojima et al. (2007)
		Trigeminal neuralgia	Cui et al. (2014)
SMAD3	Other	TMD	Xiao et al. (2015)
SPINK1	Protein degradation	Visceral	Witt et al. (2000), Pfuetzer et al. (2001), Király et al. (2007)
STAT6	Other	Migraine	Anttila et al. (2013)
TAAR1	Neurotransmission	Fibromyalgia	Smith et al. (2012)
TBC1D7	Cellular growth	Migraine	Anttila et al. (2013)
TGFB1	Cellular growth	TMD	Slade et al. (2011)
		Migraine	Schürks et al. (2009)
TGFBR2	Cellular growth	Migraine	Freilinger et al. (2012), Esserlind et al. (2015), Gormley et al. (2015)
TNF	Immune response	Migraine	Mazaheri et al. (2006), Ghosh et al. (2010), Ylmaz et al. (2010), Ates et al. (2011), Gu et al. (2012), Schürks et al. (2009), Trabace et al. (2002), Asuni et al. (2009)
		Cancer pain	Reyes-Gibby et al. (2009)
TNFRSF1B	Immune response	Migraine	Dong et al. (2012)
		Cancer pain	Reyes-Gibby et al. (2013)
TRPA1	Neurotransmission	Sensory neuropathy	Binder et al. (2012)
TRPM8	Neurotransmission	Migraine	Chasman et al. (2011), Freilinger et al. (2012), Esserlind et al. (2015), Gormley et al. (2015)
TRPV1	Neurotransmission	Migraine	Carreño et al. (2012)
		sensory neuropathy	Binder et al. (2012)
TRPV3	Neurotransmission	Migraine	Carreño et al. (2012)
TSPAN2	Other	Migraine	Anttila et al. (2013), Esserlind et al. (2015), Gormley et al. (2015)
WSCD1	Metabolism	Migraine	Gormley et al. (2015)
YAP1	Apoptosis	Migraine	Gormley et al. (2015)
ZCCHC14	Other	Migraine	Gormley et al. (2015)

Abbreviations: FHM, familial hemiplegic migraine; TMD, temporomandibular disorder.

changing the amino acid. Whether intronic or exonic, synonymous or non-synonymous, most common SNPs are silent and have no clearly observable or discernible phenotypic effect.

Several databases, such as NCBI dbSNP (http://www.ncbi.nlm.nih.gov/snp), the 1000genomes project (http://www.1000genomes.org), and Ensembl (http://www.ensembl.org), inventory known SNPs and annotate

them with genomic location, population distribution, expression, and functional effect, adding disease association information where available. The recently launched Human Pain Genetics Database (http://diatchenko.lab.mcgill.ca/hpgdb) is a manually-curated repository for SNPs in human genes reported to be associated with pain conditions or intermediate phenotypes.

Human genetic studies

With few exceptions, chronic pain does not follow the Mendelian transmission model. Rather, chronic pain pathologies are typically aggregates of endophenotypes, each of which may be governed by Mendelian law. A construct developed for the study of complex diseases in neuropsychiatry, endophenotypes must (1) be heritable, (2) be associated with the disease of interest, (3) be manifest in subjects independently of active pathology, and (4) cosegregate with disease in pedigree studies (Gottesman and Gould, 2003). In this case, endophenotypes are symptoms of chronic pain conditions. They include sleep disturbance, fatigue, depression, cognitive decline, and hypersensitivity to external stimuli.

The two predominant ways geneticists screen human subjects for mutations associated with chronic pain are linkage analysis and association studies. For linkage analysis available family members are phenotyped and genotyped to see which genetic locus or loci will segregate with the disease. This method has been used to identify a rare mutation in *KCNK18*, encoding the above-mentioned potassium channel TRESK (Lafrenière et al., 2010). Naturally, this type of study depends on access to several generations of a pedigree. Linkage analysis is efficient for the identification of rare familial mutations.

Association studies, used to identify common functional SNPs, require large populations of unrelated subjects with the pathology of interest to be matched against a population of healthy controls. Their DNA is genotyped using either a targeted selection or a genome-wide high-density panel of SNPs. Given the high number of subjects needed in order to provide sufficient statistical power, genome-wide association studies (GWAS) are usually done through collaboration of many research institutions. Results from association studies can be further combined in meta-analysis to get reliable association metrics for tested SNPs. The implementation and maturation of large consortia during the past decade have led to valuable online resources, such as NHGRI (https://www.genome.gov) and NCBI dbGaP (http://ncbi.nlm.nih.gov/gap), which offer comprehensive catalogs of GWAS results. However, to date the number of GWAS on chronic pain conditions is very limited. Study design is complicated by lack of standardized chronic pain phenotype definitions, heterogeneity in clinical reporting, and comorbidities (Holliday and McBeth, 2011). Migraine is the exception: four GWAS (I.H.G. Consortium et al., 2010; Chasman et al., 2011; Freilinger et al., 2012; Cox et al., 2012) and three GWAS meta-analyses (Ligthart et al., 2011; Anttila et al., 2013; Gormley et al., 2015) have been reported for this condition. A fibromyalgia GWAS (Docampo et al., 2014) and a GWAS meta-analysis for chronic widespread pain (CWP) (Peters et al., 2013) have been recently published as well.

Animal models

While human studies are limited by accessibility to subjects with the genotypes of interest, in animal models, target genotypes can be engineered and screened. The mouse is the most common model organism in pain genetics. Back-crossing and selective inbreeding are done to isolate a particular locus on a wild-type background. A gene of interest is knocked out, knocked down, or a human clone is knocked in to observe its effect on a particular pathology. Transgenic mouse models have been reviewed in Mogil and Grisel (1998). Certainly, phenotype characterization is more difficult given non-verbal subjects, and genomic and physiological differences between the two species necessarily result in phenotypic discrepancies. Mouse model developers must demonstrate that their models are sufficiently similar to the human condition under study to be informative. Despite these difficulties, a number of models (Mogil, 2009) have been very instrumental in either identifying genes involved in chronic pain conditions or confirming their relevance after identification in a human study. Neuropathic pain models include spared nerve injury (SNI), chronic constriction injury (CCI), diabetic, and cancer pain (Wang and Wang, 2003). Inflammatory pain models use injections of immune system stimulants, such as Freund's adjuvant and carrageenan, as well as nociceptor sensitizer brandykinin, and pro-inflammatory cytokines. Orofacial and visceral chronic pain states are modeled using site-specific injections of inflammatory agents (Krzyzanowska and Avendaño, 2012). Several migraine mouse models have been likewise described. While earlier studies focused on brain structural-anatomical singularities and electrophysiology experiments in transgenic animals with alterations in causal genes (van den Maagdenberg et al., 2004), more recent models have endeavored to find a behavioral proxy for migraine symptoms in mice (Langford et al., 2010).

METHODS

The list of studies reporting genes associated with chronic pain disorders was drawn from the Human Pain Genetics Database (http://diatchenko.lab.mcgill.ca/hpgdb). This list was supplemented with a literature search in Google Scholar for studies reporting suggested association or negative results. For each disorder, the search terms included the name of the disorder and the gene as well as one of the following terms: "genetic association", "variant", or "polymorphism". Studies of disorders in which pain is not the primary symptom, such as diabetes and cancer, were only included if the finding specifically stated association with pain. Publications were screened by title and abstract; in cases where these presented insufficient information, the text of the publication and relevant tables was read. Reviews and

publications reporting duplicate results from the same cohort were excluded.

With the exception of several large populations studies, which are specified below, the majority of the studies conducted to date have been done on small population samples (fewer than 1000 individuals). Additionally, excepting four migraine GWAS (I.H.G. Consortium et al., 2010; Chasman et al., 2011; Cox et al., 2012; Freilinger et al., 2012), three migraine GWAS meta-analyses (Ligthart et al., 2011; Anttila et al., 2013; Gormley et al., 2015), one fibromyalgia GWAS (Docampo et al., 2014), and one CWP GWAS meta-analysis (Peters et al., 2013), all studies were candidate-gene studies or gene panel studies. While the number of GWAS and sequencing studies continues to rise, candidate gene association studies have played an important role in our understanding of the genotypic structure of human pain phenotypes. Although these hypothesis-driven studies risk oversight of untested causal genetic variants and augment the chances of false positive associations (Rivadeneira et al., 2009; Rajasekaran et al., 2013), when replicated in multiple cohorts, they point to functional variants and the direction of their effects.

RESULTS

Migraine

Migraine, a complex and debilitating pain disorder, is estimated to affect up to 25% of women and 8% of men (Launer et al., 1999). Similar to musculoskeletal conditions, up to 50% of migraine etiology has been attributed to genetic factors (Honkasalo et al., 1995). Numerous migraine genetics reviews have been published in the last decade (de Vries et al., 2009; Schürks, 2012; Rudkjobing et al., 2012; Kurth, 2013; Persico et al., 2015), and the number of genes with reported statistically significant association exceeds that of all other chronic pain conditions (Fig. 1). Notably, some of these genes were identified in GWAS. Partly as a testament to its clearly defined diagnostic criteria – lacking for most other pathologies discussed here – migraine is one of the few chronic pain conditions to have undergone GWAS, of which there are four to date (I.H.G. Consortium et al., 2010; Chasman et al., 2011; Cox et al., 2012; Freilinger et al., 2012). The last of these was done in a genetically-isolated Norfolk Island population (Cox et al., 2012). In addition, there have been three meta-analyses (Ligthart et al., 2011; Anttila et al., 2013; Gormley et al., 2015), the last of which is the most comprehensive reported migraine genetic study of individuals with European ancestry, having analyzed a total of 375,000 individuals and having identified 38 loci of susceptibility, replicating 10 previously published associations.

The paradigm of migraine causality continues to shift between vascular dysregulation and neuronal hyperexcitability, as compelling evidence continues to accumulate for both theories. Genetic studies have contributed significantly to the current understanding of its molecular pathophysiology.

Familial hemiplegic migraine (FHM). Rare mutations in three genes have been reported as causal in FHM: *CACNA1A* in FHM1 (Ophoff et al., 1996); *ATP1A2* in FHM2 (Moskowitz et al., 2004); and *SCN1A* in FHM3 (Dichgans et al., 2005). The *CACNA1A*-encoded alpha-1 subunit of a P/Q voltage-gated calcium channel, also reported to be involved in cortical spreading depression, has gain-of-function mutations that lead to channel responsiveness at lower voltages and contribute to a state of neuronal hyperexcitability. *ATP1A1*-encoded alpha-1 subunit of the sodium–potassium ATPase pump affects its ability to pump sodium ions against the concentration gradient, necessary for glutamate and calcium flow (Moskowitz et al., 2004). *SCN1A* encodes the alpha-1 subunit of a voltage-gated neuronal sodium channel, and its minor allele hastens the channel's recovery from fast inactivation, increasing cortical neuron firing frequency (Dichgans et al., 2005). Proline- rich transmembrane protein 2, *PRRT2*, is a recent addition to the list. Mutations in this gene have also been implicated in hemiplegic migraine (Dale et al., 2012; Riant et al., 2012). Not an ion channel like the other three FHM variants, PRRT2 may be involved in neuronal exocytosis and release of neurotransmitters by affecting localization and kinetics of channels such as CACNA1A (Riant et al., 2012). FHM1-3 causal variants and *PRRT2*, discovered through pedigree linkage mapping, are responsible for rare migraine disorders.

Migraine: vascular origins. Genetic association studies have also identified variants with higher frequency and lower effect, thought to be involved in the much more prevalent nonhemiplegic migraine. Unlike the FHM disorders, the hypothesized causality of the more common migraine may or may not be limited to hyper-neuroexcitation. Evidence continues to accumulate for the involvement of the originally-suspected vascular system dysregulation. According to the vascular hypothesis, cogently summarized in Tietjen (2009), a combination of inadequate response to oxidative stress, lower levels of vasodilators, and increased numbers of vasoconstrictors brings about endothelial dysfunction, which may lead to an elevated level of proinflammatory cytokines circulating in the extracellular matrix. Genetic variants supporting vascular dysregulation in migraine include *EDNRA*, encoding endothelin type A receptor (Tzourio et al., 2001; Tikka-Kleemola et al., 2009); *MTHFR*, encoding methylenetetrahydrofolate reductase (Kowa et al., 2000; Bassi et al., 2003; Kara et al., 2003; Lea et al., 2004; Lea et al., 2005; Oterino et al., 2005; Bottini et al., 2006; Scher et al., 2006; Pezzini et al., 2007; Schürks et al., 2008; Schürks et al., 2009; Tietjen et al., 2009; An et al., 2013; Azimova et al., 2013; Liu et al., 2010); *NOS3*, encoding endothelial nitric oxide synthase (Borroni et al., 2006; Schürks et al., 2009); *ACE*, encoding angiotensin-1 converting enzyme (Paterna et al., 2000; Kowa et al., 2005; Lea et al., 2005; Lin et al., 2005; Kara et al., 2007; Joshi et al., 2009); *NOTCH3*, encoding a receptor involved in vascular development and integrity (Iso et al., 2003; Alva and Iruela-Arispe, 2004); *TGFB1*, encoding beta-2 transform-

ing growth factor (Schürks et al., 2009); and *TGFBR2*, encoding beta-2 transforming growth factor receptor (Freilinger et al., 2012; Esserlind et al., 2015; Gormley et al., 2015) (which has not shown an association in a North Indian population (Ghosh et al., 2013)). As further evidence for the involvement of the vascular system in migraine pathophysiology, Winsvold et al. have recently reported a large overlap between associated loci in a multi-study migraine GWAS meta-analysis and coronary artery disease GWAS (Winsvold et al., 2015). Specifically, migraine without aura and coronary artery disease share significantly associated SNPs but in opposite directions.

Migraine: inflammatory markers. A vast number of genetic association studies have implicated a modified inflammatory state in migraine directly by showing a correlation between alleles of cytokines TNF-alpha, *TNF* (Mazaheri et al., 2006; Schürks et al., 2009; Ghosh et al., 2010; Ylmaz et al., 2010; Ates et al., 2011; Gu et al., 2012) (not replicated in Trabace et al. (2002) and Asuni et al. (2009)), and TNF-beta, *LTA*, with migraine (Trabace et al., 2002; Asuni et al., 2009; Ghosh et al., 2010; Ishii et al., 2012). A tumor necrosis factor receptor superfamily member, *TNFRSF1B*, has also been implicated as a risk factor in migraine susceptibility in a Han Chinese population (Dong et al., 2012); as have interleukin 1-beta, *IL1B* (Ylmaz et al., 2010); interleukin 9, *IL9*; chemokine receptor, *CCR2* (Schürks et al., 2009); and prostaglandin endoperoxide synthase 2, *PTGS2* (Dasdemir et al., 2013; Mozaffari et al., 2015).

Migraine: neuronal origins. Current evidence is arguably strongest for susceptibility to migraine lying at the intersection of increased ascending nociceptive signaling and reduced descending inhibition (Akerman et al., 2011). Implicated signaling systems involve glutamatergic, serotonergic, dopaminergic, GABAergic, orexinergic and purinergic transmission.

In the glutamatergic system, whose involvement in migraine has been recently reviewed in Gasparini and Griffiths (2013), AMPA receptors, *GRIA1* (Formicola et al., 2010) (not found to be associated in Cargnin et al. (2014) and Maher et al. (2013)) and *GRIA3* (Formicola et al., 2010; Maher et al., 2013); glutamate receptor *GRM7* (Cox et al., 2012); as well as glutamate-regulating metahedrin, *MTDH* (I.H.G. Consortium et al., 2010; Freilinger et al., 2012; Gormley et al., 2015); lipoprotein receptor, *LRP1* (Chasman et al., 2011; Ghosh et al., 2013; Esserlind et al., 2015; Gormley et al., 2015); myocyte enhancer factor, *MEF2D* (Freilinger et al., 2012; Esserlind et al., 2015; Gormley et al., 2015); and a variant near plasma glutamate carboxypeptidase, *CPQ* (I.H.G. Consortium et al., 2010) have been reported as associated with migraine. Except for the two AMPA receptors, all these genes were top hits in migraine GWAS, replicated in a later GWAS or in subsequent targeted SNP genotyping projects (Freilinger et al., 2012; Esserlind et al., 2015).

The role of serotonergic transmission in migraine has been comprehensively reviewed in Hamel (2007). Serotonin receptor, *HTR7*, has been shown to be associated in a Norfolk Island population GWAS (Cox et al., 2012). Likewise, an association with migraine has been reported for serotonin transporter, *SLC6A4*, in a Turkish population (Ylmaz et al., 2001) and a Japanese population (Kotani et al., 2002). Furthermore, Gonda et al. have reported an association between this locus and migraine comorbid with anxiety (Gonda et al., 2007). However, *SLC6A4* has not been found to be significantly associated in a German cohort (Todt et al., 2006), which may indicate that the effect is race-specific.

Dopaminergic involvement, recently reviewed in Barbanti et al. (2013), is of particular interest given its reported association not only with migraine but also with anxiety and depression (both well-established comorbidities with migraine (Pesa and Lage, 2004; Ligthart et al., 2013)). Peroutka et al. and Del Zompo et al. have discussed dopaminergic pathway-mediated changes in cerebral blood flow (observed during cortical spreading depression) and somatosensory hyperactivity (Del Zompo et al., 1998; Peroutka et al., 1998), which would explain prodromal symptoms such as moodiness, drowsiness, and nausea (Fanciullacci et al., 1999; D'Andrea et al., 2006). Dopamine beta-hydroxylase, *DBH* (Lea et al., 2000; Fernandez et al., 2006, 2009; Ghosh et al., 2013); dopamine D2 receptor, *DRD2* (Del Zompo et al., 1998; Peroutka et al., 1998; Ghosh et al., 2013); and dopamine D4 receptor, *DRD4* (Mochi et al., 2003; de Sousa et al., 2007) (which has been reported not associated in Del Zompo et al. (1998)) have all been implicated in migraine and some of the associated non-headache symptoms. *DRD2* has also been reported to be associated with aura, anxiety and depression (Del Zompo et al., 1998; Peroutka et al., 1998), as well as aortic stenosis, another vascular disorder (Guauque-Olarte et al., 2015). Cargnin et al. have reported on the role of dopamine-degrading catechol-*O*-methyl transferase *COMT* in the response to triptans for migraine (Cargnin et al., 2013).

GABAergic involvement has been demonstrated through association with a GABA-A receptor, *GABRB3* (Russo et al., 2005; Netzer et al., 2008) (not replicated in Oswell et al. (2008)). Additionally, a sodium channel, *SCN1A*, hypoactive variant has been shown to suppress the activity of GABAergic inhibitory interneurons (Persico et al., 2015).

The orexinergic system, whose suspected role in migraine has been recently reviewed in Hoffmann et al. (2015), is implicated through an association between migraine and hypocretin receptor 1, *HCRTR1* (Rainero et al., 2011). Hypocretin is a neuropeptide that regulates arousal, wakefulness, and appetite.

The purinergic system may be involved as well, as evidenced by association for adenosine deaminase, *ADARB2* (Cox et al., 2012) and mitochondrial ATP synthase, *ATP5B* (Anttila et al., 2013), both GWAS results, and purinergic receptor 7, *P2RX7*, which has so far been linked to migraine in a mouse model (Gölöncsér and Sperlágh, 2014).

Further evidence for dysregulated neuronal excitability comes from associations between migraine

Gene	# of citations
MTHFR	15
ACE	6
PRDM16	6
TNF	6
ESR1	5
AJAP1	4
C7orf10	4
DBH	4
FHL5	4
LRP1	4
LTA	4
MMP16	4
TRPM8	4
Other	46

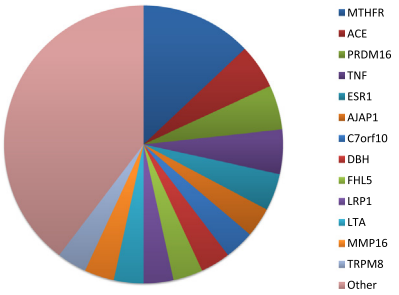

Fig. 3. Genetic loci associated with migraine, quantified by the number of genetic association studies. Only genes with association reported in at least two studies are included in the analysis, and only genes with association reported in at least four studies are listed individually. Genes with fewer reported associations are grouped under "Other." *Abbreviations: MTHFR*, methelynetetrahydrofolate reductase; *ACE*, angiotensin I converting enzyme; *PRDM16*, PR domain-containing 16; *TNF*, tumor necrosis factor; *ESR1*, estrogen receptor 1; *AJAP1*, adherens junctions-associated protein 1; *C7orf10*, succinyl-CoA:glutarate-CoA transferase; *DBH*, dopamine beta-hydroxylase; *FHL5*, four-and-a-half LIM domains 5; *LRP1*, low density lipoprotein receptor related protein 1; *LTA*, lymphotoxin alpha; *MMP16*, matrix metalloproteinase 16; *TRPM8*, transient receptor potential cation channel, subfamily M, member 8 (menthol and cold receptor). Rare Mendelian disorder variants from linkage studies are not included.

Condition	# of citations
Neurotransmission	14
Metabolism	3
Immune response	2
Cellular growth	2
Apoptosis	1
Protein degradation	1
Other	9

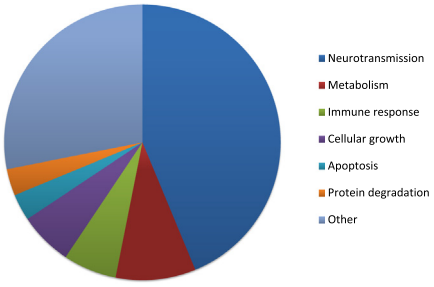

Fig. 4. Functional pathways of genetic loci associated with migraine quantified by the number of loci. Only genes with at least one replicated association are included. Rare Mendelian disorder variants from linkage studies are not included. For genes reported to be involved in multiple pathways, the pathway of the translated gene's most direct involvement was chosen.

Gene	# of citations
COMT	16
HTR2A	7
ESR1	4
ADRB2	3
IL1A	3
OPRM1	3
SLC6A4	3
Other	13

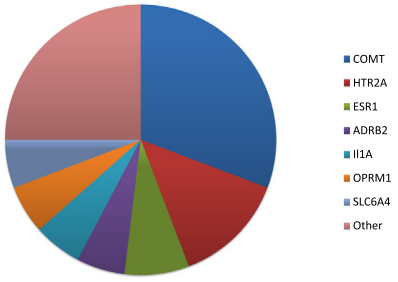

Fig. 5. Genetic loci associated with musculoskeletal pain disorders, quantified by the number of genetic association studies. Only genes reported to be associated with a musculoskeletal pain disorder in at least two studies are included, and only genes with association reported in at least three studies are listed individually. Genes with fewer reported associations are grouped under "Other." *Abbreviations: COMT*, catechol-O-methyl transferase; *HTR2A*, 5-hydroxytryptamine (serotonin) receptor 2A; *ESR1*, estrogen receptor 1; *ADRB2*, beta-2 adrenergic receptor; *GCH1*, GTP cyclohydrolase; *OPRM1*, mu-1 opioid receptor; *SLC6A4*, solute carrier family 6 (serotonin transporter).

and four synaptic plasticity mediators in GWAS: neuronal cation exchanger, *SLC24A3* (Gormley et al., 2015); phosphatase and actin regulator, *PHACTR1*; astrotactin, *ASTN2* (Freilinger et al., 2012; Esserlind et al., 2015; Gormley et al., 2015); and transcription enhancer, *FHL5* (Anttila et al., 2013; Esserlind et al., 2015; Gormley

Condition	# of citations
Neurotransmission	7
Immune response	3
Apoptosis	1
Protein degradation	1
Other	1

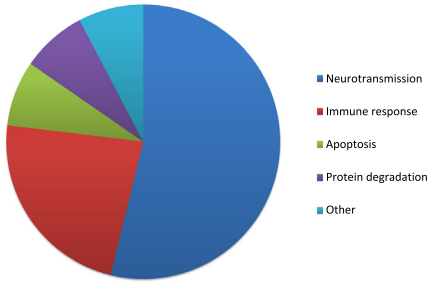

Fig. 6. Functional pathways of genetic loci associated with musculoskeletal disorders quantified by the number of loci. Only genes with at least one replicated association are included. For genes reported to be involved in multiple pathways, the pathway of the translated gene's most direct involvement was chosen.

et al., 2015; Lin et al., 2015). Two recent publications have announced key rare variants in the first gene to be implicated through a linkage mapping pedigree study in nonhemiplegic migraine: *KCNK18*, encoding the potassium channel TRESK (Lafrenière et al., 2010; Lafrenière and Rouleau, 2011). Considering the likelihood of neuroexcitability as the main culprit, the same research group has targeted a panel of ion channels, transporters, exchangers and accessory subunits and found two more potassium channels, *KCNG4* and *KCNAB3*, to be associated with migraine (Lafrenière and Rouleau, 2012). Likewise, Cox et al. (2011) have reported a calcium-activated potassium ion channel, *KCNN3*, variant to be protective against migraine. Lemos et al. have shown a significant interaction between brain-derived neurotrophic factor, *BDNF* (also reported to be associated in Sutherland et al. (2014) but not in Marziniak et al. (2008)), and calcitonin gene-related peptide, *CGRP*, with migraine (Lemos et al., 2010). Histamine-degrading enzyme, diamine decarboxylase, *DAO*, has likewise been reported associated in a Caucasian Spanish population (García-Martín et al., 2015). A mild association has been reported for a variant in *RAMP1* – a CGRP receptor subunit – with migraine in Sutherland et al. (2013) and with migraine changing into medication-overuse headache (Cargnin et al., 2015) (although another group has reported no significant association with medication overuse headache in migraineurs (Ishii et al., 2015).

Other genes that have been identified in genetic association studies include estrogen receptors, *ESR1* (Colson et al., 2004; Oterino et al., 2006, 2008; Ghosh et al., 2012; Rodriguez-Acevedo et al., 2013) (not replicated in Corominas et al. (2009)) and *ESR2* (Oterino et al., 2008) (not replicated in Ghosh et al. (2012)); follicle stimulating hormone receptors *FSHR* (Oterino et al., 2008); progesterone receptor, *PGR* (Colson et al., 2005) (not replicated in Corominas et al. (2009)); low-density lipoprotein, *LDLR* (Mochi et al., 2003) (not replicated in Curtain et al. (2004)); and human leukocyte antigen, *HLA-DRB1* (Rainero et al., 2005); insulin receptor, *INSR* (McCarthy et al., 2001); and ankyrin repeat and kinase domain containing 1, *ANKK1* (Ghosh et al., 2013). Another is *PRDM16*, whose minor allele was one of three significantly associated risk variants coming from the second migraine GWAS (the other two being *TRPM8*, discussed below, and *LRP1*, discussed above) (Chasman et al., 2011). As a transcription factor involved in brown fat development, PRDM16 is a dubious suspect in terms of migraine pathology. This association has, however, been replicated in two Chinese population studies (An et al., 2013; Fan et al., 2014) and two large-population European studies (Esserlind et al., 2015; Gormley et al., 2015). Another replication attempt has reported association in the opposite direction (as a protective variant) (Ghosh et al., 2013), and the same study has also reported positive replication for *LRP1*. In addition, Christensen et al. have reported a role for *PRDM16* in modulating migraineurs' response to treatment with triptans (Christensen et al., 2015). Rubino et al. have reported an association for neurogenic locus notch homolog protein *NOTCH4* with migraine (Rubino et al., 2013), replicated in the largest GWAS meta-analysis to date (Gormley et al., 2015).

Another high-powered meta-analysis of 23,285 individuals with migraine and 95,425 controls demonstrated significant associations with adherens junction-associated protein 1, *AJAP1*; tetraspanin, *TSPAN2*; succinyl–CoA:glutarate–CoA transferase, *C7orf10*; matrix metalloproteinase 16, *MMP16*; apolipoprotein A–I binding protein, *APOA1BP*; fucosyltransferase 9, *FUT9*; interleukin 4-induced activator of transcription 6, *STAT6*; and TBC1 domain family member, *TBC1D7* (Anttila et al., 2013). *AJAP1*, *MMP16* and *C7orf10* have been replicated in a Chinese population (Lin et al., 2015) and two other GWAS (Esserlind et al., 2015; Gormley et al., 2015), which have also replicated the association for *TSPAN2*. Nerve growth factor receptor-encoding *NGFR* has also been found associated in a six-center GWAS meta-analysis in Dutch and Icelandic populations (Ligthart et al., 2011). There has likewise been an association reported for a locus in the mitochondrial DNA with migraine, both with and without aura (Guo et al., 2015).

Migraine has been aptly styled "a cycle of painful signaling and interpretation of nonpainful stimuli as painful" (Karsan and Goadsby, 2015). In line with the latter part of this statement, the reported contribution of primary afferent nociceptor-expressed transient receptor potential receptors adds a central sensitization component to the pathophysiological agglomerate that leads to the migraine disorder. Light, heat, and mechanical sensors – vanilloid receptors, *TRPV1* and *TRPV3* (Carreño et al., 2012), – and a cold temperature and menthol receptor, *TRPM8*, found to be associated with migraine

in a number of GWAS (Chasman et al., 2011; Freilinger et al., 2012; Esserlind et al., 2015; Gormley et al., 2015), suggest that migraineurs' pain is engendered by nociceptive response to physiologically-innocuous stimuli.

Migraine genetics: summary. Among chronic pain conditions, genetic studies of migraine are the most abundant (Fig. 2) and have output at least 30 different genes with replicated association (Fig. 3). The most highly cited gene is *MTHFR*, (Fig. 3) encoding a metabolic mediator that participates in the conversion of homocysteine to methionine. Given that homocysteine derivatives can activate NMDA receptors, there is a connection between *MTHFR* and glutamatergic signaling. Neurotransmission is furthermore the best represented pathway in migraine (Fig. 4). Nevertheless, migraine etiology, which continues to mystify basic and clinical researchers alike, is well represented by the proportional distribution of the other functional pathways in Fig. 4. The large variety of genetic mediators of migraine is consistent with the observed heterogeneous nature of this disorder.

Musculoskeletal conditions

Musculoskeletal pain conditions include temporomandibular disorder (TMD), low back pain, fibromyalgia, and CWP. These disorders, whose heritability estimate is up to 50%, have been recently characterized in terms of their phenotypic and genetic markers in Diatchenko et al. (2013). Additionally, a number of publications have reported a possible role for genetic variants in susceptibility to chronic musculoskeletal pain following a psychologically-traumatizing event, or stress-induced chronic pain.

TMD. TMD is the most frequently occurring class of orofacial pain conditions, with an estimated prevalence between 3% and 12% worldwide (Lavigne and Sessle, 2015). This heterogeneous set of conditions exhibits great interindividual variability in manifestation and response to treatment as well as high comorbidity with other pain conditions. Their etiology, however, is still unclear. There is lack of understanding of orofacial pain mechanisms and their modifying factors (Sessle, 2014), which leads to lack of accurate diagnoses and effective treatment. Given a reported heritability of 27% (Plesh et al., 2011), TMD genetics, reviewed recently in Visscher and Lobbezoo (2015), has emerged as a powerful tool to aid in research and help clinicians deepen their comprehension of causal factors with the ultimate goal of providing effective and suitable treatment to patients.

While most studies to date have been done on small populations, the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) project represents a multi-center, high-powered effort to identify genetic markers contributing to TMD (Dworkin, 2011). Although the OPPERA GWAS is underway (Munzenmaier et al., 2014), to date only targeted genotyping studies have been published by this group on a subset of this cohort and by others. These studies have nevertheless identified a number of genetic variants that implicate catecholaminergic, estrogenic, and serotonergic systems. Evidence also exists for the involvement of cytokines and other molecules in causal pain pathways, but their role is still poorly understood.

Involvement of the catecholaminergic system in TMD is exemplified by *COMT*, the most studied and cited gene in human pain genetics (Mogil, 2012). This gene encodes the catechol-*O*-methyltransferase enzyme, which regulates the levels of catechol neurotransmitters. Its hypoactivity leads to a higher level of epinephrine, which potentiates beta adrenergic receptor-mediated pain signaling (Nackley et al., 2007). *COMT* is a highly polymorphic gene with multiple functional SNPs. The most studied SNP is the non-synonymous *val158met* variation implicated in multiple pain conditions, mood disorders and cognitive function in a number of studies (Goldberg et al., 2003; Zubieta et al., 2003; Tunbridge et al., 2006; McLean et al., 2011; Smith et al., 2011; Michelotti et al., 2014). Furthermore, three major functional haplotypes in the coding region of the gene have shown strong association with response to noxious stimuli and risk of myogenous TMD in humans (Diatchenko et al., 2005). A recently identified regulatory SNP in the 3′-untranslated region of *COMT* has led to the discovery of a functional alternate isoform of the COMT enzyme, shown *in vitro* to have preferred enzymatic activity toward dopamine, which may contribute to pain by lowering the level of dopamine rather than increasing the level of epinephrine (Meloto et al., 2015). On the other hand, variants in *COMT* have been reported not to be significantly associated with TMD in a Turkish population (Erdal et al., 2003).

Adrenergic receptor involvement has also been reported. Both hyperactive and hypoactive variants of beta adrenergic receptor *ADRB2* have been shown as possible modulators of TMD risk (Diatchenko et al., 2006). Two alpha adrenergic receptors, *ADRA2C* and *ADRA1D*, have been reported as possibly significant TMD risk modulators (Smith et al., 2011).

Two common genetic variants in the human estrogen receptor *ESR1* have been implicated in painful temporomandibular joint (TMJ) disk displacement in a Brazilian female population (Ribeiro-Dasilva et al., 2009). One of the associations has been replicated in Korean patients with TMJ osteoarthritis (TMJ-OA) (Kang et al., 2007), although another Korean cohort with TMD has shown a trend but no statistically significant association for the same SNP (Kim et al., 2010). Recently, another study has shown these variants as associated with the TMJ degenerative process, possibly via modulation of ESR1 activity in the bone (Stemig et al., 2015). Given that TMJ is a well-documented target tissue for estrogen (Abubaker et al., 1993; Yamada et al., 2003; Galal et al., 2008), it is not surprising to find estrogen receptor genetic variants involved in the pathophysiology of its disorders.

The serotonergic system has been implicated in TMD pathophysiology via polymorphisms in serotonin receptor, *HTR2A*, (Mutlu et al., 2004; Smith et al., 2011; de Freitas et al., 2013; Slade et al., 2013) (not replicated in Ojima et al. (2007)), and serotonin transporter, *SLC6A4*, which have shown association in different populations (Herken

et al., 2001; Ojima et al., 2007). *SLC6A4* has a 44bp insertion/deletion polymorphism within the promoter region, presenting two allelic forms, long (*l*) and short (*s*). It also has a polymorphic region of a 17bp-variable number of tandem repeats (VNTR) in its second intron. Both polymorphic regions have shown association with TMD: the promoter region in a Japanese population (Ojima et al., 2007) and VNTR in a Turkish population (which has not shown an association for the promoter region) (Herken et al., 2001).

Numerous studies have shown that levels of proinflammatory cytokines are heightened in the TMJ fluid of TMD patients (Kubota et al., 1998; Alstergren, 2000) and that these levels correlate with greater pain sensitivity (Ferreira et al., 1988; Salemi et al., 2003; Sommer and Kress, 2004; Alexander et al., 2005), perceived stress (Maes et al., 1998) and depression (Raison et al., 2006), all of which are phenotypes associated with TMD (Maixner et al., 1998; Yap et al., 2002; Slade et al., 2007; Fillingim et al., 2013). In addition, elevated levels of proinflammatory cytokines have been consistently reported in circulating blood of patients with widespread pain (Wallace et al., 2001; Salemi et al., 2003). Genetic evidence for the involvement of cytokines in TMD has been therefore explored and reported (Slade et al., 2011). While no individual SNPs have shown association with TMD, two SNPs within the interleukin 8 gene, *CXCL8*, interacted similarly and significantly with a transforming growth factor *TGFB1* SNP, producing the greatest effect on TMD with widespread pain. A variant in interleukin 10, *IL10*, has also shown suggestive association (Smith et al., 2011).

Several loci have shown association as part of the OPPERA case-control study. DNA from chronic TMD patients was screened using a SNP panel of 358 genes implicated in pain through modulation of nociception, psychological state or inflammatory response. Of the top nine SNPs showing nominal statistically significant association, three are in the glucocorticoid receptor, *NR3C1*; one in serotonin receptor 2A, *HTR2A* (discussed above); one in muscarinic cholinergic receptor 2, *CHRM2*; two in calcium/calmodulin-dependent protein kinase 4, *CAMK4*; one in the interferon-related developmental regulator 1, *IFRD1*; and one in G protein-coupled receptor kinase 5, *GRK5* (Smith et al., 2011). Another study, designed under the hypothesis that TMD is a multifactorial syndrome related to a critical period of human life with a genetic and epigenetic basis, has investigated the possible involvement of 14 genes related to the folate cycle in TMD (Aneiros-Guerrero et al., 2011). Three genes encoding enzymes in the folate metabolizing pathway – serine hydroxymethyltransferase 1, *SHMT1*; methylenetetrahydrofolate dehydrogenase, *MTHFD1*; and methionine synthase reductase, *MTRR* – have shown significant associations with TMD. Their risk alleles were associated with odds ratios of having TMD that ranged from 2.35 to 3.99. In addition, the authors have reported that a gene-deletion polymorphism in *GSTM1*, encoding mu glutathione-S-transferase (which is associated with inflammatory oxidative stress), and the dopamine D4 receptor, *DRD4*, long allele of 48bp-repeat were associated with increased risk of TMD.

A recent study has investigated the association of SNPs occurring in five genes known to be important regulators of the TGF-beta signaling pathway, which plays a well-established role in the control of chondrocyte differentiation, matrix synthesis and homeostasis, and TMJ-OA. Of these, growth differentiation factor 5, *GDF5*; SMAD family member 3, *SMAD3*; and runt-related transcription factor 2, *RUNX2* were associated with the pathogenesis of TMJ-OA (Xiao et al., 2015). GDF5 is known to play a key role in bone and cartilage morphogenesis as well as joint formation, and the same genetic variant has been previously associated with knee osteoarthritis (OA) in Europeans and Asians (Miyamoto et al., 2007; Chapman et al., 2008). SMAD3 is a transcriptional modulator activated by TGF-beta that is crucial to the integrity of articular cartilage, and genetic variants in this gene have been implicated in pathogenesis of knee OA in European and northeastern Chinese populations (Valdes et al., 2010; Liying et al., 2013). Lastly, RUNX2 is essential for osteoblast differentiation and skeletal morphogenesis. Its contribution to OA has been suggested in a large GWAS in Europeans (arcOGEN Consortium, 2012).

In light of all the reported genetic associations, the suggested pathophysiology of TMD pain is modulated by pain regulators, inflammation-mediating cytokines, and relevant tissue morphogenesis proteins.

Low back pain. Low back pain, whose heritability is estimated to be up to 46% (Battié et al., 2007) is mainly caused by disk disease (Sambrook et al., 1999) and characterized by the desiccation of the spinal disk matrix (Guo et al., 2011). Perhaps unsurprisingly, it has been associated with variants of genes encoding apoptosis-mediating caspase, *CASP9* (Guo et al., 2011; Mu et al., 2013), and extracellular protein digestion enzyme, matrix metalloproteinase, *MMP1* (Song et al., 2008; Jacobsen et al., 2013). Upstream of pathological proteoglycan degradation is the overactive mixture of proinflammatory cytokines, namely associated interleukins: interleukin 1A, *IL1A* (Solovieva et al., 2004; Omair et al., 2013; Schistad et al., 2014) (which is also associated with treatment response (Omair et al., 2013)); interleukin 1 receptor antagonist, *IL1RN* (Solovieva et al., 2004; Lončar et al., 2013); and interleukin 18 receptor subunits encoded by *IL18R1* and *IL18RAP*, both of which modulate response to low back pain treatment (Omair et al., 2013). Other associated genes include growth differentiation factor 5, *GDF5*, which participates in skeletal tissue differentiation (Mu et al., 2013); beta-2 adrenergic receptor, *ADRB2*, which is associated with low back pain comorbid with neck pain (Skouen et al., 2012); catechol-*O*-methyltransferase, *COMT* (Rut et al., 2014; Jacobsen et al., 2012; Omair et al., 2012, 2015); estrogen receptor 1, *ESR1* (Roh et al., 2013); guanosine triphosphate cyclohydrolase, *GCH1* (Tegeder et al., 2006); and mu opioid receptor, *OPRM1* (Hasvik et al., 2014) (although association of this gene with low back pain has not been replicated in Omair et al. (2015). The results of genetic

association studies outline a pathophysiology centered on disrupted tissue remodeling, with pain possibly resulting from an overabundance of proinflammatory signaling.

Fibromyalgia and CWP. Fibromyalgia is diagnosed based on the presence of chronic widespread musculoskeletal pain with tenderness in at least 11 of 18 sites on the body, fatigue, and sleep disturbance, and it is frequently comorbid with mood disorders and other chronic pain disorders (Mease, 2005; Lee et al., 2012). Given its heritability of approximately 50% (Markkula et al., 2009), genetic studies may provide valuable insight into the pathophysiology of fibromyalgia. Implicated genes show an over-representation of monoaminergic pathway members: dopamine D4 receptor, *DRD4* (Buskila et al., 2004); catechol-*O*-methyltransferase, *COMT* (Vargas-Alarcón et al., 2007; Fernández-de-las Peñas et al., 2012; Martínez-Jauand et al., 2013; Barbosa et al., 2012; Cohen et al., 2009; Finan et al., 2011; Matsuda et al., 2010); monoamine oxidase, *MAOA* (Gürsoy et al., 2008); beta-2 adrenergic receptor, *ADRB2* (Vargas-Alarcón et al., 2009); serotonin transporter, *SLC6A4* (Offenbaecher et al., 1999); serotonin receptor 2A, *HTR2A* (Bondy et al., 1999; Gürsoy et al., 2001; Holliday et al., 2010; Mergener et al., 2011); GTP cyclohydrolase, *GCH1*, an enzyme critical to dopamine, serotonin, and nitric oxide production (Kim et al., 2013); and trace amine associated receptor, *TAAR1* (Smith et al., 2012), a G protein-coupled receptor with a regulatory role in dopaminergic neurotransmission (Miller, 2011). Other associations include genes encoding proteins more or less directly involved in neuronal inhibition and excitation, namely gamma-aminobutyric acid (GABA) A receptor, *GABRB3*, Smith et al. (2012); sodium channel NaV1.7, *SCN9A* (Vargas-Alarcon et al., 2012); and two genes identified in a fibromyalgia GWAS and awaiting replication: myelin transcription factor 1-like, *MYT1L*, which has a role in neuronal differentiation, and neurexin, *NRXN3*, a synaptic scaffolding stabilizer involved in glutamatergic and GABAergic neurotransmission (Docampo et al., 2014). Additionally, associations for fibromyalgia have been reported for apolipoprotein, *APOE* (Reeser et al., 2011), and guanylate binding protein, *GBP1* (Smith et al., 2012), a possible contributor to inflammatory disease (de Buhr et al., 2006).

CWP, which substantially correlates with fibromyalgia, is defined as pain present in the axial skeleton and in two contralateral bodily quadrants for at least three months (Gupta et al., 2007). A study targeting genes of the HPA axis in CWP has found an association for glucosteroid binding globulin, *SERPINA6*; corticotropin-releasing hormone-binding protein, *CRHBP*; pro-opiomelanocortin, *POMC*; and adrenocorticotropic hormone receptor, *MC2R* (Holliday et al., 2010). A subsequent GWAS meta-analysis conducted by the same group has found a locus of susceptibility to CWP in a non-conding region between the chaperonin-containing T-complex polypeptide 1 (TCP1)-complex-5 gene, *CCT5*, and FAMily with sequence similarity 183 member B gene, *FAM183B* (Peters et al., 2013). While the function of the latter protein is not known, CCT5 is a structural scaffolding subunit that interacts with protein phosphatase PP4C and may be involved in central sensitization (Peters et al., 2013). Together, the genetic landscapes of fibromyalgia and CWP implicate a rewired nociceptive signaling system, possibly disrupted by excessive stress response.

Stress-induced chronic pain. Recently, a number of studies have shown an overlap of symptoms between post-traumatic stress disorder and musculoskeletal pain conditions (Cohen et al., 2002; Afari et al., 2008). Associations with glucocorticoid receptor co-chaperone, *FKBP5* (Bortsov et al., 2013), and corticotropin releasing hormone-binding protein, *CRHBP* (Linnstaedt et al., 2016), two HPA axis-related genes, as well as mu opioid receptor, *OPRM1*, and chronic musculoskeletal pain following a motor vehicle collision have been reported in a cohort of 950 Caucasian Americans (Linnstaedt et al., 2015) with replication in a sexual assault survivors' cohort for *FKBP5* (Bortsov et al., 2013). The same study has also shown that catechol-*O*-methyltransferase, *COMT*, is associated with musculoskeletal pain several weeks following motor vehicle collision (McLean et al., 2011; Bortsov et al., 2014). Ballina et al. have furthermore reported a correlation between the same *OPRM1* variant, A118G, and muscle pain after sexual assault (Ballina et al., 2013). They have also shown that widespread pain after a motor vehicle collision is associated with pre-accident depression, suggesting that pain was a factor of the patient's psychological characteristics (presumably a proxy for genetic predisposition) rather than tissue injury (Bortsov et al., 2013). In sum, these findings suggest that genetic variability in the endogenous stress-management and analgesia systems modulate susceptibility to musculoskeletal pain conditions triggered by stress and psychological trauma.

Musculoskeletal condition genetics: summary. The above overview of genes associated with musculoskeletal chronic pain conditions highlights a possible underlying pathophysiology. By the number of reports, the contribution from the catecholaminergic system, represented by *COMT* and *ADRB2* associations, is seconded by the involvement of the serotonergic system, exemplified by associations with *HTR2A* and *SLC6A4* (Fig. 5). In terms of functional pathways, neurotransmission is the most common contributor (Fig. 6), followed by immune response mediators. While neurotransmitters and inflammatory cytokines are directly involved in pain signaling, the other three functional groups may contribute to musculoskeletal conditions by increasing susceptibility to the underlying tissue damage.

Neuropathic pain disorders

Neuropathic pain disorders result from nerve dysfunction. The effect of genetic contributors differs according to the origin of this dysfunction. In rare monogenic disorders, somatosensory function is maligned by causal mutations in a single gene. The more common disorders with a chronic neuropathic component are cancer, diabetes, postoperative pain, and trigeminal neuralgia. For this

class of conditions, genetic variants have been shown to modify an individual's susceptibility to neuropathic pain on the background of a different underlying cause.

Rare neuropathic pain disorders. Rare neuropathic pain conditions fall into two categories: painless disorders and painful disorders. Congenital insensitivity to pain with anhidrosis, or inability to sense and respond to noxious stimuli and to sweat, was the first monogenic neuropathic disorder to be reported. The causal mutations were identified in the *NTRK1* gene, which encodes neurotrophic tyrosine kinase receptor (Indo et al., 1996), an extensively replicated finding (Shatzky et al., 2000; Miura et al., 2000; Bodzioch et al., 2001; Indo, 2001; Indo et al., 2001; Bonkowsky et al., 2003; Huehne et al., 2008; Li et al., 2012; Gao et al., 2013; Liu et al., 2014; Yis et al., 2015; Tang et al., 2014; Wang et al., 2015). A related disorder, congenital insensitivity to pain, has been reported to be caused by loss-of-function mutations in sodium channel Nav1.7-encoding *SCN9A* (Cox et al., 2006, 2010; Kurban et al., 2010; Klein et al., 2012; Peddareddygari et al., 2014; Mansouri et al., 2014; Shorer et al., 2014). Interestingly, gain-of-function mutations in another sodium channel, Nav1.9, *SCN11A*, have also been implicated in this condition (Leipold et al., 2013; Phatarakyijnirund et al., 2015). Hyperactivity in Nav1.9 prolongs cell membrane depolarization thereby inactivating Nav1.7 and Nav1.8 – the drivers of the action potential in nociceptive neurons – and blocking pain signal transmission.

Painful rare neuropathic pain disorders include erythromelalgia, characterized by painful swelling and severe redness in feet and hands, and paroxysmal extreme pain disorder, characterized by rectal, periocular and perimandibular pain. Causal *SCN9A* mutations in erythromelalgia, discovered (Yang et al., 2004) and replicated in a number of Chinese Asian families (Li et al., 2005; Han et al., 2006; Zhang et al., 2006; Lee et al., 2007; Lin et al., 2008) and Caucasian families (Dib-Hajj et al., 2005; Drenth et al., 2005; Michiels et al., 2005; Drenth et al., 2008; Samuels et al., 2008) have been shown to change the electrophysiological properties of dorsal root ganglion (DRG) neurons, believed to affect pain sensitivity (Cummins et al., 2004; Dib-Hajj et al., 2005; Estacion et al., 2009). The effects of paroxysmal extreme pain disorder causal mutations (Fertleman et al., 2006; Dib-Hajj et al., 2008; Estacion et al., 2008) have been postulated to lie on a physiological continuum with erythromelalgia. Estacion et al. have demonstrated that alleles responsible for the former condition contribute to impaired fast inactivation in pain-transmitting neurons, while those responsible for the latter condition contribute to a lower firing threshold, slow deactivation and enhanced ramp currents (Estacion et al., 2008).

Cancer pain. Unlike the rare conditions discussed above, in which chronic pain is caused by genetic mutations of large effect in one gene locus, genetic variants contributing to cancer pain are found in several loci and their effect on pain is much more moderate. The cause of cancer pain is usually a growing tumor directly stimulating nociceptors, nerve damage during chemotherapy (Costigan et al., 2009), and/or inflammatory cytokines released by cancerous cells (Reyes-Gibby et al., 2007). Interleukin-8, *CXCL8* (Reyes-Gibby et al., 2007); interleukin 1 receptor, *IL1R1*; and interleukin 13, *IL13* (McCann et al., 2012), have been reported to be associated with cancer pain severity. Reyes-Gibby et al. have reported on the effect of inflammation-related gene polymorphisms on lung cancer pain severity, with associations for prostaglandin-endoperoxide synthase 2, *PTGS2*; tumor necrosis factor, *TNF*; and NF-kappa B inhibitor alpha, *NFKBIA*, with severe pain (Reyes-Gibby et al., 2009). The additive effect of variants in *NOS3*, *IL1B*, *TNFRSF1B*, *PTGS2*, and *IL10RB* has been reported to be implicated in the severe symptom cluster in cancer patients, characterized by high pain intensity, depression, and fatigue (Reyes-Gibby et al., 2013). As with diabetes, while it may not be directly involved in the pathophysiology of the underlying condition, hypersensitivity of the body's defense system appears to be conducive to more pain accompanying cancer.

Diabetic neuropathy. Diabetic neuropathy, characterized by pain at one extreme and insensitivity at the other is observed in up to 50% of diabetic patients (Tesfaye and Selvarajah, 2012). Exacerbated by prolonged diabetic condition, glycemic mismanagement (Tesfaye et al., 1996), and disruption of nerve microvasculature (Tesfaye and Selvarajah, 2012) this neuropathy presents as a multifactorial pathology that is likely to be substantially driven by genetic factors. Unfortunately, diabetic pain genetic association studies are scarce, and existing results have to date painted a far-from-complete picture of its pathophysiology. Nevertheless, it is noteworthy that a hypofunctional polymorphism in mu opioid receptor, *OPRM1*, is associated with foot ulcer pain in diabetic patients (Cheng et al., 2010), while hyperfunctional variants in purinergic receptor 7, *P2RX7*, are reported to be associated with higher pain sensitivity in diabetic neuropathic women (Ursu et al., 2014). Insufficient endogenous pain regulation (*OPRM1*) and excess high alert signaling (*P2RX7*) appear to contribute to baseline nociceptive hypersensitivity, which exacerbates diabetes-related pain.

Postoperative pain. Postoperative pain is usually considered persistent, or chronic, when it is reported at least three months after surgery. The complementary nociceptive and inhibitory systems are implicated in several examples from postoperative pain studies: Kim et al. have reported an association between a variant in GTP hydrolase, *GCH1*, and postoperative pain (Kim et al., 2010); Tegeder et al. have identified an association between postoperative pain and a haplotype of the same gene (Tegeder et al., 2006) (not replicated either at the SNP or haplotype level in Hendry et al. (2013)); and two groups have reported that mu opioid receptor, *OPRM1*, genotypes predict the extent of chronic postoperative pain (Kolesnikov et al., 2013; Olsen et al., 2012). The latter group has shown that the effect of the *OPRM1* variant is sex-specific, such that allele G118 confers risk of pain in

women but correlates with less pain in men. Similarly, a variant in voltage-gated potassium channel subunit, *KCNS1*, has been reported as correlated with postoperative chronic pain intensity in two limb amputation cohorts and one post-mastectomy cohort (Costigan et al., 2010). Another post-mastectomy cohort study (Sorge et al., 2012) has reported an association for a purinergic receptor 7, *P2RX7*, variant. Additionally, a *COMT* polymorphism has been reported to be associated with pain one year after lumbar discectomy (Rut et al., 2014).

Genetic variants of inflammatory cytokines have also been demonstrated to play a role in the risk of neuropathic pain following surgery. Stephens et al. have reported an association between a SNP of interleukin 1 receptor, *IL1R2*, and a haplotype within interleukin 10, *IL10*, with persistent breast pain after surgery for breast cancer (Stephens et al., 2014).

Trigeminal neuralgia. Trigeminal neuralgia is the most common type of neuralgia in adults with an estimated annual incidence of 4–13 per 100,000 people (Katusic et al., 1991; MacDonald et al., 2000). Trigeminal neuralgia is characterized by sudden, usually unilateral, severe, brief, stabbing recurrent episodes of pain within the distribution of one or more branches of the trigeminal nerve, triggered by innocuous stimuli (Krafft, 2008). To date, the precise mechanisms of trigeminal neuralgia remain unclear, and only a few studies have been conducted on the genetics of this condition.

The role of the serotonin transporter, *SLC6A4*, 44bp insertion/deletion polymorphism in susceptibility to trigeminal neuralgia and its clinical features, especially the pain severity and treatment response to analgesics, has been recently investigated (Cui et al., 2014). The *s* variant carriers had a significantly higher risk of trigeminal neuralgia pain severity and of carbamazepine treatment failure. These findings are contrary to those reported for TMD (Ojima et al., 2007); however, chronic pain conditions of musculoskeletal and neuropathic origins have substantially different components, and this apparent contradiction is not surprising.

Other painful peripheral neuropathic conditions. Several other peripheral neuropathic pain conditions have been reported. Haplotypes in voltage-gated potassium channel subunit, *KCNS1*, have shown association with pain intensity in HIV-associated sensory neuropathy among black South Africans (Hendry et al., 2013). Channels, *TRPA1* and *TRPV1*, have been reported to affect somatosensory sensitivity in neuropathic pain patients who suffered from a variety of neuropathic conditions (Binder et al., 2012). *SCN9A* has likewise been reported to be associated with unexplained chronic neuropathic pain (Dabby et al., 2011).

Three sodium channels have also been reported to be associated with a more common neuropathic pain condition, painful small-fiber neuropathy. Affecting small-diameter A-delta and C fibers and characterized by sudden bouts of pain originating in the extremities, this condition has been reported to be associated with Nav1.7, *SCN9A* (Faber et al., 2012a; Han et al., 2012); Nav1.8, *SCN10A* (Faber et al., 2012b; Huang et al., 2013; Dabby et al., 2016); and Nav1.9, *SCN11A* (Huang et al., 2014; Han et al., 2015). The relevant mutations in these channels have been functionally characterized and found to contribute to sensory neuron hyperexcitability (Faber et al., 2012a,b; Han et al., 2012, 2015; Huang et al., 2013, 2014).

Neuropathic condition genetics: summary. Unlike in migraine and musculoskeletal pain conditions, our understanding of genetic contributors to neuropathic pain is largely derived from rare familial mutations and is dominated by sodium channels. While Nav1.7, and to a lesser extent Nav1.8 and Nav1.9, have been repeatedly reported as causal in rare neuropathic pain conditions, the direction and extent of functional effect on the disease phenotype is tied to the specific mutation or mutations within each locus. Moreover, extensive pedigree segregation analysis and electrophysiological characterization have occasionally shown previously reported causal mutations as benign or conferring a mild risk (Klein et al., 2012; Waxman et al., 2014).

Genetic variants underlying common neuropathic pain conditions also point to modulation of neurotransmission and related pathways. Three of the four genes whose association has been replicated at least once – *GCH1*, a regulator in the dopamine, serotonin, and nitric oxide biosynthesis pathway; *KCNS1*, a voltage-gated potassium channel subunit; and *OPRM1*, one of the body's endogenous pain regulators – implicate dysregulation in pain processing. The other gene, twice reported to be associated with cancer pain, is *PTGS2*, which indicates involvement of the immune system.

Visceral pain disorders

Visceral pain disorders, reviewed in Dabby et al. (2011) and Cervero and Laird (1999), are characterized by pain stemming from visceral organs. At least in part due to lack of consensus on diagnostic criteria for these conditions, genetic studies have been few and have provided but a glimpse into their pathophysiology, with tenuous connections between implicated genes. Possible involvement of genetic polymorphisms has been reported for chronic pelvic pain, chronic pancreatitis and interstitial cystitis.

Chronic pelvic pain is a pathology believed to result from certain bacterial infections and sexually-transmitted disease sequelae (Pontari, 2013). Evidence for inflammatory dysregulation comes from a study showing that chronic pelvic pain patients were more likely to express the genotype associated with reduced production of the regulatory cytokine interleukin 10, *IL10* (Shoskes et al., 2002). An early study by Riley et al. has implicated a short tandem repeat region of the X chromosome near the phosphoglycerate kinase gene, *PGK1*, in chronic prostatitis/chronic pelvic pain (Riley and Krieger, 2002). Two other genes possibly implicated in chronic pelvic pain are manganese superoxide dismutase, *MNSOD* (Arisan et al., 2006), and androgen receptor, *AR* (Pontari, 2013).

Several genes have been reported to be associated with chronic pancreatitis with pain. Variants of cystic fibrosis transmembrane conductance regulator, *CFTR*

(Cohn et al., 1997; Sharer et al., 1998; Noone et al., 2001) (a chloride channel whose more damaging mutations lead to cystic fibrosis); serine protease inhibitor, *SPINK1* (Witt et al., 2000; Pfuetzer et al., 2001), which regulates trypsinogen; cationic trypsinogen, *PRSS1* (Gorry et al., 1997), which in its hyperactive form essentially autodigests the pancreas; and trypsin inhibitor, *PSTI* (Noone et al., 2001), have all been reported to be associated with chronic pancreatitis with pain. *PRSS1* also carries mutations that cause hereditary pancreatitis (Whitcomb et al., 1996; Noone et al., 2001; Simon et al., 2002; Le Marechal et al., 2004; Le Maréchal et al., 2006), as does *SPINK1* (Király et al., 2007).

Interstitial cystitis, characterized by bladder pain, has been found associated with a potentiating variant of sodium channel NaV1.7, *SCN9A* (Reeder et al., 2013).

Visceral condition genetics: summary. Genetic studies of visceral conditions have thus far not painted a clear picture of the biological pathways involved in their pathophysiology. *SCN9A*, whose involvement in visceral chronic pain has been reported four times, appears to be the most frequent contributor to chronic pain accompanying visceral disorders. Given this gene's well-established role in a number of rare monogenic pain conditions, its possible role in visceral pain may be yet another manifestation of disrupted pain signaling. Furthermore, the four genes whose associations with visceral disorders have been replicated at least once represent three different functional pathways: *SCN9A* – neurotransmission, *PRSS1* and *SPINK1* – protein degradation, and *CFTR* – immune response. This evidence from genetic studies to date suggests that visceral pain disorders may not have a common pathophysiology and are rather grouped together primarily based on the anatomical proximity of the affected organs.

CONCLUSION

Genetic studies conducted in the last two decades have been invaluable in elucidating the molecular pathophysiology mechanisms of chronic pain conditions. While these studies have occasionally suffered from contradictory results or insufficient statistical power to confirm the involvement of specific genes, the network of causal mechanisms is nevertheless gradually coming into focus. Genetic variants contributing to chronic pain conditions characterize these conditions as multifactorial pathologies with overlapping etiologies. All chronic pain condition categories show an enrichment for genes involved in neurotransmission, underscoring the importance of neuronal signaling – specifically ascending nociceptive and descending inhibitory signaling – in pain chronicity. Nevertheless, secondary functional pathways differ between the etiologically grouped categories and shed light on possible pathophysiological differences between them. This suggests that distinct combinations of genetic variants, presumably interacting with environmental factors, determine the specific pathology that develops. Thus identification of genetic contributors of chronic pain conditions builds our understanding not only of the genotypic structure of these diseases but also of their molecular pathophysiology.

Furthermore, currently available chronic pain treatments are fraught with significant obstacles, including unmanageable side effects (Furlan et al., 2006; Chou et al., 2015) and variable effectiveness at the population level (Turk, 2002; Ballantyne and Shin, 2008; Finnerup et al., 2010), which are attributable to interindividual variability in pharmacokinetic and pharmacodynamic properties of analgesics. Perhaps even more importantly, given that chronic pain conditions are a heterogeneous class of disorders, driven by different pathways of vulnerability that include differential molecular genetic contribution, genetic studies promise to identify key molecular markers of susceptibility and targets for personalized treatment of chronic pain. Therefore the results of genetic studies should be exploited for drug development targeting of molecular pathways unique – or as close to unique as possible – to each pathology.

Acknowledgments—The authors would like to thank Dr. Ryan Nicholas Lichtenwalter for his careful reading of the manuscript and helpful comments as well as for his invaluable assistance with LaTeX formatting.

REFERENCES

Abubaker AO, Raslan WF, Sotereanos GC (1993) Estrogen and progesterone receptors in temporomandibular joint discs of symptomatic and asymptomatic persons: a preliminary study. J Oral Maxillofac Surg 51(10):1096–1100.

Afari N, Wen Y, Buchwald D, Goldberg J, Plesh O (2008) Are post-traumatic stress disorder symptoms and temporomandibular pain associated? Twin study. J Orofac Pain 22(1):41–49.

Akerman S, Holland PR, Goadsby PJ (2011) Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci 12 (10):570–584.

Alexander GM, Van Rijn M, Van Hilten J, Perreault MJ, Schwartzman RJ (2005) Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. Pain 116(3):213–219.

Alicakmak E, Cataloluk O, Yoldas T, Arslan A, Herken H, Barlas O, Gorucu S, Yigiter R (2003) Migraine and angiotensin-converting enzyme association in Turkish patients. Pain Clin 15(4):473–477.

Alstergren P (2000) Cytokines in temporomandibular joint arthritis. Oral Dis 6(6):331–334.

Alva JA, Iruela-Arispe ML (2004) Notch signaling in vascular morphogenesis. Curr Opin Hematol 11(4):278–283.

An X-K, Lu C-X, Ma Q-L, Zhang X-R, Burgunder J-M, Lin Q, Qu H-L (2013) Association of MTHFR C677T polymorphism with susceptibility to migraine in the Chinese population. Neurosci Lett 549:78–81.

An X-K, Ma Q-L, Lin Q, Zhang X-R, Lu C-X, Qu H-L (2013) PRDM16 rs2651899 variant is a risk factor for Chinese common migraine patients. Headache J Head Face Pain 53(10):1595–1601.

Aneiros-Guerrero A, Lendinez AM, Palomares AR, Perez-Nevot B, Aguado L, Mayor-Olea A, Ruiz-Galdon M, Reyes-Engel A (2011) Genetic polymorphisms in folate pathway enzymes, DRD4 and GSTM1 are related to temporomandibular disorder. BMC Med Genet 12(1):75–84.

Anttila V, Winsvold BS, Gormley P, Kurth T, Bettella F, McMahon G, Kallela M, Malik R, de Vries B, Terwindt G, et al. (2013) Genome-wide meta-analysis identifies new susceptibility loci for migraine. Nat Genet 45(8):912–917.

arcOGEN Consortium et al (2012) Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet 380(9844):815–823.
Arisan E, Arisan S, Kiremit M, Tiğli H, Caşkurlu T, Palavan-Unsal N, Ergenekon E (2006) Manganase superoxide dismutase polymorphism in chronic pelvic pain syndrome patients. Prostate Cancer Prostat Dis 9(4):426–431.
Asuni C, Stochino ME, Cherchi A, Manchia M, Congiu D, Manconi F, Squassina A, Piccardi MP, Del Zompo M (2009) Migraine and tumour necrosis factor gene polymorphism. J Neurol 256 (2):194–197.
Ates O, Kurt S, Altinisik J, Karaer H, Sezer S (2011) Genetic variations in tumor necrosis factor alpha, interleukin-10 genes, and migraine susceptibility. Pain Med 12(10):1464–1469.
Azimova JE, Sergeev AV, Korobeynikova LA, Kondratieva NS, Kokaeva ZG, Shaikhaev GO, Skorobogatykh KV, Fokina NM, Tabeeva GR, Klimov EA (2013) Effects of MTHFR gene polymorphism on the clinical and electrophysiological characteristics of migraine. BMC Neurol 13(1):103.
Ballantyne JC, Shin NS (2008) Efficacy of opioids for chronic pain: a review of the evidence. Clin J Pain 24(6):469–478.
Ballina LE, Ulirsch JC, Soward AC, Rossi C, Rotolo S, Linnstaedt SD, Heafner T, Foley KA, Batts J, Collette R, et al. (2013) μ-Opioid receptor gene A118G polymorphism predicts pain recovery after sexual assault. J Pain 14(2):165–171.
Barbanti P, Fofi L, Aurilia C, Egeo G (2013) Dopaminergic symptoms in migraine. Neurol Sci 34(1):67–70.
Barbosa FR, Matsuda JB, Mazucato M, de Castro França S, Zingaretti SM, Da Silva LM, Martinez-Rossi NM, Júnior MF, Marins M, Fachin AL (2012) Influence of catechol-O-methyltransferase (COMT) gene polymorphisms in pain sensibility of Brazilian fibromialgia patients. Rheumatol Int 32 (2):427–430.
Bassi B, Parodi E, Messina M, Boffi P, Bobba B, Campagnoli MF, Rigardetto R, Saracco P (2003) Screening for genetic and acquired thrombophilia in a cohort of young migrainous patients. J Headache Pain 4(3):138–145.
Battié MC, Videman T, Levalahti E, Gill K, Kaprio J (2007) Heritability of low back pain and the role of disc degeneration. Pain 131 (3):272–280.
Binder A, May D, Baron R, Maier C, Tölle TR, Treede R-D, Berthele A, Faltraco F, Flor H, Gierthmühlen J, et al. (2012) Transient receptor potential channel polymorphisms are associated with the somatosensory function in neuropathic pain patients. vol. 6, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU).
Bodzioch M, Lapicka K, Aslanidis C, Kacinski M, Schmitz G (2001) Two novel mutant alleles of the gene encoding neurotrophic tyrosine kinase receptor type 1(NTRK 1) in a patient with congenital insensitivity to pain with anhidrosis: A splice junction mutation in intron 5 and cluster of four mutations in exon 15. Hum Mutat 17(1). 72-72.
Bondy B, Spaeth M, Offenbaecher M, Glatzeder K, Stratz T, Schwarz M, de Jonge S, Krüger M, Engel RR, Färber L, et al. (1999) The T102C polymorphism of the 5-HT2A-receptor gene in fibromyalgia. Neurobiol Dis 6(5):433–439.
Bonkowsky JL, Johnson J, Carey JC, Smith AG, Swoboda KJ (2003) An infant with primary tooth loss and palmar hyperkeratosis: a novel mutation in the NTRK1 gene causing congenital insensitivity to pain with anhidrosis. Pediatrics 112(3):e237–e241.
Borroni B, Rao R, Liberini P, Venturelli E, Cossandi M, Archetti S, Caimi L, Padovani A (2006) Endothelial nitric oxide synthase (Glu298Asp) polymorphism is an independent risk factor for migraine with aura. Headache J Head Face Pain 46 (10):1575–1579.
Bortsov AV, Diatchenko L, McLean SA (2014) Complex multilocus effects of catechol-O-methyltransferase haplotypes predict pain and pain interference 6 weeks after motor vehicle collision. Neuromol Med 16(1):83–93.
Bortsov AV, Platts-Mills TF, Peak DA, Jones JS, Swor RA, Domeier RM, Lee DC, Rathlev NK, Hendry PL, Fillingim RB, et al. (2013) Pain distribution and predictors of widespread pain in the immediate aftermath of motor vehicle collision. Eur J Pain 17 (8):1243–1251.
Bortsov AV, Smith JE, Diatchenko L, Soward AC, Ulirsch JC, Rossi C, Swor RA, Hauda WE, Peak DA, Jones JS, et al. (2013) Polymorphisms in the glucocorticoid receptor co-chaperone FKBP5 predict persistent musculoskeletal pain after traumatic stress exposure. Pain 154(8):1419–1426.
Bottini F, Celle M, Calevo M, Amato S, Minniti G, Montaldi L, Di Pasquale D, Cerone R, Veneselli E, Molinari A (2006) Metabolic and genetic risk factors for migraine in children. Cephalalgia 26 (6):731–737.
Buskila D, Cohen H, Neumann L, Ebstein R (2004) An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and relationship to novelty seeking personality traits. Mol Psychiatry 9(10). 973-973.
Cargnin S, Magnani F, Viana M, Tassorelli C, Mittino D, Cantello R, Sances G, Nappi G, Canonico PL, Genazzani AA, et al. (2013) An opposite-direction modulation of the COMT Val158Met polymorphism on the clinical response to intrathecal morphine and triptans. J Pain 14(10):1097–1106.
Cargnin S, Pautasso C, Viana M, Sances G, Mittino D, Cantello R, Tassorelli C, Nappi G, Terrazzino S (2015) Association of RAMP1 rs7590387 with the risk of migraine transformation into medication overuse headache. Headache J Head Face Pain 55(5): 658–668.
Cargnin S, Viana M, Mittino D, Bellomo G, Tassorelli C, Nappi G, Canonico PL, Terrazzino S (2014) Lack of association between GRIA1 polymorphisms and haplotypes with migraine without aura or response to triptans. Neurol Sci 35(3):421–427.
Carreño O, Corominas R, Fernández-Morales J, Camina M, Sobrido M-J, Fernández-Fernández JM, Pozo-Rosich P, Cormand B, Macaya A (2012) SNP variants within the vanilloid TRPV1 and TRPV3 receptor genes are associated with migraine in the Spanish population. Am J Med Genet B Neuropsychiatr Genet 159(1):94–103.
Cervero F, Laird JM (1999) Visceral pain. Lancet 353 (9170):2145–2148.
Chapman K, Takahashi A, Meulenbelt I, Watson C, Rodriguez-Lopez J, Egli R, Tsezou A, Malizos KN, Kloppenburg M, Shi D, et al. (2008) A meta-analysis of European and Asian cohorts reveals a global role of a functional SNP in the 5′ UTR of GDF5 with osteoarthritis susceptibility. Hum Mol Genet 17(10):1497–1504.
Chasman DI, Schürks M, Anttila V, de Vries B, Schminke U, Launer LJ, Terwindt GM, van den Maagdenberg AM, Fendrich K, Völzke H, et al. (2011) Genome-wide association study reveals three susceptibility loci for common migraine in the general population. Nat Genet 43(7):695–698.
Cheng K-I, Lin S-R, Chang L-L, Wang J-Y, Lai C-S (2010) Association of the functional A118G polymorphism of OPRM1 in diabetic patients with foot ulcer pain. J Diabetes Complicat 24 (2):102–108.
Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA (2015) The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Inter Med 162(4):276–286.
Christensen AF, Esserlind A-L, Werge T, Stefánsson H, Stefánsson K, Olesen J (2015) The influence of genetic constitution on migraine drug responses. Cephalalgia.
Cohen H, Neumann L, Glazer Y, Ebstein R, Buskila D, et al. (2009) The relationship between a common catechol-O-methyltransferase (COMT) polymorphism val158met and fibromyalgia. Clin Exp Rheumatol 27(5):S51.
Cohen H, Neumann L, Haiman Y, Matar MA, Press J, Buskila D (2002) Prevalence of post-traumatic stress disorder in fibromyalgia patients: overlapping syndromes or post-traumatic fibromyalgia syndrome? Seminars in arthritis and rheumatism, vol. 32. Elsevier. p. 38–50.
Cohn J, Friedman K, Silverman L, Noone P, Knowles M, Jowell P (1997) CFTR mutations predispose to chronic pancreatitis without cystic fibrosis lung disease [abstr]. Gastroenterology 112:A434.

Colson NJ, Lea RA, Quinlan S, MacMillan J, Griffiths LR (2004) The estrogen receptor 1 G594A polymorphism is associated with migraine susceptibility in two independent case/control groups. Neurogenetics 5(2):129–133.
Colson NJ, Lea RA, Quinlan S, MacMillan J, Griffiths LR (2005) Investigation of hormone receptor genes in migraine. Neurogenetics 6(1):17–23.
Corominas R, Ribases M, Cuenca-León E, Cormand B, Macaya A (2009) Lack of association of hormone receptor polymorphisms with migraine. Eur J Neurol 16(3):413–415.
Costigan M, Belfer I, Griffin RS, Dai F, Barrett LB, Coppola G, Wu T, Kiselycznyk C, Poddar M, Lu Y, et al. (2010) Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain 133(9):2519–2527.
Costigan M, Scholz J, Woolf CJ (2009) Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci 32:1–32.
Cox HC, Lea RA, Bellis C, Carless M, Dyer T, Blangero J, Griffiths LR (2011) Variants in the human potassium channel gene (KCNN3) are associated with migraine in a high risk genetic isolate. J headache Pain 12(6):603–608.
Cox HC, Lea RA, Bellis C, Carless M, Dyer TD, Curran J, Charlesworth J, Macgregor S, Nyholt D, Chasman D, et al. (2012) A genome-wide analysis of'Bounty'descendants implicates several novel variants in migraine susceptibility. Neurogenetics 13 (3):261–266.
Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, Karbani G, Jafri H, Mannan J, Raashid Y, et al. (2006) An SCN9A channelopathy causes congenital inability to experience pain. Nature 444(7121):894–898.
Cox JJ, Sheynin J, Shorer Z, Reimann F, Nicholas AK, Zubovic L, Baralle M, Wraige E, Manor E, Levy J, et al. (2010) Congenital insensitivity to pain: novel SCN9A missense and in-frame deletion mutations. Hum Mutat 31(9):E1670–E1686.
Cui W, Yu X, Zhang H (2014) The serotonin transporter gene polymorphism is associated with the susceptibility and the pain severity in idiopathic trigeminal neuralgia patients. J Headache Pain 15(1):42–48.
Cummins TR, Dib-Hajj SD, Waxman SG (2004) Electrophysiological properties of mutant Nav1. 7 sodium channels in a painful inherited neuropathy. J Neurosci 24(38):8232–8236.
Curtain R, Lea RA, Quinlan S, Bellis C, Tajouri L, Hughes R, Macmillan J, Griffiths L (2004) Investigation of the low-density lipoprotein receptor gene and cholesterol as a risk factor for migraine. J Neurol Sci 227(1):95–100.
Dabby R, Sadeh M, Broitman Y, Yosovich K, Dickman R, Leshinsky E (2016) Silver, painful small fiber neuropathy with gastroparesis: a new phenotype with a novel mutation in the SCN10A gene. J Clin Neurosci 26:84–88.
Dabby R, Sadeh M, Gilad R, Lampl Y, Cohen S, Inbar S, Leshinsky-Silver E (2011) Chronic non-paroxysmal neuropathic pain – novel phenotype of mutation in the sodium channel SCN9A gene. J Neurol Sci 301(1):90–92.
Dale RC, Gardiner A, Antony J, Houlden H (2012) Familial PRRT2 mutation with heterogeneous paroxysmal disorders including paroxysmal torticollis and hemiplegic migraine. Dev Med Child Neurol 54(10):958–960.
D'Andrea G, Granella F, Perini F, Farruggio A, Leone M, Bussone G (2006) Platelet levels of dopamine are increased in migraine and cluster headache. Headache J Head Face Pain 46(4):585–591.
Dasdemir S, Cetinkaya Y, Gencer M, Ozkok E, Aydin M, Cakmakoglu B (2013) Cox-2 gene variants in migraine. Gene 518(2):292–295.
de Buhr MF, Mähler M, Geffers R, Hansen W, Westendorf AM, Lauber J, Buer J, Schlegelberger B, Hedrich HJ, Bleich A (2006) Cd14, Gbp1, and Pla2g2a: three major candidate genes for experimental IBD identified by combining QTL and microarray analyses. Physiol Genom 25(3):426–434.
de Freitas LVS, Lopes ACP, Piatto VB, Maniglia JV (2013) Association of temporomandibular dysfunction with the 102T-C polymorphism in the serotonin receptor gene in Brazilian patients. Arch Med Sci 9(6):1013–1018.
de Sousa SC, Karwautz A, Wöber C, Wagner G, Breen G, Zesch H-E, Konrad A, Zormann A, Wanner C, Kienbacher C, et al. (2007) A dopamine D4 receptor exon 3 VNTR allele protecting against migraine without aura. Ann Neurol 61(6):574–578.
de Vries B, Frants RR, Ferrari MD, van den Maagdenberg AM (2009) Molecular genetics of migraine. Hum Genet 126(1):115–132.
Del Zompo M, Cherchi A, Palmas M, Ponti M, Bocchetta A, Gessa G, Piccardi M (1998) Association between dopamine receptor genes and migraine without aura in a Sardinian sample. Neurology 51 (3):781–786.
Diatchenko L, Anderson AD, Slade GD, Fillingim RB, Shabalina SA, Higgins TJ, Sama S, Belfer I, Goldman D, Max MB, et al. (2006) Three major haplotypes of the β2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. Am J Med Genet B Neuropsychiatr Genet 141(5):449–462.
Diatchenko L, Fillingim RB, Smith SB, Maixner W (2013) The phenotypic and genetic signatures of common musculoskeletal pain conditions. Nat Rev Rheumatol 9(6):340–350.
Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagin D, et al. (2005) Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 14 (1):135–143.
Dib-Hajj S, Rush A, Cummins T, Hisama F, Novella S, Tyrrell L, Marshall L, Waxman S (2005) Gain-of-function mutation in Nav1. 7 in familial erythromelalgia induces bursting of sensory neurons. Brain 128(8):1847–1854.
Dib-Hajj SD, Estacion M, Jarecki BW, Tyrrell L, Fischer TZ, Lawden M, Cummins TR, Waxman SG (2008) Paroxysmal extreme pain disorder M1627K mutation in human Nav1. 7 renders DRG neurons hyperexcitable. Mol Pain 4(1):37–51.
Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, Ferrari MD, Herzog J, van den Maagdenberg AM, Pusch M, et al. (2005) Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 366(9483):371–377.
Docampo E, Escaraís G, Gratacòs M, Villatoro S, Puig A, Kogevinas M, Collado A, Carbonell J, Rivera J, Vidal J, et al. (2014) Genome-wide analysis of single nucleotide polymorphisms and copy number variants in fibromyalgia suggest a role for the central nervous system. Pain 155(6):1102–1109.
Dong D, Yao M, Liu B, Sun C, Jiang Y, Wang Y (2007) Association between the-1306C/T polymorphism of matrix metalloproteinase-2 gene and lumbar disc disease in Chinese young adults. Eur Spine J 16(11):1958–1961.
Dong W, Jia S, Ye X, Ni J (2012) Association analysis of TNFRSF1B polymorphism with susceptibility for migraine in the Chinese Han population. J Clin Neurosci 19(5):750–752.
Drenth JP, te Morsche RH, Guillet G, Taieb A, Kirby RL, Jansen JB (2005) SCN9A mutations define primary erythermalgia as a neuropathic disorder of voltage gated sodium channels. J Invest Dermatol 124(6):1333–1338.
Drenth JP, te Morsche RH, Mansour S, Mortimer PS (2008) Primary erythermalgia as a sodium channelopathy: screening for SCN9A mutations: exclusion of a causal role of SCN10A and SCN11A. Arch Dermatol 144(3):320–324.
Dworkin S (2011) The OPPERA study: act one. J Pain 12(11 Suppl): T1–T3.
Elzahaf RA, Tashani OA, Unsworth BA, Johnson MI (2012) The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. Curr Med Res Opin 28(7):1221–1229.
Erdal ME, Herken H, Mutlu MN, Bayazit YA (2003) Significance of catechol-O-methyltransferase gene polymorphism in myofacial pain syndrome. Pain Clin 15(3):309–313.
Esserlind A-L, Christensen AF, Steinberg S, Grarup N, Pedersen O, Hansen T, Werge T, Hansen TF, Husemoen LLN, Linneberg A, et al. (2015) The association between candidate migraine susceptibility loci and severe migraine phenotype in a clinical sample. Cephalalgia. pii: 0333102415570492.

Estacion M, Dib-Hajj S, Benke P, te Morsche RH, Eastman E, Macala L, Drenth J, Waxman S (2008) NaV1. 7 gain-of-function mutations as a continuum: A1632E displays physiological changes associated with erythromelalgia and paroxysmal extreme pain disorder mutations and produces symptoms of both disorders. J Neurosci 28(43):11079–11088.

Estacion M, Harty TP, Choi J-S, Tyrrell L, Dib-Hajj SD, Waxman SG (2009) A sodium channel gene SCN9A polymorphism that increases nociceptor excitability. Ann Neurol 66(6):862–866.

Faber CG, Hoeijmakers JG, Ahn H-S, Cheng X, Han C, Choi J-S, Estacion M, Lauria G, Vanhoutte EK, Gerrits MM, et al. (2012a) Gain of function Nav1. 7 mutations in idiopathic small fiber neuropathy. Ann Neurol 71(1):26–39.

Faber CG, Lauria G, Merkies IS, Cheng X, Han C, Ahn H-S, Persson A-K, Hoeijmakers JG, Gerrits MM, Pierro T, et al. (2012b) Gain-of-function Nav1. 8 mutations in painful neuropathy. Proc. Natl. Acad. Sci. 109(47):19444–19449.

Fan X, Wang J, Fan W, Chen L, Gui B, Tan G, Zhou J (2014) Replication of migraine GWAS susceptibility loci in Chinese Han population. Headache J Head Face Pain 54(4):709–715.

Fanciullacci M, Alessandri M, Del Rosso A (1999) Dopamine involvement in the migraine attack. Funct Neurol 15:171–181.

Fernández-de-las Peñas C, Ambite-Quesada S, Gil-Crujera A, Cigarán-Méndez M, Peñacoba-Puente C (2012) Catechol-O-methyltransferase Val158Met polymorphism influences anxiety, depression, and disability, but not pressure pain sensitivity, in women with fibromyalgia syndrome. J Pain 13(11):1068–1074.

Fernandez F, Colson N, Quinlan S, MacMillan J, Lea RA, Griffiths LR (2009) Association between migraine and a functional polymorphism at the dopamine β-hydroxylase locus. Neurogenetics 10(3):199–208.

Fernandez F, Lea RA, Colson NJ, Bellis C, Quinlan S, Griffiths LR (2006) Association between a 19 bp deletion polymorphism at the dopamine beta-hydroxylase (DBH) locus and migraine with aura. J Neurol Sci 251(1):118–123.

Ferreira S, Lorenzetti B, Bristow A, Poole S (1988) Interleukin-1β as a potent hyperalgesic agent antagonized by a tripeptide analogue. Nature 334:698–700.

Ferro A, Castro M-J, Lemos C, Santos M, Sousa A, Pereira-Monteiro J, Sequeiros J, Maciel P (2008) The C677T polymorphism in MTHFR is not associated with migraine in Portugal. Dis Markers 25(2):107–113.

Fertleman CR, Baker MD, Parker KA, Moffatt S, Elmslie FV, Abrahamsen B, Ostman J, Klugbauer N, Wood JN, Gardiner RM, et al. (2006) SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron 52(5):767–774.

Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Diatchenko L, Dubner R, Bair E, Baraian C, Mack N, Slade GD, et al. (2013) Psychological factors associated with development of TMD: the OPPERA prospective cohort study. J Pain 14(12):T75–T90.

Finan PH, Zautra AJ, Davis MC, Lemery-Chalfant K, Covault J, Tennen H (2011) COMT moderates the relation of daily maladaptive coping and pain in fibromyalgia. Pain 152 (2):300–307.

Finnerup NB, Sindrup SH, Jensen TS (2010) The evidence for pharmacological treatment of neuropathic pain. Pain 150 (3):573–581.

Formicola D, Aloia A, Sampaolo S, Farina O, Diodato D, Griffiths LR, Gianfrancesco F, Di Iorio G, Esposito T (2010) Common variants in the regulative regions of GRIA1 and GRIA3 receptor genes are associated with migraine susceptibility. BMC Med Genet 11(103).

Freilinger T, Anttila V, de Vries B, Malik R, Kallela M, Terwindt GM, Pozo-Rosich P, Winsvold B, Nyholt DR, van Oosterhout WP, et al. (2012) Genome-wide association analysis identifies susceptibility loci for migraine without aura. Nat Genet 44(7):777–782.

Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E (2006) Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. Can Med Assoc J 174(11):1589–1594.

Galal N, Beialy WE, Deyama Y, Yoshimura Y, Yoshikawa T, Suzuki K, Totsuka Y (2008) Effect of estrogen on bone resorption and inflammation in the temporomandibular joint cellular elements. Int J Mol Med 21(6):785–790.

Gao L, Guo H, Ye N, Bai Y, Liu X, Yu P, Xue Y, Ma S, Wei K, Jin Y, et al. (2013) Oral and craniofacial manifestations and two novel missense mutations of the NTRK1 gene identified in the patient with congenital insensitivity to pain with anhidrosis. PLoS One 8 (6):e66863.

García-Martín E, Martínez C, Serrador M, Alonso-Navarro H, Ayuso P, Navacerrada F, Agúndez JA, Jiménez-Jiménez FJ (2015) Diamine oxidase rs10156191 and rs2052129 variants are associated with the risk for migraine. Headache J Head Face Pain 55(2):276–286.

Gasparini CF, Griffiths LR (2013) The biology of the glutamatergic system and potential role in migraine. Int J Biomed Sci IJBS 9 (1):1–8.

Ghosh J, Joshi G, Pradhan S, Mittal B (2010) Investigation of TNFA 308G A and TNFB 252G A polymorphisms in genetic susceptibility to migraine. J Neurol 257(6):898–904.

Ghosh J, Joshi G, Pradhan S, Mittal B (2012) Potential role of aromatase over estrogen receptor gene polymorphisms in migraine susceptibility: a case control study from North India. PLoS One 7(4).

Ghosh J, Pradhan S, Mittal B (2013) Genome-wide-associated variants in migraine susceptibility: a replication study from North India. Headache J Head Face Pain 53(10):1583–1594.

Ghosh J, Pradhan S, Mittal B (2013) Identification of a novel ANKK1 and other dopaminergic (DRD2 and DBH) gene variants in migraine susceptibility. Neuromol Med 15(1):61–73.

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR (2003) Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch Gen Psychiatry 60(9):889–896.

Gölöncsér F, Sperlágh B (2014) Effect of genetic deletion and pharmacological antagonism of P2X7 receptors in a mouse animal model of migraine. J Headache Pain 15(1).

Gonda X, Rihmer Z, Juhasz G, Zsombok T, Bagdy G (2007) High anxiety and migraine are associated with the s allele of the 5HTTLPR gene polymorphism. Psychiatry Res 149(1):261–266.

Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, Farh K-H, Cuenca-Leon E, Muona M, Furlotte NA, et al. (2015) Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. bioRxiv.

Gorry M, Gabbaizedeh D, Furey W, Gates L, Preston R, Aston C, Zhang Y, Ulrich C, Ehrlich G, Whitcomb D (1997) Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology 113(4):1063–1068.

Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160(4):636–645.

Gu L, Yan Y, Long J, Su L, Hu Y, Chen Q, Xie J, Wu G (2012) The TNF-α-308G/A polymorphism is associated with migraine risk: A meta-analysis. Exp Therapeut Med 3(6):1082–1086.

Guauque-Olarte S, Messika-Zeitoun D, Droit A, Lamontagne M, Tremblay-Marchand J, Lavoie-Charland E, Gaudreault N, Arsenault BJ, Dubé M-P, Tardif J-C, et al. (2015) Calcium signaling pathway genes RUNX2 and CACNA1C are associated with calcific aortic valve disease, circulation: cardiovascular. Genetics 8:812–822.

Guo S, Esserlind A-L, Andersson Z, Frederiksen A, Olesen J, Vissing J, Ashina M (2015) Prevalence of migraine in persons with the 3243A G mutation in mitochondrial DNA. Eur J Neurol 23:175–181.

Guo T-M, Liu M, Zhang Y-G, Guo W-T, Wu S-X (2011) Association between Caspase-9 promoter region polymorphisms and discogenic low back pain. Connect Tissue Res 52(2):133–138.

Gupta A, Silman A, Ray D, Morriss R, Dickens C, MacFarlane G, Chiu Y, Nicholl B, McBeth J (2007) The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. Rheumatology 46 (4):666–671.

Gürsoy S, Erdal E, Herken H, Madenci E, Alaşehirli B (2001) Association of T102C polymorphism of the 5-HT2A receptor gene with pyschiatric status in fibromyalgia syndrome. Rheumatol Int 21(2):58–61.

Gürsoy S, Erdal E, Sezgin M, Barlas İÖ, Aydeniz A, Alaşehirli B, Şahin G (2008) Which genotype of MAO gene that the patients have are likely to be most susceptible to the symptoms of fibromyalgia? Rheumatol Int 28(4):307–311.

Hamel E (2007) Serotonin and migraine: biology and clinical implications. Cephalalgia 27(11):1293–1300.

Han C, Dib-Hajj SD, Lin Z, Li Y, Eastman EM, Tyrrell L, Cao X, Yang Y, Waxman SG (2009) Early-and late-onset inherited erythromelalgia: genotype–phenotype correlation. Brain:1–12.

Han C, Hoeijmakers JG, Liu S, Gerrits MM, te Morsche RH, Lauria G, Dib-Hajj SD, Drenth JP, Faber CG, Merkies IS, et al. (2012) Functional profiles of SCN9A variants in dorsal root ganglion neurons and superior cervical ganglion neurons correlate with autonomic symptoms in small fibre neuropathy. Brain 135 (9):2613–2628.

Han C, Rush AM, Dib-Hajj SD, Li S, Xu Z, Wang Y, Tyrrell L, Wang X, Yang Y, Waxman SG (2006) Sporadic onset of erythermalgia: a gain-of-function mutation in Nav1.7. Ann Neurol 59(3):553–558.

Han C, Yang Y, de Greef BT, Hoeijmakers JG, Gerrits MM, Verhamme C, Qu J, Lauria G, Merkies IS, Faber CG, et al. (2015) The domain II S4–S5 linker in Nav1. 9: a missense mutation enhances activation, impairs fast inactivation, and produces human painful neuropathy. Neuromol Med 17 (2):158–169.

Hasvik E, Schistad EI, Grvle L, Haugen AJ, Re C, Gjerstad J (2014) Subjective health complaints in patients with lumbar radicular pain and disc herniation are associated with a sex-OPRM1 A118G polymorphism interaction: a prospective 1-year observational study. BMC Musculoskeletal Disord 15(1):161–167.

Hendry L, Lombard Z, Wadley A, Kamerman P (2013) KCNS1, but not GCH1, is associated with pain intensity in a black southern African population with HIV-associated sensory neuropathy: a genetic association study. J Acquir Immune Defic Syndr 63 (1):27–30.

Herken H, Erdal E, Mutlu N, Barlas Ö, Cataloluk O, Oz F, Güray E (2001) Possible association of temporomandibular joint pain and dysfunction with a polymorphism in the serotonin transporter gene. Am J Orthod Dentofac Orthop 120(3):308–313.

Hocking L, Morris A, Dominiczak A, Porteous D, Smith B (2012) Heritability of chronic pain in 2195 extended families. Eur J Pain 16(7):1053–1063.

Hoffmann J, Supronsinchai W, Akerman S, Andreou AP, Winrow CJ, Renger J, Hargreaves R, Goadsby PJ (2015) Evidence for orexinergic mechanisms in migraine. Neurobiol Dis 74:137–143.

Holliday KL, McBeth J (2011) Recent advances in the understanding of genetic susceptibility to chronic pain and somatic symptoms. Curr Rheumatol Rep 13(6):521–527.

Holliday KL, Nicholl BI, Macfarlane GJ, Thomson W, Davies KA, McBeth J (2010) Genetic variation in the hypothalamic–pituitary–adrenal stress axis influences susceptibility to musculoskeletal pain: results from the EPIFUND study. Ann Rheumat Dis 69 (3):556–560.

Honkasalo M-L, Kaprio J, Winter T, Heikkilä K, Sillanpää M, Koskenvuo M (1995) Migraine and concomitant symptoms among 8167 adult twin pairs. Headache J Head Face Pain 35 (2):70–78.

Huang J, Han C, Estacion M, Vasylyev D, Hoeijmakers JG, Gerrits MM, Tyrrell L, Lauria G, Faber CG, Dib-Hajj SD, et al. (2014) Gain-of-function mutations in sodium channel NaV1. 9 in painful neuropathy. Brain 137:1627–1642.

Huang J, Yang Y, Zhao P, Gerrits MM, Hoeijmakers JG, Bekelaar K, Merkies IS, Faber CG, Dib-Hajj SD, Waxman SG (2013) Small-fiber neuropathy Nav1. 8 mutation shifts activation to hyperpolarized potentials and increases excitability of dorsal root ganglion neurons. J Neurosci 33(35):14087–14097.

Huehne K, Zweier C, Raab K, Odent S, Bonnaure-Mallet M, Sixou J-L, Landrieu P, Goizet C, Sarlangue J, Baumann M, et al. (2008) Novel missense, insertion and deletion mutations in the neurotrophic tyrosine kinase receptor type 1 gene (NTRK1) associated with congenital insensitivity to pain with anhidrosis. Neuromuscul Disord 18(2):159–166.

I.H.G. Consortium et al (2010) Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. Nat Genet 42(10):869–873.

Indo Y (2001) Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): mutations and polymorphisms in TRKA (NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. Hum Mutat 18(6):462–471.

Indo Y, Mardy S, Miura Y, Moosa A, Ismail EA, Toscano E, Andria G, Pavone V, Brown DL, Brooks A, et al. (2001) Congenital insensitivity to pain with anhidrosis (CIPA): novel mutations of the TRKA (NTRK1) gene, a putative uniparental disomy, and a linkage of the mutant TRKA and PKLR genes in a family with CIPA and pyruvate kinase deficiency. Hum Mutat 18 (4):308–318.

Indo Y, Tsuruta M, Hayashida Y, Karim MA, Ohta K, Kawano T, Mitsubuchi H, Tonoki H, Awaya Y, Matsuda I (1996) Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet 13(4):485–488.

Ishii M, Katoh H, Kurihara T, Saguchi K-I, Shimizu S, Kawamura M (2015) Lack of association between CGRP-related gene polymorphisms and medication overuse headache in migraine patients. A/A 47(100.0):22–100.

Ishii M, Onaya T, Katoh H, Kiuchi Y, Kasai H, Kawamura M, Shimizu S (2012) Association between the G252A tumor necrosis factor-β gene polymorphism and medication-overuse headache. J Clin Neurol 8(4):301–304.

Iso T, Hamamori Y, Kedes L (2003) Notch signaling in vascular development. Arterioscler Thromb Vasc Biol 23(4):543–553.

Jacobsen L, Schistad E, Storesund A, Pedersen L, Rygh L, Re C, Gjerstad J (2012) The COMT rs4680 Met allele contributes to long-lasting low back pain, sciatica and disability after lumbar disc herniation. Eur J Pain 16(7):1064–1069.

Jacobsen LM, Schistad EI, Storesund A, Pedersen LM, Espeland A, Rygh LJ, Re C, Gjerstad J (2013) The MMP1 rs1799750 2G allele is associated with increased low back pain, sciatica, and disability after lumbar disk herniation. Clin J Pain 29(11):967–971.

Joshi G, Pradhan S, Mittal B (2009) Role of the ACE ID and MTHFR C677T polymorphisms in genetic susceptibility of migraine in a north Indian population. J Neurol Sci 277(1):133–137.

Kang S-C, Lee D-G, Choi J-H, Kim S, Kim Y-K, Ahn H-J (2007) Association between estrogen receptor polymorphism and pain susceptibility in female temporomandibular joint osteoarthritis patients. Int J Oral Maxillofac Surg 36(5):391–394.

Kara I, Ozkok E, Aydin M, Orhan N, Cetinkaya Y, Gencer M, Kilic G, Tireli H (2007) Combined effects of ACE and MMP-3 polymorphisms on migraine development. Cephalalgia 27 (3):235–243.

Kara I, Sazci A, Ergul E, Kaya G, Kilic G (2003) Association of the C677T and A1298C polymorphisms in the 5, 10 methylenetetrahydrofolate reductase gene in patients with migraine risk. Mol Brain Res 111(1):84–90.

Karsan N, Goadsby PJ (2015) Calcitonin gene-related peptide and migraine. Curr Opin Neurol 28:250–254.

Katusic S, Williams D, Beard C, Bergstralh E, Kurland L (1991) Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945–1984. Neuroepidemiology 10(5–6):276–281.

Kaunisto M, Kallela M, Hämäläinen E, Kilpikari R, Havanka H, Harno H, Nissilä M, Säkö E, Ilmavirta M, Liukkonen J, et al. (2006) Testing of variants of the MTHFR and ESR1 genes in 1798 Finnish individuals fails to confirm the association with migraine with aura. Cephalalgia 26(12):1462–1472.

Kim B-S, Kim Y-K, Yun P-Y, Lee E, Bae J (2010) The effects of estrogen receptor α polymorphism on the prevalence of symptomatic temporomandibular disorders. J Oral Maxillofac Surg 68(12):2975–2979.

Kim DH, Dai F, Belfer I, Banco RJ, Martha JF, Tighiouart H, Tromanhauser SG, Jenis LG, Hunter DJ, Schwartz CE (2010) Polymorphic variation of the guanosine triphosphate cyclohydrolase 1 gene predicts outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. Spine 35 (21):1909–1914.

Kim S-K, Kim S-H, Nah S-S, Lee JH, Hong S-J, Kim H-S, Lee H-S, Kim HA, Joung C-I, Bae J, et al. (2013) Association of guanosine triphosphate cyclohydrolase 1 gene polymorphisms with fibromyalgia syndrome in a Korean population. J Rheumatol 40 (3):316–322.

Király O, Boulling A, Witt H, Le Maréchal C, Chen J-M, Rosendahl J, Battaggia C, Wartmann T, Sahin-Tóth M, Férec C (2007) Signal peptide variants that impair secretion of pancreatic secretory trypsin inhibitor (SPINK1) cause autosomal dominant hereditary pancreatitis. Hum Mutat 28(5):469–476.

Klein CJ, Wu Y, Kilfoyle DH, Sandroni P, Davis MD, Gavrilova RH, Low PA, Dyck PJ (2012) Infrequent SCN9A mutations in congenital insensitivity to pain and erythromelalgia. J Neurol Neurosurg Psychiatry:1–6.

Kolesnikov Y, Gabovits B, Levin A, Veske A, Qin L, Dai F, Belfer I (2013) Chronic pain after lower abdominal surgery: do catechol-O-methyl transferase/opioid receptor μ-1 polymorphisms contribute? Mol Pain 9:19–26.

Kotani K, Shimomura T, Shimomura F, Ikawa S, Nanba E (2002) A polymorphism in the serotonin transporter gene regulatory region and frequency of migraine attacks. Headache J Head Face Pain 42(9):893–895.

Kowa H, Fusayasu E, Ijiri T, Ishizaki K, Yasui K, Nakaso K, Kusumi M, Takeshima T, Nakashima K (2005) Association of the insertion/deletion polymorphism of the angiotensin I-converting enzyme gene in patients of migraine with aura. Neurosci Lett 374 (2):129–131.

Kowa H, Yasui K, Takeshima T, Urakami K, Sakai F, Nakashima K (2000) The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. Am J Med Genet 96(6):762–764.

Krafft RM (2008) Trigeminal neuralgia. Am Fam Physician 77 (9):1291–1296.

Krzyzanowska A, Avendaño C (2012) Behavioral testing in rodent models of orofacial neuropathic and inflammatory pain. Brain Behav 2(5):678–697.

Kubota E, Kubota T, Matsumoto J, Shibata T, Murakami K-I (1998) Synovial fluid cytokines and proteinases as markers of temporomandibular joint disease. J Oral Maxillofac Surg 56 (2):192–198.

Kurban M, Wajid M, Shimomura Y, Christiano AM (2010) A nonsense mutation in the SCN9A gene in congenital insensitivity to pain. Dermatology 221(2):179–183.

Kurth T (2013) The epidemiology of migraine genetics: recent findings, implications, and future directions [abstr]. J Headache Pain 14(Suppl 1):I1.

Lafrenière RG, Cader MZ, Poulin J-F, Andres-Enguix I, Simoneau M, Gupta N, Boisvert K, Lafrenière F, McLaughlan S, Dubé M-P, et al. (2010) A dominant-negative mutation in the TRESK potassium channel is linked to familial migraine with aura. Nat Med 16(10):1157–1160.

Lafrenière RG, Rouleau GA (2011) Migraine: role of the TRESK two-pore potassium channel. Int J Biochem Cell Biol 43 (11):1533–1536.

Lafrenière RG, Rouleau GA (2012) Identification of novel genes involved in migraine. Headache J Head Face Pain 52(Suppl 2):107–110.

Langford DJ, Bailey AL, Chanda ML, Clarke SE, Drummond TE, Echols S, Glick S, Ingrao J, Klassen-Ross T, LaCroix-Fralish ML, et al. (2010) Coding of facial expressions of pain in the laboratory mouse. Nat Methods 7(6):447–449.

Launer LJ, Terwindt GM, Ferrari MD (1999) The prevalence and characteristics of migraine in a population-based cohort The GEM Study. Neurology 53(3). 537-537.

Lavigne GJ, Sessle BJ (2015) Canadian Orofacial Pain Team workshop report on the Global Year Against Orofacial Pain. Pain Res Manage J Canad Pain Soc 20(1):7–14.

Le Marechal C, Chen J, Le Gall C, Plessis G, Chipponi J, Chuzhanova N, Raguenes O, Férec C (2004) Two novel severe mutations in the pancreatic secretory trypsin inhibitor gene (SPINK1) cause familial and/or hereditary pancreatitis. Hum Mutat 23(2). 205-205.

Le Maréchal C, Masson E, Chen J-M, Morel F, Ruszniewski P, Levy P, Férec C (2006) Hereditary pancreatitis caused by triplication of the trypsinogen locus. Nat Genet 38(12):1372–1374.

Lea RA, Dohy A, Jordan K, Quinlan S, Brimage P, Griffiths L (2000) Evidence for allelic association of the dopamine β-hydroxylase gene (DBH) with susceptibility to typical migraine. Neurogenetics 3(1):35–40.

Lea RA, Ovcaric M, Sundholm J, MacMillan J, Griffiths LR (2004) The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura. BMC Med 2(1):3.

Lea RA, Ovcaric M, Sundholm J, Solyom L, MacMillan J, Griffiths LR (2005) Genetic variants of angiotensin converting enzyme and methylenetetrahydrofolate reductase may act in combination to increase migraine susceptibility. Mol Brain Res 136(1):112–117.

Lee M-J, Yu H-S, Hsieh S-T, Stephenson DA, Lu C-J, Yang C-C (2007) Characterization of a familial case with primary erythromelalgia from Taiwan. J Neurol 254(2):210–214.

Lee YH, Choi SJ, Ji JD, Song GG (2012) Candidate gene studies of fibromyalgia: a systematic review and meta-analysis. Rheumatol Int 32(2):417–426.

Leipold E, Liebmann L, Korenke GC, Heinrich T, Gieelmann S, Baets J, Ebbinghaus M, Goral RO, Stödberg T, Hennings JC, et al. (2013) A de novo gain-of-function mutation in SCN11A causes loss of pain perception. Nat Genet 45(11):1399–1404.

Lemos C, Mendonça D, Pereira-Monteiro J, Barros J, Sequeiros J, Alonso I, Sousa A (2010) BDNF and CGRP interaction: implications in migraine susceptibility. Cephalalgia 30 (11):1375–1382.

Li M, Liang J, Sun Z, Zhang H, Yao Z (2012) Novel nonsense and frameshift NTRK1 gene mutations in Chinese patients with congenital insensitivity to pain with anhidrosis. Genet Mol Res 11(3):2056–2162.

Li S, Yang Y, Wang Y, Xu Z, Bu D-F, Tu P, Zhu X-J (2005) SCN9A gene mutation in a primary erythermalgia pedigree. J Clin Dermatol 2:002.

Ligthart L, De Vries B, Smith AV, Ikram MA, Amin N, Hottenga J-J, Koelewijn SC, Kattenberg VM, De Moor MH, Janssens ACJ, et al. (2011) Meta-analysis of genome-wide association for migraine in six population-based European cohorts. Eur J Hum Genet 19 (8):901–907.

Ligthart L, Gerrits MM, Boomsma DI, Penninx BW (2013) Anxiety and depression are associated with migraine and pain in general: an investigation of the interrelationships. J Pain 14(4):363–370.

Lin J, Wang P, Chen C, Yueh K, Lin S, Harn H (2005) Homozygous deletion genotype of angiotensin converting enzyme confers protection against migraine in man. Acta Neurol Taiwan 14(3):120.

Lin Q-F, Fu X-G, Yao L-T, Yang J, Cao L-Y, Xin Y-T, Hou J-X, Ye L-F, Huang G-B (2015) Association of genetic loci for migraine susceptibility in the she people of China. J Headache Pain 16 (1):1–6.

Lin Z-M, Li Y, Zhang L-L, Cao X-W, Zhang Y-L, Yang Y (2008) Mutations of SCN9A gene in five patients with primary erythermalgia. J Clin Dermatol 8:016.

Linnstaedt SD, Bortsov AV, Soward AC, Swor R, Peak DA, Jones J, Rathlev N, Lee DC, Domeier R, Hendry PL, et al. (2016) CRHBP polymorphisms predict chronic pain development following motor vehicle collision. Pain 157(1):273–279.

Linnstaedt SD, Hu J, Bortsov AV, Soward AC, Swor R, Jones J, Lee D, Peak D, Domeier R, Rathlev N, et al. (2015) Mu-opioid receptor gene a118g variants and persistent pain symptoms among men and women experiencing motor vehicle collision. J Pain 16:637–644.

Liu A, Menon S, Colson NJ, Quinlan S, Cox H, Peterson M, Tiang T, Haupt LM, Lea RA, Griffiths LR (2010) Analysis of the MTHFR C677T variant with migraine phenotypes. BMC Res Notes 3 (1):213.

Liu S, Wu N, Liu J, Ming X, Chen J, Pavelec D, Su X, Qiu G, Tian Y, Giampietro P, et al. (2014) Novel NTRK1 frameshift mutation in congenital insensitivity to pain with anhidrosis. J Child Neurol:1–5.

Liying J, Yuchun T, Youcheng W, Yingchen W, Chunyu J, Yanling Y, Hongmei J, Yujie L (2013) A SMAD3 gene polymorphism is related with osteoarthritis in a Northeast Chinese population. Rheumatol Int 33(7):1763–1768.

Lončar Z, Ćurić G, Havelka Meštrović A, Mićković V, Bilić M (2013) Do IL-1B and IL-1RN modulate chronic low back pain in patients with post-traumatic stress disorder? Coll Antropol 37 (4):1237–1244.

MacDonald B, Cockerell O, Sander J, Shorvon S (2000) The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain 123 (4):665–676.

Maes M, Song C, Lin A, De Jongh R, Van Gastel A, Kenis G, Bosmans E, De Meester I, Benoy I, Neels H, et al. (1998) The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and Th1-like response in stress-induced anxiety. Cytokine 10(4):313–318.

Maher BH, Lea RA, Follett J, Cox HC, Fernandez F, Esposito T, Gianfrancesco F, Haupt LM, Griffiths LR (2013) Association of a GRIA3 gene polymorphism with migraine in an australian case-control cohort. Headache J Head Face Pain 53(8):1245–1249.

Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S (1998) Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. Pain 76(1):71–81.

Mansouri M, Elalaoui SC, Bencheikh BOA, El Alloussi M, Dion PA, Sefiani A, Rouleau GA (2014) A novel nonsense mutation in SCN9A in a moroccan child with congenital insensitivity to pain. Pediatr Neurol 51(5):741–744.

Markkula R, Järvinen P, Leino-Arjas P, Koskenvuo M, Kalso E, Kaprio J (2009) Clustering of symptoms associated with fibromyalgia in a Finnish Twin Cohort. Eur J Pain 13(7):744–750.

Martínez-Jauand M, Sitges C, Rodriguez V, Picornell A, Ramon M, Buskila D, Montoya P (2013) Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (COMT) gene. Eur J Pain 17(1):16–27.

Marziniak M, Herzog A, Mössner R, Sommer C (2008) Investigation of the functional brain-derived neurotrophic factor gene variant Val66Met in migraine. J Neural Transm 115(9):1321–1325.

Matsuda JB, Barbosa FR, Morel LJF, França SDC, Zingaretti SM, Silva LMD, Pereira AMS, Marins M, Fachin AL (2010) Serotonin receptor (5-HT 2A) and catechol-O-methyltransferase (COMT) gene polymorphisms: triggers of fibromyalgia? Rev Brasil Reumatol 50(2):141–145.

Mazaheri S, Hajilooi M, Rafiei A (2006) The G-308A promoter variant of the tumor necrosis factor-alpha gene is associated with migraine without aura. J Neurol 253(12):1589–1593.

McCann B, Miaskowski C, Koetters T, Baggott C, West C, Levine JD, Elboim C, Abrams G, Hamolsky D, Dunn L, et al. (2012) Associations between pro-and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery. J Pain 13(5):425–437.

McCarthy LC, Hosford DA, Riley JH, Bird MI, White NJ, Hewett DR, Peroutka SJ, Griffiths LR, Boyd PR, Lea RA, et al. (2001) Single-nucleotide polymorphism alleles in the insulin receptor gene are associated with typical migraine. Genomics 78(3):135–149.

McLean SA, Diatchenko L, Lee YM, Swor RA, Domeier RM, Jones JS, Jones CW, Reed C, Harris RE, Maixner W, et al. (2011) Catechol O-methyltransferase haplotype predicts immediate musculoskeletal neck pain and psychological symptoms after motor vehicle collision. J Pain 12(1):101–107.

Mease P (2005) Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol 75:6–21.

Meloto CB, Segall SK, Smith S, Parisien M, Shabalina SA, Rizzatti-Barbosa CM, Gauthier J, Tsao D, Convertino M, Piltonen MH, et al. (2015) COMT gene locus: new functional variants. Pain 156 (10):2072–2083.

Mergener M, Becker RMR, Santos AFD, Santos GAD, Andrade FMD (2011) Influence of the interaction between environmental quality and T102C SNP in the HTR2A gene on fibromyalgia susceptibility. Rev Brasil Reumatol 51(6):594–602.

Michelotti A, Liguori R, Toriello M, D'Antò V, Vitale D, Castaldo G, Sacchetti L (2014) Catechol-O-methyltransferase (COMT) gene polymorphisms as risk factor in temporomandibular disorders patients from southern Italy. Clin J Pain 30(2):129–133.

Michiels JJ, te Morsche RH, Jansen JB, Drenth JP (2005) Autosomal dominant erythermalgia associated with a novel mutation in the voltage-gated sodium channel α subunit Nav1.7. Arch Neurol 62 (10):1587–1590.

Miller GM (2011) The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. J Neurochem 116(2):164–176.

Miura Y, Mardy S, Awaya Y, Nihei K, Endo F, Matsuda I, Indo Y (2000) Mutation and polymorphism analysis of the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families. Hum Genet 106(1):116–124.

Miyamoto Y, Mabuchi A, Shi D, Kubo T, Takatori Y, Saito S, Fujioka M, Sudo A, Uchida A, Yamamoto S, et al. (2007) A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis. Nat Genet 39(4):529–533.

Mochi M, Cevoli S, Cortelli P, Pierangeli G, Scapoli C, Soriani S, Montagna P (2003) Investigation of an LDLR gene polymorphism (19p13. 2) in susceptibility to migraine without aura. J Neurol Sci 213(1):7–10.

Mochi M, Cevoli S, Cortelli P, Pierangeli G, Soriani S, Scapoli C, Montagna P (2003) A genetic association study of migraine with dopamine receptor 4, dopamine transporter and dopamine-beta-hydroxylase genes. Neurol Sci 23(6):301–305.

Mogil JS (2009) Animal models of pain: progress and challenges. Nat Rev Neurosci 10(4):283–294.

Mogil JS (2012) Pain genetics: past, present and future. Trends Genet 28(6):258–266.

Mogil JS, Grisel JE (1998) Transgenic studies of pain. Pain 77 (2):107–128.

Moskowitz MA, Bolay H, Dalkara T (2004) Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. Ann Neurol 55(2):276–280.

Mozaffari E, Doosti A, Nemati R, Faghani M, Makhlooei M (2015) Evaluating COX-2-765 G-C Genetic Polymorphism in Migraineurs. SSU J 23(5):452–463.

Mu J, Ge W, Zuo X, Chen Y, Huang C (2013) Analysis of association between IL-1β, CASP-9, and GDF5 variants and low-back pain in Chinese male soldiers: Clinical article. J Neurosurg Spine 19 (2):243–247.

Munzenmaier DH, Wilentz J, Cowley Jr AW (2014) Genetic, epigenetic, and mechanistic studies of temporomandibular disorders and overlapping pain conditions. Mol Pain 10(1):72–75.

Mutlu N, Emin Erdal M, Herken H, Ozkaya M, Erdal N, Oz G, Bayazit YA (2005) Monoamine oxidase-A gene promoter polymorphism in temporomandibular joint pain and dysfunction, The. Pain Clin 17 (1):39–44.

Mutlu N, Erdal M, Herken H, Oz G, Bayazt Y (2004) T102C polymorphism of the 5-HT2A receptor gene may be associated with temporomandibular dysfunction. Oral Dis 10(6):349–352.

Nackley AG, Tan KS, Fecho K, Flood P, Diatchenko L, Maixner W (2007) Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both β 2-and β 3-adrenergic receptors. Pain 128(3):199–208.

Netzer C, Freudenberg J, Toliat MR, Heinze A, Heinze-Kuhn K, Thiele H, Goebel I, Nürnberg P, Ptáček LJ, Göbel H, et al. (2008) Genetic association studies of the chromosome 15 GABA-A receptor cluster in migraine with aura. Am J Med Genet B Neuropsychiatr Genet 147(1):37–41.

Nielsen C, Knudsen G, Steingrímsdóttir Ó (2012) Twin studies of pain. Clin Genet 82(4):331–340.
Noone PG, Zhou Z, Silverman LM, Jowell PS, Knowles MR, Cohn JA (2001) Cystic fibrosis gene mutations and pancreatitis risk: relation to epithelial ion transport and trypsin inhibitor gene mutations. Gastroenterology 121(6):1310–1319.
Offenbaecher M, Bondy B, De Jonge S, Glatzeder K, Krüger M, Shoeps P, Ackenheil M (1999) Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. Arthritis Rheum 42(11):2482–2488.
Ojima K, Watanabe N, Narita N, Narita M (2007) Temporomandibular disorder is associated with a serotonin transporter gene polymorphism in the Japanese population. Biopsychosoc Med 1 (3):b22.
Olsen MB, Jacobsen LM, Schistad EI, Pedersen LM, Rygh LJ, Re C, Gjerstad J (2012) Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor mu 1 gene: evidence of a sex and genotype interaction. J Neurosci 32(29):9831–9834.
Omair A, Holden M, Lie BA, Reikeras O, Brox JI (2013) Treatment outcome of chronic low back pain and radiographic lumbar disc degeneration are associated with inflammatory and matrix degrading gene variants: a prospective genetic association study. BMC Musculoskeletal Dis 14(1):105–114.
Omair A, Lie BA, Reikeras O, Holden M, Brox JI (2012) Genetic contribution of catechol-O-methyltransferase variants in treatment outcome of low back pain: a prospective genetic association study. BMC Musculoskeletal Dis 13(1):76–85.
Omair A, Mannion AF, Holden M, Fairbank J, Lie BA, Hägg O, Fritzell P, Brox JI (2015) Catechol-O-methyltransferase (COMT) gene polymorphisms are associated with baseline disability but not long-term treatment outcome in patients with chronic low back pain. Eur Spine J 24:2425–2431.
Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, Lamerdin JE, Mohrenweiser HW, Bulman DE, Ferrari M, et al. (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca 2+ channel gene CACNL1A4. Cell 87(3):543–552.
Oswell G, Kaunisto M, Kallela M, Hämäläinen E, Anttila V, Kaprio J, Färkkilä M, Wessman M, Palotie A (2008) No association of migraine to the GABA-A receptor complex on chromosome 15. Am J Med Genet B Neuropsychiatr Genet 147(1):33–36.
Oterino A, Pascual J, de Alegŕa CR, Valle N, Castillo J, Bravo Y, González F, Sánchez-Velasco P, Cayón A, Leyva-Cobián F, et al. (2006) Association of migraine and ESR1 G325C polymorphism. Neuroreport 17(1):61–64.
Oterino A, Toriello M, Cayón A, Castillo J, Colas R, Alonson-Arranz A, Ruiz-Alegria C, Quintela E, Monton F, Ruiz-Lavilla N, et al. (2008) Multilocus analyses reveal involvement of the ESR1, ESR2, and FSHR genes in migraine. Headache J Head Face Pain 48(10):1438–1450.
Oterino A, Valle N, Pascual J, Bravo Y, Muñoz P, Castillo J, Ruiz-Alegŕa C, Sánchez-Velasco P, Leyva-Cobián F, Cid C (2005) Thymidylate synthase promoter tandem repeat and MTHFD1 R653Q polymorphisms modulate the risk for migraine conferred by the MTHFR T677 allele. Mol Brain Res 139(1):163–168.
Paterna S, Di Pasquale P, D'Angelo A, Seidita G, Tuttolomondo A, Cardinale A, Maniscalchi T, Follone G, Giubilato A, Tarantello M, et al. (2000) Angiotensin-converting enzyme gene deletion polymorphism determines an increase in frequency of migraine attacks in patients suffering from migraine without aura. Eur Neurol 43(3):133–136.
Peddareddygari LR, Oberoi K, Grewal RP (2014) Congenital insensitivity to pain: a case report and review of the literature. Case Rep Neurol Med.
Peroutka SJ, Price SC, Wilhoit TL, Jones KW (1998) Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. Mol Med 4(1):14–21.
Persico A, Verdecchia M, Pinzone V, Guidetti V (2015) Migraine genetics: current findings and future lines of research. Neurogenetics 16(2):77–95.
Pesa J, Lage MJ (2004) The medical costs of migraine and comorbid anxiety and depression. Headache J Head Face Pain 44 (6):562–570.
Peters MJ, Broer L, Willemen HL, Eiriksdottir G, Hocking LJ, Holliday KL, Horan MA, Meulenbelt I, Neogi T, Popham M (2013) Genome-wide association study meta-analysis of chronic widespread pain: evidence for involvement of the 5p15.2 region. Ann Rheumat Dis 72(3):427–436.
Pezzini A, Grassi M, Del Zotto E, Giossi A, Monaste ro R, Dalla Volta G, Archetti S, Zavarise P, Camarda C, Gasparotti R (2007) Migraine mediates the influence of C677T MTHFR genotypes on ischemic stroke risk with a stroke-subtype effect. Stroke 38 (12):3145–3151.
Pfuetzer RH, Finch R, Shapiro SE, Barmada MM, Myers ES, Chensny LJ, Whitcomb DC (2001) SPINK 1 mutations modify phenotypic expression in hereditary pancreatitis (HP) caused by cationic trypsinogen (PRSS1) mutations R122H and N291. Gastroenterology 120(5 Suppl 1):A33.
Phatarakyijnirund V, Mumm S, McAlister WH, Novack D, Wenkert D, Clements KL, Whyte MP (2015) Congenital insensitivity to pain: fracturing without apparent skeletal pathobiology caused by an autosomal dominant, second mutation in SCN11A encoding voltage-gated sodium channel 1.9. Bone 84:289–298.
Plesh O, Noonan C, Buchwald DS, Goldberg J, Afari N (2011) Temporomandibular disorder-type pain and migraine headache in women: a preliminary twin study. J Orofac Pain 26(2):91–98.
Pontari MA (2013) Etiology of chronic prostatitis/chronic pelvic pain syndrome: psychoimmunoneurendocrine dysfunction (PINE syndrome) or just a really bad infection? World J Urol 31 (4):725–732.
Rainero I, Fasano E, Rubino E, Rivoiro C, Valfrè W, Gallone S, Savi L, Gentile S, Giudice RL, De Martino P, et al. (2005) Association between migraine and HLA–DRB1 gene polymorphisms. J Headache Pain 6(4):185–187.
Rainero I, Rubino E, Gallone S, Fenoglio P, Picci LR, Giobbe L, Ostacoli L, Pinessi L (2011) Evidence for an association between migraine and the hypocretin receptor 1 gene. J Headache Pain 12 (2):193–199.
Raison CL, Capuron L, Miller AH (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 27(1):24–31.
Rajasekaran S, Kanna RM, Senthil N, Raveendran M, Cheung KM, Chan D, Subramaniam S, Shetty AP (2013) Phenotype variations affect genetic association studies of degenerative disc disease: conclusions of analysis of genetic association of 58 single nucleotide polymorphisms with highly specific phenotypes for disc degeneration in 332 subjects. Spine J 13(10):1309–1320.
Reeder JE, Byler TK, Foster DC, Landas SK, Okafor H, Stearns G, Wood RW, Zhang Y, Mayer RD (2013) Polymorphism in the SCN9A voltage-gated sodium channel gene associated with interstitial cystitis/bladder pain syndrome. Urology 81(1). 210. e1–e.4.
Reeser JC, Payne E, Kitchner T, McCarty CA (2011) Apolipoprotein e4 genotype increases the risk of being diagnosed with posttraumatic fibromyalgia. PM&R 3(3):193–197.
Reyes-Gibby CC, Spitz M, Wu X, Merriman K, Etzel C, Bruera E, Kurzrock R, Shete S (2007) Cytokine genes and pain severity in lung cancer: exploring the influence of TNF-α-308 G/A IL6-174G/C and IL8-251T/A. Cancer Epidemiol Biomark Prevent 16 (12):2745–2751.
Reyes-Gibby CC, Spitz MR, Yennurajalingam S, Swartz M, Gu J, Wu X, Bruera E, Shete S (2009) Role of inflammation gene polymorphisms on pain severity in lung cancer patients. Cancer Epidemiol Biomark Prevent 18(10):2636–2642.
Reyes-Gibby CC, Swartz MD, Yu X, Wu X, Yennurajalingam S, Anderson KO, Spitz MR, Shete S (2013) Symptom clusters of pain, depressed mood, and fatigue in lung cancer: assessing the role of cytokine genes. Support. Care Cancer 21(11): 3117–3125.
Riant F, Roze E, Barbance C, Méneret A, Guyant-Maréchal L, Lucas C, Sabouraud P, Trébuchon A, Depienne C, Tournier-Lasserve E

(2012) PRRT2 mutations cause hemiplegic migraine. Neurology 79(21):2122–2124.
Ribeiro-Dasilva MC, Line SRP, dos Santos MCLG, Arthuri MT, Hou W, Fillingim RB, Barbosa CMR (2009) Estrogen receptor-α polymorphisms and predisposition to TMJ disorder. J Pain 10 (5):527–533.
Riley DE, Krieger JN (2002) X chromosomal short tandem repeat polymorphisms near the phosphoglycerate kinase gene in men with chronic prostatitis. Biochim Biophys Acta 1586(1): 99–107.
Rivadeneira F, Styrkársdottir U, Estrada K, Halldórsson BV, Hsu Y-H, Richards JB, Zillikens MC, Kavvoura FK, Amin N, Aulchenko YS, et al. (2009) Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. Nat Genet 41(11):1199–1206.
Rodriguez-Acevedo AJ, Maher BH, Lea RA, Benton M, Griffiths LR (2013) Association of oestrogen-receptor gene (ESR1) polymorphisms with migraine in the large Norfolk Island pedigree. Cephalalgia.
Roh HL, Lee JS, Suh KT, Kim JI, Lee HS, Goh TS, Park SH (2013) Association between estrogen receptor gene polymorphism and back pain intensity in female patients with degenerative lumbar spondylolisthesis. J Spinal Disord Tech 26(2):E53–E57.
Rubino E, Fenoglio P, Gallone S, Govone F, Vacca A, De Martino P, Giobbe ML, Boschi S, Pinessi L, Gentile S, et al. (2013) Genetic variants in the NOTCH4 gene influence the clinical features of migraine. J Headache Pain 14(1):1–5.
Rudkjobing LA, Esserlind A-L, Olesen J (2012) Future possibilities in migraine genetics. J Headache Pain 13(7):505–511.
Russo L, Mariotti P, Sangiorgi E, Giordano T, Ricci I, Lupi F, Chiera R, Guzzetta F, Neri G, Gurrieri F (2005) A new susceptibility locus for migraine with aura in the 15q11-q13 genomic region containing three GABA-A receptor genes. Am J Hum Genet 76 (2):327–333.
Rut M, Machoy Mokrzyńska A, Ręcawo wicz D, Soniewski P, Kurzawski M, Droździk M, Safranow K, Morawska M, Biaecka M (2014) Influence of variation in the catechol-O-methyltransferase gene on the clinical outcome after lumbar spine surgery for one-level symptomatic disc disease: a report on 176 cases. Acta Neurochir 156(2):245–252.
Salemi S, Rethage J, Wollina U, Michel BA, Gay RE, Gay S, Sprott H (2003) Detection of interleukin 1beta (IL-1beta), IL-6, and tumor necrosis factor-alpha in skin of patients with fibromyalgia. J Rheumatol 30(1):146–150.
Sambrook P, MacGregor A, Spector T (1999) Genetic influences on cervical and lumbar disc degeneration. Arthritis Rheum 42 (2):336–372.
Samuels ME, Te Morsche R, Lynch ME, Drenth JP (2008) Compound heterozygosity in sodium channel Nav1. 7 in a family with hereditary erythermalgia. Mol Pain 4:21.
Scher AI, Terwindt GM, Verschuren W, Kruit MC, Blom HJ, Kowa H, Frants RR, van den Maagdenberg AM, van Buchem M, Ferrari MD, et al. (2006) Migraine and MTHFR C677T genotype in a population-based sample. Ann Neurol 59(2):372–375.
Schistad EI, Jacobsen LM, Re C, Gjerstad J (2014) The interleukin-1α gene C T polymorphism rs1800587 is associated with increased pain intensity and decreased pressure pain thresholds in patients with lumbar radicular pain. Clin J Pain 30 (10):869–874.
Schürks M (2012) Genetics of migraine in the age of genome-wide association studies. J Headache Pain 13(1):1–9.
Schürks M, Kurth T, Buring JE, Zee RY (2009) A candidate gene association study of 77 polymorphisms in migraine. J Pain 10 (7):759–766.
Schürks M, Zee RY, Buring JE, Kurth T (2008) Interrelationships among the MTHFR 677C T polymorphism, migraine, and cardiovascular disease. Neurology 71(7):505–513.
Schürks M, Zee RY, Buring JE, Kurth T (2009) ACE D/I polymorphism, migraine, and cardiovascular disease in women. Neurology 72(7):650–656.
Schürks M, Zee RY, Buring JE, Kurth T (2009) MTHFR 677C-T and ACE D/I polymorphisms and migraine attack frequency in women. Cephalalgia:1–10.
Sessle BJ (2014) The societal, political, educational, scientifc, and clinical context of orofacial pain. In: Sessle BJ, editor. Orofacial pain: recent advances in assessment, management, and understanding of mechanisms. Washington, DC: IASP Press. p. 1–15 (chap. 1).
Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, Braganza J (1998) Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Engl J Med 339(10):645–652.
Shatzky S, Moses S, Levy J, Pinsk V, Hershkovitz E, Herzog L, Shorer Z, Luder A, Parvari R (2000) Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: genetic heterogeneity, novel mutations in the TrkA/NGF receptor gene, clinical findings, and results of nerve conduction studies. Am J Med Genet 92(5):353–360.
Shorer Z, Wajsbrot E, Liran T-H, Levy J, Parvari R (2014) A novel mutation in SCN9A in a child with congenital insensitivity to pain. Pediatr Neurol 50(1):73–76.
Shoskes DA, Albakri Q, Thomas K, Cook D (2002) Cytokine polymorphisms in men with chronic prostatitis/chronic pelvic pain syndrome: association with diagnosis and treatment response. J Urol 168(1):331–335.
Simon P, Weiss FU, Sahin-Tóth M, Parry M, Nayler O, Lenfers B, Schnekenburger J, Mayerle J, Domschke W, Lerch MM (2002) Hereditary pancreatitis caused by a novel PRSS1 mutation (Arg122Cys) that alters autoactivation and autodegradation of cationic trypsinogen. J Biol Chem 277(7):5404–5410.
Skouen J, Smith A, Warrington N, O'Sullivan P, McKenzie L, Pennell C, Straker L (2012) Genetic variation in the beta-2 adrenergic receptor is associated with chronic musculoskeletal complaints in adolescents. Eur J Pain 16(9):1232–1242.
Slade G, Diatchenko L, Bhalang K, Sigurdsson A, Fillingim R, Belfer I, Max M, Goldman D, Maixner W (2007) Influence of psychological factors on risk of temporomandibular disorders. J Dent Res 86 (11):1120–1125.
Slade GD, Conrad MS, Diatchenko L, Rashid NU, Zhong S, Smith S, Rhodes J, Medvedev A, Makarov S, Maixner W, et al. (2011) Cytokine biomarkers and chronic pain: association of genes, transcription, and circulating proteins with temporomandibular disorders and widespread palpation tenderness. Pain 152 (12):2802–2812.
Slade GD, Smith SB, Zaykin DV, Tchivileva IE, Gibson DG, Yuryev A, Mazo I, Bair E, Fillingim R, Ohrbach R, et al. (2013) Facial pain with localized and widespread manifestations: separate pathways of vulnerability. Pain 154(11):2335–2343.
Smith SB, Maixner DW, Fillingim RB, Slade G, Gracely RH, Ambrose K, Zaykin DV, Hyde C, John S, Tan K, et al. (2012) Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia. Arthritis Rheum 64 (2):584–593.
Smith SB, Maixner DW, Greenspan JD, Dubner R, Fillingim RB, Ohrbach R, Knott C, Slade GD, Bair E, Gibson DG, et al. (2011) Potential genetic risk factors for chronic TMD: genetic associations from the OPPERA case control study. J Pain 12 (11):T92–T101.
Solovieva S, Leino-Arjas P, Saarela J, Luoma K, Raininko R, Riihimäki H (2004) Possible association of interleukin 1 gene locus polymorphisms with low back pain. Pain 109(1):8–19.
Solovieva S, Noponen N, Männikkö M, Leino-Arjas P, Luoma K, Raininko R, Ala-Kokko L, Riihimäki H (2007) Association between the aggrecan gene variable number of tandem repeats polymorphism and intervertebral disc degeneration. Spine 32 (16):1700–1705.
Sommer C, Kress M (2004) Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci Lett 361(1):184–187.
Song Y-Q, Ho DW, Karppinen J, Kao PY, Fan B-J, Luk KD, Yip S-P, Leong JC, Cheah KS, Sham P, et al. (2008) Association between

promoter-1607 polymorphism of MMP1 and lumbar disc disease in Southern Chinese. BMC Med Genet 9(1):38–44.
Sorge RE, Trang T, Dorfman R, Smith SB, Beggs S, Ritchie J, Austin J-S, Zaykin DV, Vander Meulen H, Costigan M, et al. (2012) Genetically determined P2X7 receptor pore formation regulates variability in chronic pain sensitivity. Nat Med 18(4):595–599.
Stemig M, Myers SL, Kaimal S, Islam MS (2015) Estrogen receptor-alpha polymorphism in patients with and without degenerative disease of the temporomandibular joint. Cranio 33(2):129–133.
Stephens K, Cooper BA, West C, Paul SM, Baggott CR, Merriman JD, Dhruva A, Kober KM, Langford DJ, Leutwyler H, et al. (2014) Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. J Pain 15(2):169–180.
Sutherland H, Buteri J, Menon S, Haupt L, MacGregor E, Lea RA, Griffiths L (2013) Association study of the calcitonin gene-related polypeptide-alpha (CALCA) and the receptor activity modifying 1 (RAMP1) genes with migraine. Gene 515(1):187–192.
Sutherland HG, Maher BH, Rodriguez-Acevedo AJ, Haupt LM, Griffiths LR (2014) Investigation of brain-derived neurotrophic factor (BDNF) gene variants in migraine. Headache J Head Face Pain 54(7):1184–1193.
Takahashi M, Haro H, Wakabayashi Y, Kawa-Uchi T, Komori H, Shinomiya K (2001) The association of degeneration of the intervertebral disc with 5a/6a polymorphism in the promoter of the human matrix metalloproteinase-3 gene. J Bone Joint Surg Br 83 (4):491–495.
Tang Y, Zheng D, Li Q, Wang Z, Lin Y, Lan F (2014) A novel mutation of NTRK1 gene in a family with congenital insensitivity to pain with anhidrosis. Chin J Med Genet 31(5):574–577.
Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, et al. (2006) GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 12(11):1269–1277.
Tesfaye S, Selvarajah D (2012) Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev 28(S1):8–14.
Tesfaye S, Stevens L, Stephenson J, Fuller J, Plater M, Ionescu-Tirgoviste C, Nuber A, Pozza G, Ward J, E.I.C.S. Group, et al. (1996) Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM complications study. Diabetologia 39 (11):1377–1384.
Tietjen G (2009) Migraine as a systemic vasculopathy. Cephalalgia 29(9):987–996.
Tietjen G, Herial N, Utley C, White L, Yerga-Woolwine S, Joe B (2009) Association of von Willebrand factor activity with ACE I/D and MTHFR C677T polymorphisms in migraine. Cephalalgia 29 (9):960–968.
Tikka-Kleemola P, Kaunisto M, Hämäläinen E, Todt U, Göbel H, Kaprio J, Kubisch C, Färkkilä M, Palotie A, Wessman M, et al. (2009) Genetic association study of Endothelin-1 and its receptors EDNRA and EDNRB in migraine with aura. Cephalalgia 29 (11):1224–1231.
Todt U, Freudenberg J, Goebel I, Heinze A, Heinze-Kuhn K, Rietschel M, Göbel H, Kubisch C (2006) Variation of the serotonin transporter gene SLC6A4 in the susceptibility to migraine with aura. Neurology 67(9):1707–1709.
Todt U, Freudenberg J, Goebel I, Netzer C, Heinze A, Heinze-Kuhn K, Göbel H, Kubisch C (2006) MTHFR C677T polymorphism and migraine with aura. Ann Neurol 60(5):621–622.
Trabace S, Brioli G, Lulli P, Morellini M, Giacovazzo M, Cicciarelli G, Martelletti P (2002) Tumor necrosis factor gene polymorphism in migraine. Headache J Head Face Pain 42(5):341–345.
Tronvik E, Stovner LJ, Bovim G, White LR, Gladwin AJ, Owen K, Schrader H (2008) Angiotensin-converting enzyme gene insertion/deletion polymorphism in migraine patients. BMC Neurol 8(1):4–9.
Tunbridge EM, Harrison PJ, Weinberger DR (2006) Catechol-o-methyltransferase, cognition, and psychosis: Val 158 Met and beyond. Biol Psychiatry 60(2):141–151.
Turk DC (2002) Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. Clin J Pain 18 (6):355–365.
Tzourio C, El Amrani M, Poirier O, Nicaud V, Bousser M-G, Alperovitch A (2001) Association between migraine and endothelin type A receptor (ETA- 231 A/G) gene polymorphism. Neurology 56(10):1273–1277.
Ursu D, Ebert P, Langron E, Ruble C, Munsie L, Zou W, Fijal B, Qian Y-W, McNearney TA, Mogg A, et al. (2014) Gain and loss of function of P2X7 receptors: mechanisms, pharmacology and relevance to diabetic neuropathic pain. Mol Pain 10:37–48.
Valdes AM, Spector TD, Tamm A, Kisand K, Doherty SA, Dennison EM, Mangino M, Tamm A, Kerna I, Hart DJ, et al. (2010) Genetic variation in the SMAD3 gene is associated with hip and knee osteoarthritis. Arthritis Rheum 62(8):2347–2352.
van den Maagdenberg AM, Pietrobon D, Pizzorusso T, Kaja S, Broos LA, Cesetti T, van de Ven RC, Tottene A, van der Kaa J, Plomp JJ, et al. (2004) A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron 41(5):701–710.
Vargas-Alarcon G, Alvarez-Leon E, Fragoso J-M, Vargas A, Martinez A, Vallejo M, Martinez-Lavin M (2012) A SCN9A gene-encoded dorsal root ganglia sodium channel polymorphism associated with severe fibromyalgia. BMC Musculoskeletal Disord 13 (1):23–28.
Vargas-Alarcón G, Fragoso J-M, Cruz-Robles D, Vargas A, Martinez A, Lao-Villadóniga J-I, Garća-Fructuoso F, Vallejo M, Martínez-Lavín M (2009) Association of adrenergic receptor gene polymorphisms with different fibromyalgia syndrome domains. Arthritis Rheum 60(7):2169–2173.
Vargas-Alarcón G, Fragoso J-M, Cruz-Robles D, Vargas A, Vargas A, Lao-Villadóniga J-I, Garća-Fructuoso F, Ramos-Kuri M, Hernández F, Springall R, et al. (2007) Catechol-O-methyltransferase gene haplotypes in Mexican and Spanish patients with fibromyalgia. Arthritis Res Ther 9(5):R110.
Visscher C, Lobbezoo F (2015) TMD pain is partly heritable. A systematic review of family studies and genetic association studies. J Oral Rehabil 42(5):386–399.
Wallace D, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman M (2001) Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. Rheumatology 40 (7):743–749.
Wang LX, Wang ZJ (2003) Animal and cellular models of chronic pain. Adv Drug Deliv Rev 55(8):949–965.
Wang Q, Guo S, Duan G, Xiang G, Ying Y, Zhang Y, Zhang X (2015) Novel and novel de novo mutations in NTRK1 associated with congenital insensitivity to pain with anhidrosis: a case report. Medicine 94(19):e871.
Waxman SG, Merkies IS, Gerrits MM, Dib-Hajj SD, Lauria G, Cox JJ, Wood JN, Woods CG, Drenth JP, Faber CG (2014) Sodium channel genes in pain-related disorders: phenotype–genotype associations and recommendations for clinical use. Lancet Neurol 13(11):1152–1160.
Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, Martin SP, Gates LK, Amann ST, Toskes PP, et al. (1996) Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 14(2):141–145.
Winsvold BS, Nelson CP, Malik R, Gormley P, Anttila V, Vander Heiden J, Elliott KS, Jacobsen LM, Palta P, Amin N (2015) Genetic analysis for a shared biological basis between migraine and coronary artery disease. Neurol Genet 1(1):e10.
Witt H, Luck W, Hennies HC, Claen M, Kage A, La U, Landt O, Becker M (2000) Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet 25(2):213–216.
Xiao J-L, Meng J-H, Gan Y-H, Zhou C-Y, Ma X-C (2015) Association of GDF5, SMAD3 and RUNX2 polymorphisms with temporomandibular joint osteoarthritis in female Han Chinese. J Oral Rehabil 42:529–536.
Yamada K, Nozawa-Inoue K, Kawano Y, Kohno S, Amizuka N, Iwanaga T, Maeda T (2003) Expression of estrogen receptor α

(ERα) in the rat temporomandibular joint. Anatom Record A Discov Mol Cell Evolut Biol 274(2):934–941.

Yang Y, Wang Y, Li S, Xu Z, Li H, Ma L, Fan J, Bu D, Liu B, Fan Z, et al. (2004) Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet 41(3):171–174.

Yap AU, Tan KB, Prosthodont C, Chua EK, Tan HH (2002) Depression and somatization in patients with temporomandibular disorders. J Prosthet Dent 88(5):479–484.

Ylmaz IA, Özge A, Erdal ME, Edgünlü TG, Çakmak SE, Yaln OÖ (2010) Cytokine polymorphism in patients with migraine: some suggestive clues of migraine and inflammation. Pain Med 11 (4):492–497.

Ylmaz M, Erdal ME, Herken H, Çataloluk O, Barlas Ö, Bayazt YA (2001) Significance of serotonin transporter gene polymorphism in migraine. J Neurol Sci 186(1):27–30.

Yis U, Mademan I, Kavukçu S, Baets J (2015) A novel NTRK1 mutation in a patient with congenital insensitivity to pain with anhidrosis. Acta Neurol Belg.

Zhang L-L, Lin Z-M, Ma Z-H, et al. (2006) Hot Mutation Spots of SCN9A Gene in Primary Erythermalgia. Chin J Dermatovenereol 11:002.

Zubieta J-K, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D (2003) COMT val158met genotype affects μ-opioid neurotransmitter responses to a pain stressor. Science 299(5610):1240–1243.

(Accepted 25 April 2016)
(Available online 30 April 2016)