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The Genetic Basis of Delayed Puberty

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Abstract

The genetic control of puberty remains an important but mostly unanswered question. Late pubertal timing affects over 2% of adolescents and is associated with adverse health outcomes including short stature, reduced bone mineral density and compromised psychosocial health. Self-limited delayed puberty (DP) is a highly heritable trait, which often segregates in an autosomal dominant pattern; however, its neuroendocrine pathophysiology and genetic regulation remain unclear. Some insights into the genetic mutations that lead to familial DP have come from sequencing genes known to cause GnRH deficiency, most recently via next generation sequencing, and others from large-scale genome wide association studies in the general population. Investigation of the genetic control of DP is complicated by the fact that this trait is not rare and that the phenotype is likely to represent a final common pathway, with a variety of different pathogenic mechanisms affecting the release of the puberty 'brake'. These include abnormalities of GnRH neuronal development and function, GnRH receptor and LH/FSH abnormalities, metabolic and energy homeostasis derangements and transcriptional regulation of the HPG axis. Thus, genetic control of pubertal timing can range from early fetal life via development of the GnRH network, to those factors directly influencing the puberty brake during mid-childhood.

Introduction

Puberty is the maturational process of the reproductive endocrine system that results in achievement of adult height and body proportion, in addition to development of the genital organs and the capacity to reproduce. The onset of puberty is driven by an increase in the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. This activation results in increased luteinizing hormone (LH) and follicular-stimulating hormone (FSH) release from the anterior pituitary, which act on the gonads to stimulate their development, gametogenesis and sex steroid production.

The development of the hypothalamic-pituitary-gonadal (HPG) axis is exceptional in that GnRH neurons develop in metazoan embryos outside of the central nervous system. Immature GnRH precursor neurons are first detectable in the olfactory placode in the nose from an early embryological stage, and then begin a complex journey towards the hypothalamus [1].

The axis is active in fetal and in early infant life, the so-called 'mini-puberty', and then becomes dormant between the age of one and 8-9 years [2]. Development of the clinical features of puberty is initiated by the reactivation of the HPG axis after this relative quiescence during childhood. What drives this suppression of the axis during childhood, and what controls the release of this 'brake' and the timing at which this occurs, is little understood.

Despite the demonstrated importance of environmental factors such as body mass, psychosocial stressors and endocrine disrupting chemicals (EDCs) [3], genetic influence on the timing of puberty is clearly fundamental. Whilst the timing of pubertal onset varies within and between different populations, it is a highly heritable trait. The timing of sexual maturation is highly correlated within families and in twin studies, suggesting strong genetic determinants [4]. Previous epidemiological studies and genetic approaches estimate that 60-80% of the variation in pubertal onset is under genetic regulation [5, 6]. However, despite this strong heritability, little is known about the genetic control of human puberty; either in the normal population or in cases of disturbed pubertal timing [7].

Investigating the Inheritance of Delayed Puberty

Self-limited delayed puberty (DP), also known as constitutional delay of growth and puberty (CDGP), represents the extreme end of normal pubertal timing, and is defined as the absence of testicular enlargement in boys or breast development in girls at an age that is 2 to 2.5 standard deviations (SD) later than the population mean [7]. In addition, self-limited DP may also encompass older children with delayed pubertal progression, a diagnosis that is aided by the use of puberty normograms [8]. Self-limited DP is associated with adverse health outcomes including short stature, reduced bone mineral density and compromised psychosocial health [9].

Self-limited DP represents the commonest cause of DP in both sexes. Up to 63% of boys with pubertal delay have self-limited DP [10]. Self limited DP segregates within families with complex patterns of inheritance including autosomal dominant, autosomal recessive, bilineal and X-linked [11], although sporadic cases are also observed (Figure 1). The majority of families display an autosomal dominant pattern of inheritance (with or without complete penetrance) [4, 11]. 50 to 75% of subjects with self-limited DP have a family history of delayed pubertal onset [11].

Analysis of self-limited DP families is complicated by the fact that this phenotype represents the tail of a normally distributed trait within the population, so it is expected that variants that govern the inheritance of this condition will also be present in the general population at a low level. Thus, the absence of these variants in population databases cannot be used as an exclusion criterion. Instead, a comparison of prevalence of such variants must be made to identify those that are enriched in patients compared to the general population. In the majority of patients with DP the neuroendocrine pathophysiology and its genetic regulation remain unclear. Linkage analysis and targeted sequencing strategies appear to have been superseded by whole exome and genome sequencing strategies to identify novel candidate genes.

Evidence from population studies

Attempts to identify key genetic regulators of the timing of puberty in humans have led to several large genome wide association studies (GWAS) of age-at-

menarche, examining pubertal timing in healthy women [12-14]. These studies demonstrate genetic heterogeneity in pubertal timing, with the observation that the genetic architecture of the timing of puberty in healthy subjects is likely to involve at least hundreds of common variants. The first of many loci associated with age of menarche was the gene *LIN28B* [15]. *LIN28B* is a human ortholog of the gene that controls, through microRNAs, developmental timing in the Caenorhabditis elegans. However, mutations in *LIN28B* have not to date been identified in human patients with DP [16] or precocious puberty [17].
The most recent study of this type comprises 1000 Genomes Project-imputed genotype data in up to ~370,000 women, and identifies 389 independent signals ($P < 5 \times 10^{-8}$) for age at menarche [18]. Per-allele effect sizes ranged from 1 week to five months. These signals explain ~7.4% of the population variance in age at menarche, corresponding to ~25% of the estimated heritability. Many of these signals have concordant effects on the age at voice breaking, a corresponding milestone in males. However, in women the signals identified had stronger effects on early than on late age of menarche, but in contrast had larger effect estimates for relatively late than relatively early voice breaking in males [18]. Around 250 genes were identified via coding variation or associated expression, particularly those expressed in neural tissues. Importantly, genes already implicated in rare disorders of puberty were identified, including *LEPR*, *GNRH1*, *KISS1*, *TACR3.* Two imprinted genes were also reported: *MKRN3*, paternally-inherited mutations in which have been identified as causal in pedigrees of central precocious puberty (CPP) [19]; and *DLK1* [20]. *MKRN3* is the third, and to date the most frequently mutated, gene in pedigrees with CPP [19], the others being *KISS1* [21] and its receptor *GPR54* [22] which have been reported only rarely. *MKRN3* is thought to contribute to the puberty 'brake' restraining the HPG axis via inhibition of GnRH release. Very recently a complex defect in *DLK1* has been identified in one pedigree with CPP [20]. However, neither *MKRN3* nor *DLK1* mutations have been implicated in the pathogenesis of DP (Figure 2).

Genetics of GnRH deficiency or signalling

At the extreme end of the spectrum of DP are conditions of GnRH deficiency including hypogonadotropic hypogonadism (HH), with complete failure to enter

puberty. The condition may be due to failure of development of GnRH neurons, lack of activation of GnRH secretion or disrupted GnRH signaling. Because of different causes and incomplete penetrance, there is a wide spectrum of phenotypes, ranging from complete HH with lack of pubertal development to a partial hypogonadism with an arrest of pubertal development, and even reversible HH in some patients post treatment [23, 24]. Despite recent advances, with over twenty genes linked to this disorder identified, the pathophysiological basis of HH in approximately 50% of individuals remains unclear [2]. In view of the possible overlap between the pathophysiology of DP and conditions of GnRH deficiency, a few studies have examined the contribution of mutations in HH genes to the phenotype of self-limited DP.

Loss-of-function mutations within the GnRH receptor are the most frequent cause of autosomal recessive IHH, accounting for 16% to 40% of patients. Mutations have been found within the extracellular, transmembrane and intracellular domains of the receptor leading to impaired GnRH action [25]. A homozygous partial loss-of-function mutation in *GNRHR* was found in two brothers, one with self-limited DP and one with idiopathic HH [26], and a further heterozygous mutation found in one male with self-limited DP [27]. A small cohort of 31 patients was analysed for mutations in *GHSR* and 5 patients were found to have point mutations in this gene [28]. Additionally, mutations in *HS6ST1*, *FGFR1* and newly in *KLB* have been found in a small number of kindreds of HH patients and their relatives with DP [29-31]. Recently, variants in several HH genes including *GNRHR*, *TAC3*, *TACR3*, *IL17RD* and *SEMA3A* have been identified by whole exome sequencing in some cases of DP, including self-limited DP [32]. However, these variants have not been tested *in vitro* or *in vivo* for pathogenicity and thus may be an over-estimation. However, the current picture indicates that the genetic background of HH and DP may be largely different, or shared by as yet undiscovered genes [27].

Genetic defects affecting the development of the anterior pituitary may also cause GnRH deficiency. The pituitary transcription factors *LHX3, SOX2* and *HESX1* are vital for early patterning of the forebrain and pituitary, and mutations in these developmental genes result in syndromic hypopituitarism with gonadotropin deficiency in humans [33]. *PROP1* is important for the

development of gonadotropin-secreting cells and mutations in this gene are the most common cause of combined pituitary hormone deficiency in humans [34]. Patients with *PROP1* mutations have variable GnRH deficiency ranging from DP to congenital HH [33]. Mutations in *DAX1* cause X-linked adrenal hypoplasia congenita with associated HH, but have not been found in isolated DP [35]. GnRH deficiency may also be associated with other conditions, particularly with neurological phenotypes. Mutations in *POLR3A/B* result in the 4H syndrome (Hypomyelination, Hypodontia and Hypogonadotropic Hypogonadism) [36] whilst those in *RNF216, OTUD4* and *PNPLA6* produce the phenotypic combination of HH and ataxia (also know as Gordon-Holmes syndrome) [37, 38]. *DMXL2* mutations are associated with congenital HH, other endocrine deficiencies and polyneuropathies [39]. Dysregulation of the RAB3 cycle, such as with mutations in *RAB3GAP1*, lead to Warburg Micro syndrome with ocular, neurodevelopmental and central reproductive defects [40, 41].
Downstream mutations in the GnRH signaling pathway can also present with DP. LH and FSH are glycoprotein hormones encoded by a common α-subunit gene and a specific β-subunit gene. Mutations of the β-subunits genes of LH or FSH are extremely rare causes of pubertal abnormalities [42]. Males with inactivating mutations of the *LHB* have absent pubertal development with Leydig cell hypoplasia leading to T deficiency and azoospermia. Females with inactivating mutations of *LHB* present with onset of normal puberty, but with normal or late menarche followed by infertility due to lack of ovulation [42]. Individuals with inactivating *FSHB* mutations present with incomplete pubertal development and azoospermia in males and primary amenorrhea in females [43].

Upstream regulation of the HPG axis

Kisspeptin, an excitatory neuropeptide, was identified as a permissive factor in puberty onset by the discovery of patients with GnRH deficiency with loss-of-function mutations in the *KISS1* receptor, *KISS1R* (previously known as *GPR54*) [44, 45]. Mice with knockout of *Kiss1r* were simultaneously discovered to be infertile despite anatomically normal GnRH neurons and normal hypothalamic GnRH levels [45], with a phenotype consistent with normosmic GnRH deficiency.

However, to date, only very rarely have human mutations in *KISS1* been found in patients with delayed or absent puberty [46].

The excitatory neuropeptide, neurokinin b, also plays a role in the upstream control of GnRH secretion. Identification of this pathway was also via discovery of loss-of-function mutations in *TAC3*, encoding neurokinin b, and its receptor *TACR3*, in patients with normosmic GnRH deficiency and pubertal failure [47]. Kisspeptin, neurokinin b and dynorphin are coexpressed in KNDy neurons of the arcuate nucleus of the hypothalamus [48], which project to and directly interact with GnRH neurons. Their expression is downregulated by oestrogen and testosterone as part of the negative feedback regulation of gonadotropin secretion [49, 50]. However, administration of neurokinin b agonists failed to stimulate GnRH release in rodents, and *Tacr3* knockout mice have grossly normal fertility [51, 52]. Of 50 self-limited DP patients investigated for mutations in *TAC3* and *TAC3R*, only one mutation in a single patient was found in the latter gene [53].

The inhibitory role of GABAergic neurotransmission has been clearly shown in primates [54] but is more ambiguous in rodents. Opioid peptides provide additional inhibitory input but this appears to be less critical than the GABAergic signals in restraining the initiation of puberty [55]. Additionally, *RFamide-related peptide* gene (*RFRP*), the mammalian ortholog of the avian peptide *gonadotrophin-inhibiting hormone* (*GnIH*), has been identified as a further inhibitory regulator of GnRH neuronal activity in mice [56]. Glial inputs appear to be predominantly facilitatory during puberty and consist of growth factors and small diffusible molecules, including TGFβ1, IGF-1 and neuregulins, that directly or indirectly stimulate GnRH secretion [57].

Upstream regulation of GnRH transcription is less well established. Candidate transcriptional regulators identified from a systems biology approach and animal models include *Oct-2*, *TTF*-1 and *EAP1* [58]. *Oct-2* mRNA is upregulated in the hypothalamus in juvenile rodents, blockage of Oct-2 synthesis delays age at first ovulation whilst activation of Oct-2 expression (e.g. hamartomas) induces precocious puberty [59]. *TTF-1* (thyroid transcription factor-1) enhances GnRH expression, with increased expression in pubertal rhesus monkeys [60]. *EAP1* mRNA levels also increase in primate and rodent hypothalamus during puberty.

EAP1 transactivates the *GnRH* promoter, and EAP1 knockdown with siRNA caused DP and disrupted estrous cyclicity in a rodent model [61]. However, to date no mutations in these upstream or regulatory factors have been reported in patients with DP.

Epigenetic regulators are potential mediators of the effects of the environment on the hypothalamic regulation of puberty. However, whilst experimental data from rats gives evidence for changes in histone acetylation and gene methylation leading to altered gene expression during puberty, the link between environmental factors and epigenetic control of puberty via the hypothalamus has not been established. Recent evidence highlights the importance in mice of microRNAs (particularly the miR-200/429 family and miR-155) in the epigenetic upregulation of GnRH transcription during the critical period (murine equivalent of the mini-puberty) [62]. Epigenetic changes during foetal life are also a potential mechanism for the effects of EDCs in utero [63].

Metabolism and timing of puberty

Nutritional changes play an important role in the observed secular trend towards an earlier age of pubertal onset in the developed world [64], as shown by the positive correlation between age at puberty onset and childhood body size, particularly in girls [65]. In contrast, under-nutrition in females, for example in chronic disease or anorexia nervosa, can result in delay in both the onset and tempo of puberty. [66]

This relationship between fat mass and pubertal timing is mediated, at least in part, through the permissive actions of the metabolic hormone leptin, a key regulator of body mass, produced from white adipose tissue [67]. Humans and mice lacking leptin (Lep ob/ob) or the leptin receptor (LepR db/db) fail to complete puberty and are infertile [68]. GWAS studies of pubertal timing found, in addition to leptin signaling, overlap with several genes implicated in body mass index including *FTO*, *SEC16B*, *TMEM18*, and *NEGR1* [18]. However, whilst self-limited DP in boys is associated with hypoleptinaemia [69], there have been no identified association of specific leptin or leptin receptor polymorphisms with DP [70]. Ghrelin and other gut-derived peptides may also form part of the mechanism by which energy homeostasis regulates reproductive development

[71]. Notably, children with CDGP have a dual phenotype of slow growth in childhood with DP. In contrast, both low birth weight and prematurity are associated with earlier onset of puberty [72], particularly in those children with rapid increase in length or weight in the first two years of life [73]. It remains unclear, however, if childhood obesity, insulin resistance, excess androgens or underlying genetic or epigenetic factors may explain this association [74].

Recent advances

Loss-of-function mutations in a member of the immunoglobulin superfamily, *IGSF1*, have been identified in patients with X-linked central hypothyroidism [75]. Notably, male patients with *IGSF1* mutations have a late increase in testosterone levels with a delayed pubertal growth spurt. However, pathogenic mutations in *IGSF1* have not been conclusively found in patients with isolated DP [76].

More recently, whole exome and targeted resequencing methods have implicated two pathogenic mutations in *IGSF10* as the causal factor for late puberty in six unrelated families from a large Finnish cohort with familial DP [77]. A further two rare variants of unknown significance were identified in four additional families from the cohort. Mutations in *IGSF10* appear to cause a dysregulation of GnRH neuronal migration during embryonic development (Figure 3). An intact GnRH neurosecretory network is necessary for the correct temporal pacing of puberty. Pathogenic *IGSF10* mutations leading to disrupted IGSF10 signaling potentially result in reduced numbers or mis-timed arrival of GnRH neurons at the hypothalamus; producing a functional defect in the GnRH neuroendocrine network. With this impaired GnRH system there would follow an increased 'threshold' for the onset of puberty, with an ensuing delay in pubertal timing. *IGSF10* loss-of-function mutations were also discovered in patients with a hypothalamic amenorrhoea-like phenotype. These findings represent a new fetal origin of self-limited DP, and reveal a potential shared pathophysiology between DP and other forms of functional hypogonadism.

Conclusions

This review serves to highlight the fascinating heterogeneity of genetic defects resulting in delayed and disordered puberty. Although our understanding of the highly complex underlying biological network remains imperfect, results to date demonstrate the importance of defects in GnRH neuronal development and function, GnRH receptor and LH/FSH abnormalities, transcriptional regulation of the HPG axis and metabolic and energy homeostasis derangements, in the control of pubertal timing.

Clinically the distinction in adolescence between the conditions of DP and congenital idiopathic HH is an important but difficult one. Both disorders can present with a picture of functional hypogonadotropism and in some cases may share an underlying pathophysiology. There remains no definitive test to accurately discriminate between the two diagnoses. More complex and involved management is required in patients with hypogonadism to achieve both development of secondary sexual characteristics and to maximize the potential for fertility [78]. Rapid and efficient diagnosis of patients in clinic would represent a huge leap forward in patient care and a likely significant economic advantage. While presently next generation sequencing in individuals presenting with delayed or incomplete pubertal development is only a reasonable option in a research setting, future progress in gene discovery and technical developments may facilitate the availability of genetic diagnosis as part of clinical care for patients with both GnRH deficiency and self-limiting DP.

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Figures

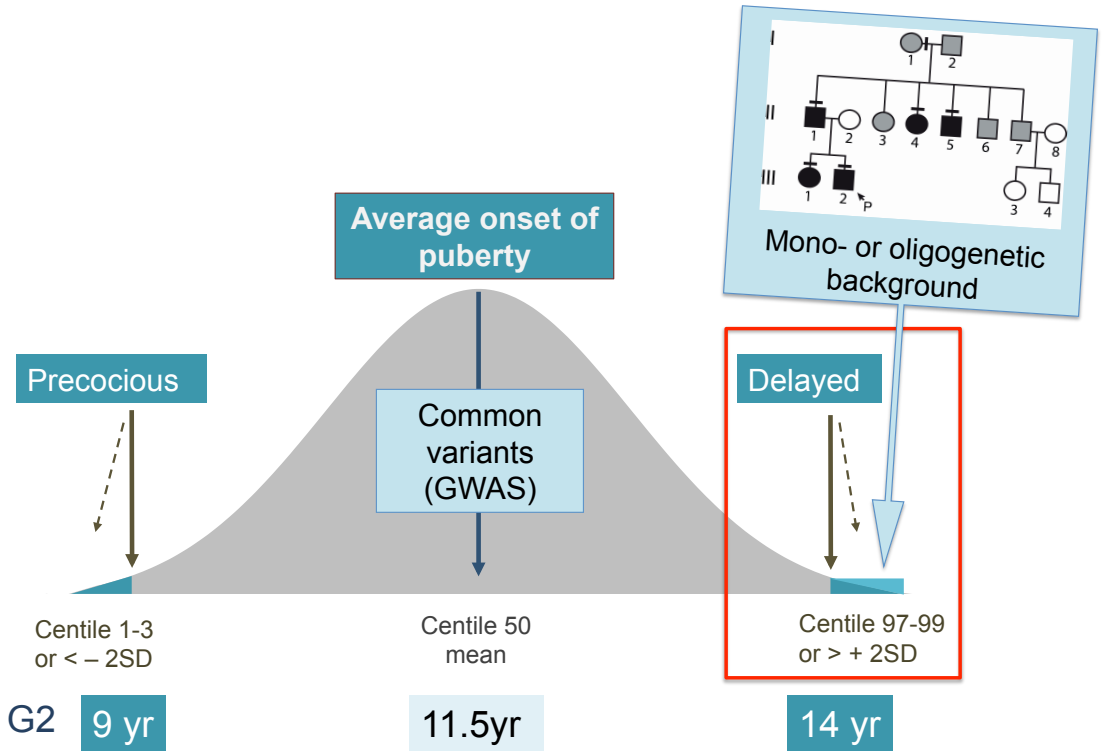

Figure 1 – The Genetics of Pubertal Timing. In the general population there is a near-normal distribution of the timing of pubertal onset, with the definitions of precocious and delayed being statistically determined (+/- 2 standard deviations, SD). Strategies to determine key genetic determinants in the timing of puberty include large genome wide association studies (GWAS) of age-at-menarche and voice breaking in the general population, and identification of rare high-impact variants causing early, late or absent puberty in patients and their families. G2 – Tanner genital stage 2 in boys.

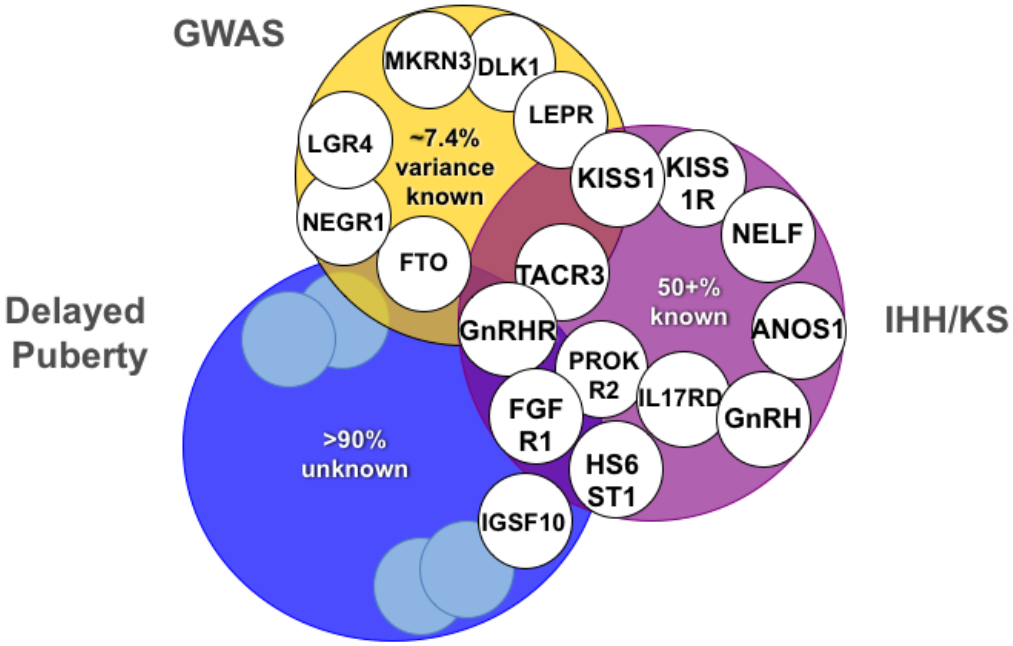

Figure 2 – Overlap between genetic regulation in the general population and extreme phenotypes.

Examples of genes implicated in timing of puberty from genome wide association studies in the general population (GWAS), conditions of GnRH deficiency such as idiopathic hypogonadotropic hypogonadism (IHH) and Kallmann Syndrome (KS), and self-limited delayed puberty.

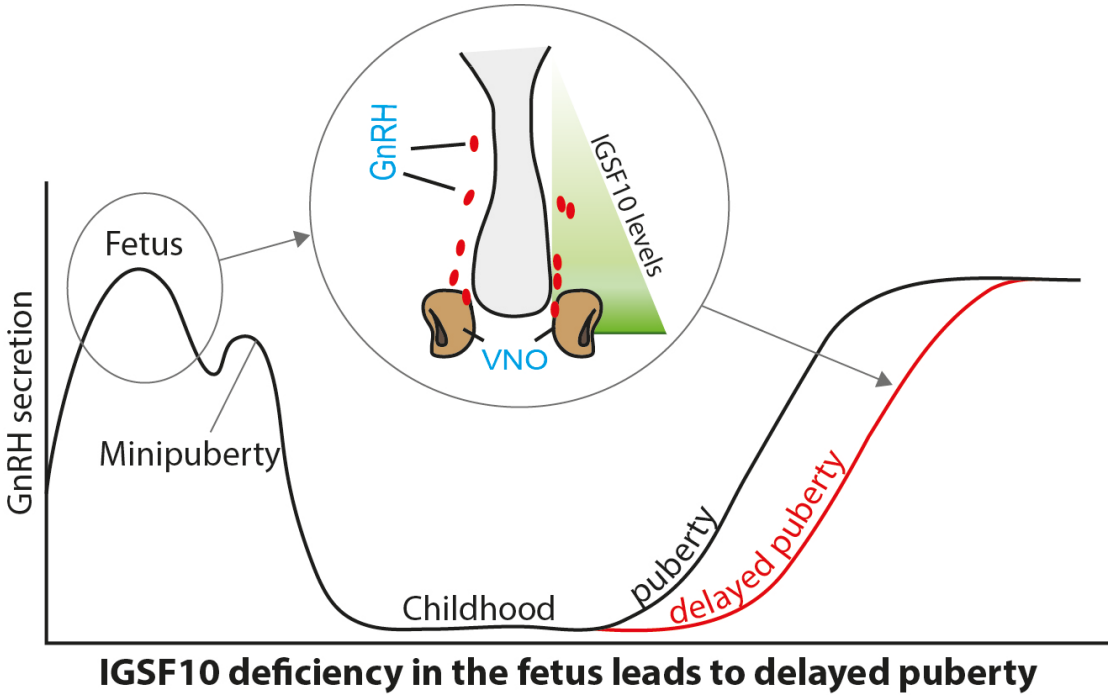

Figure 3 – Schematic of the mechanism by which *IGSF10* mutations lead to DP. Reduced levels of *IGSF10* expression during embryogenesis in the corridor of nasal mesenchyme from the vomeronasal organ to the olfactory bulbs result in delayed migration of GnRH neurons to the hypothalamus. This presents for the first time in adolescence as a phenotype of DP due to abnormalities of the GnRH neuronal network.