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Role of Fibroblast Growth Factor (FGF) Signaling in the Neuroendocrine Control of Human Reproduction

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Abstract

Fibroblast growth factor (FGF) signaling is critical for a broad range of developmental processes. In 2003, Fibroblast growth factor receptor 1 (*FGFR1)* was discovered as a novel locus causing both forms of isolate GnRH Deficiency, Kallmann syndrome ([KS with anosmia] and normosmic idiopathic hypogonadotropic hypogonadism [nIHH] eventually accounting for approximately 10% of gonadotropin-releasing hormone (GnRH) deficiency cases. Such cases are characterized by a broad spectrum of reproductive phenotypes from severe congenital forms of GnRH deficiency to reversal of HH. Additionally, the variable expressivity of both reproductive and non-reproductive phenotypes among patients and family members harboring the identical FGFR1 mutations has pointed to a more complex, oligogenic model for GnRH deficiency. Further, reversal of HH in patients carrying *FGFR1* mutations suggests potential gene-environment interactions in human GnRH deficiency disorders.

Keywords

GnRH deficiency; Kallmann syndrome; FGF signaling; FGFR1; FGF8; Oligogenicity

Introduction

Puberty is a signal developmental event leading to fertility. Its timing varies greatly in the general population and is influenced by both genetic and environmental factors (Nathan and Palmert 2005). In extreme cases of pubertal delay, sexual maturation progresses only partially or not at all, resulting in the clinical picture of idiopathic hypogonadotropic hypogonadism (IHH). This rare form of congenital gonadotropin-releasing hormone (GnRH) deficiency (incidence 1: 10,000 – 1: 40,000) results in incomplete/absent of sexual maturation and infertility and may present with anosmia (termed Kallmann syndrome [KS]) or with a normal sense of smell (nIHH). These disorders have a male to female ratio of 4:1 (Seminara, Hayes et al. 1998; Hu, Tanriverdi et al. 2003) and are both clinically and genetically heterogeneous. Notably, studies on the critical roles of mutated genes causing human GnRH deficiency in the fate specification, proliferation, developmental migration, secretory function, and/or survival of GnRH neurons have formed the basis for much of our current understanding of GnRH biology (Bianco and Kaiser 2009). In this review, we focus on the role of fibroblast growth factor (FGF) signaling pathway in human GnRH deficiency.

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Lessons from *FGFR1*

In 2003, Fibroblast growth factor receptor 1 (*FGFR1)* was identified as the first gene causing the autosomal dominant form of KS by mapping overlapping deletions on chromosome 8p11-p12 in two KS patients with contiguous gene syndromes (Dode, Levilliers et al. 2003). Mutations in *FGFR1* have now been identified in as many as 10% of KS cases, mostly in the heterozygous state (Dode, Levilliers et al. 2003; Sato, Katsumata et al. 2004; Pitteloud, Acierno et al. 2006; Trarbach, Costa et al. 2006; Raivio, Sidis et al. 2009; Sykiotis, Plummer et al. 2010; Shaw, Seminara et al. 2011).

FGFR1 encodes one of 4 FGFRs, which are cell surface receptors of the tyrosine kinase family. The extracellular immunoglobulin domains 2 and 3 (D2 and D3) determine ligand binding, affinity, and specificity. Alternative splicing of the carboxy-terminal half of D3 plays a pivotal role in modulating FGF binding specificity via the generation of the isoforms FGFR1-IIIb and FGFR1-IIIc. The IIIb isoform encoded by exon 8a is expressed in epithelial tissue, while IIIc isoform enocoded by exon 8b is mesenchymal tissue specific. Activation of FGFR1 requires dimerization that is mediated by the binding of two FGFs and heparan sulfate (HS) proteoglycans to the receptor leading to the autophosphorylation of the tyrosine kinase domains (TKD). These interactions then induce the downstream signaling pathways (Figure 1) (mitogen activated protein kinase [MAPK], phosphatidylinositide 3 kinase/AKT [PI3K/AKT], and phospholipase C gamma [PLCγ] pathways)(Mohammadi, Olsen et al. 2005; Miraoui and Marie 2010).

During development, *FGFR1* has a critical role in gastrulation, organ specification, and patterning of many tissues including the brain (Itoh and Ornitz 2011). Further, the FGF pathway has a crucial role for the development of the olfactory system, with *Fgfr1* hypomorphs showing grossly normal cortex development but lacking olfactory bulbs (OB) (Hebert, Lin et al. 2003). Transgenic mice with targeted expression of dominant-negative *Fgfr1* in the GnRH neurons exhibit delayed puberty and decreased number of GnRH neurons in the hypothalamus (Tsai, Moenter et al. 2005). These mice studies revealed a role for FGFR1 in the olfactory system and GnRH ontogeny consistent with the KS patient phenotype.

While initially thought to underlie only KS (Dode, Levilliers et al. 2003), subsequent reports revealed that *FGFR1* mutations also underlie normosmic IHH (nIHH) (Figure 2)suggesting a role for *FGFR1* beyond olfactory bulb formation (Sato, Katsumata et al. 2004; Kim, Herrick et al. 2005; Pitteloud, Acierno et al. 2006; Trarbach, Costa et al. 2006; Zenaty, Bretones et al. 2006; Xu, Qin et al. 2007; Raivio, Sidis et al. 2009). In addition, the association of identical mutations with both KS and nIHH suggested that these two related clinical entities might be different manifestations of the same pathological process. GnRH deficient carrying *FGFR1* mutations exhibit variable reproductive phenotypes with different degrees of GnRH deficiency as evidenced by complete absent puberty with microphallus and cryptorchidism in some cases, to partial puberty, or the fertile eunuch subset, where patients are fertile but totally un-virilized (Pitteloud, Meysing et al. 2006; Trarbach, Silveira et al. 2007). Further, demonstrated reversals of the GnRH deficiency later in adult life in patients carrying an *FGFR1* mutation indicating a gene-environment interaction in this disorder (Pitteloud, Acierno et al. 2005; Raivio, Falardeau et al. 2007; Raivio, Sidis et al. 2009). Moreover, loss-of-function mutation in *FGFR1* can cause delayed puberty in family members of GnRH deficient probands (Pitteloud, Acierno et al. 2005). Finally, *FGFR1* mutations underlying cases of hypothalamic amenorrhea (a form of female infertility caused by transient GnRH deficiency), a condition previously thought to be functional in nature (Caronia, Martin et al. 2011), further expands the spectrum of GnRH deficient states associated with perturbed FGF signaling.

While patients harboring *FGFR1* mutations exhibit a spectrum of reproductive phenotypes, there is an equally broad range of associated, non-reproductive phenotypes (Table 1). However, to date, *FGFR1* mutations have not been associated with unilateral renal agenesis as is seen commonly in KS patients with *KAL1* mutations, a point that could be used in targeting genetic testing. This broad array of associated phenotypes mirrors the pleiotropic roles of FGF signaling in brain, ear, craniofacial structures, kidney, and limb formation (Beenken and Mohammadi 2009). A number of groups have reported the variable expressivity of GnRH deficiency and associated phenotypes within and across families carrying identical *FGFR1* mutations (de Roux, Young et al. 1999; Dode, Levilliers et al. 2003; Pitteloud, Acierno et al. 2006; Xu, Qin et al. 2007; Raivio, Sidis et al. 2009). These puzzling observations are difficult to reconcile with a simple Mendelian (monogenic) model for KS/nIHH. As such, they presented the first inklings of a more complex genetic architecture underlying GnRH deficiency.

The human *FGFR1* mutations identified in Pfeiffer syndrome and osteoglophonic dysplasia were shown to be gain-of-function (Muenke, Schell et al. 1994; Roscioli, Flanagan et al. 2000; White, Cabral et al. 2005; Farrow, Davis et al. 2006; Cunningham, Seto et al. 2007; Sow, Ramli et al. 2010). In contrast, in KS/nIHH, deletions, nonsense and missense mutations, and splice variants in FGFR1 have been identified, spanning the entire gene (Kim, Hu et al. 2008). Further, a few KS *FGFR1* mutations map to the spliced region of the receptor affecting the FGFR1c isoform (Pitteloud, Meysing et al. 2006; Dode, Fouveaut et al. 2007) suggesting a critical role for this isoform in GnRH ontogeny. *FGFR1* mutations in KS are loss-of-function as demonstrated by deletions and stop codons (Figure 2) (Dode, Levilliers et al. 2003)D. Further, additional structural and functional studies have revealed *FGFR1* missense mutations underlying GnRH deficiency are also loss-of-function, yet mutants exert their effects via different mechanisms including: i) decreased ligand binding affinity, ii) altered glycosylation resulting in decreased cell surface expression and likely abnormal receptor trafficking, and iii) decreased tyrosine kinase activity. Importantly, the severity of the loss-of-function does not accurately predict the severity of the reproductive phenotypes (Table 2). In summary, human genetics has uncovered a previously uncharted role of *FGFR1* in the neuroendocrine control of human reproduction.

Lessons from *FGF8*

The L342S *FGFR1* mutation, was originally found in a proband with KS, absent puberty, and cleft palate. Such a severe phenotype was suggestive of a severe *FGFR1* loss-of-function mutation. Yet the mutant showed normal binding to FGF2 (a universal FGF ligand) and normal MAP kinase (MAPK) activation upon FGF2 stimulation (Pitteloud, Quinton et al. 2007). Further mapping of the L342S FGFR1 amino-acid mutation onto the crystal structure of the extracellular domain of FGFR1 with FGF8 predicted the L342S would cause a dramatic decrease in FGF8b-FGFR1c binding. This structural prediction was confirmed via surface plasmon resonance, demonstrating that L342S was indeed a loss of function mutant which selectively and dramatically reduced binding affinity of FGF8 but did not affect FGF1 or FGF2 (Pitteloud, Quinton et al. 2007). This single *FGFR1* mutation was prismatic for elucidating FGF8 as a critical FGF ligand for *FGFR1* in GnRH ontogeny and uncovered a new area of investigation.

Subsequently, a large population of more than 400 GnRH deficient patients was screened for mutations in *FGF8* identifying both heterozygous and homozygous *FGF8* mutations in KS and nIHH patients (Falardeau, Chung et al. 2008), thus confirming this as a novel locus for GnRH deficiency (Figure 3). Subjects harboring *FGF8* mutations similarly display a broad spectrum of pubertal development ranging from absent, to partial, to complete puberty (in a male with adult onset hypogonadotropic hypogonadism (Nachtigall, Boepple et al. 1997)).

Their associated non-reproductive phenotypes are equally variable including hearing loss and a range of skeletal features (high arched palate, cleft lip/palate, severe osteoporosis, camptodactyly, and hyperlaxity of the digits). Notably, variable expressivity among family members is evident with anosmia, delayed puberty, and IHH present in family members harboring the identical heterozygous R127X mutation in *FGF8*. Indeed, this theme of incomplete penetrance was also displayed in a report of a Brazilian family including an asymptomatic father and his 5 affected children, with variable phenotypes ranging from IHH with cleft lip/palate, KS, IHH, neurosensorial deafness and delayed puberty all of whom harbor the identical heterozygous stop codon in *FGF8* and thus a nonfunctional ligand (Trarbach, Abreu et al. 2010). Notably, the first heterozygous *FGF8* mutation identified in humans was reported in relation to a male with non-syndromic cleft lip and palate whose reproductive status was unknown (Riley, Mansilla et al. 2007) (Figure 3).

FGF8 is a powerful morphogen during development not only for the olfactory placode, but also for the anterior cortex, limbs, ears, and kidney. Thus, its expression and activity are under tight temporal and spatial regulation during development (Niehrs and Meinhardt 2002). *Fgf8* hypomorphic mice die at birth with midline, cerebellar, and cardiac defects (Meyers, Lewandoski et al. 1998). Interestingly, fgf8 expression overlaps with fgfr1 as *Fgf8* mRNA is found in the ectoderm region ventral/lateral of the telencephalic commissural plate on E9.5, which later forms the olfactory placode (Crossley and Martin 1995; Kawauchi, Shou et al. 2005). Murine expression studies suggest that fgf8 signaling is critically important for the induction and differentiation of the mouse olfactory placode (Chung, Moyle et al. 2008; Chung and Tsai 2010).

Human FGF8 genetics pointed to a critical role for FGF8 in GnRH ontogeny. Indeed, Fgf8 hypomorph mice exhibit absent GnRH neurons in the hypothalamus and lack fate specification of GnRH neurons in the olfactory placode with no signs of apoptosis, supporting a critical role for FGF8 in GnRH specification. The heterozygous mice had significantly decreased numbers of GnRH neurons, implying an exquisite sensitivity of the GnRH neuron population to Fgf8 dosage (Falardeau, Chung et al. 2008). These murine studies are consistent with olfactory and reproductive phenotypes observed in patients harboring heterozygous *FGF8* mutations.

Modes of inheritance and oligogenicity

Much like the genetic story of Bardet-Biedl syndrome (BBS), wherein a “monogenic” disorder was subsequently shown to be oligogenic in nature with mutations in more than one BBS gene (Badano and Katsanis 2002), oligogenicity underlying human GnRH deficiency has become an emerging theme. Human GnRH deficiency has been traditionally considered a monogenic disorder. Rare variants in *FGFR1* were first thought to cause autosomal dominant form of KS (Dode, Levilliers et al. 2003). However, reports of the same mutation (i.e. R622X *FGFR1* in 3 unrelated kindreds (Dode, Levilliers et al. 2003; Pitteloud, Acierno et al. 2005; Xu, Qin et al. 2007)) (Figure 4) demonstrate significant phenotypic variability both within and across IHH family members carrying the identical mutation and incomplete penetrance. Such variable expressivity has been noted by others (Parenti, Rizzolo et al. 1995; de Roux, Young et al. 1999), supporting the notion that a genotype at a single locus cannot reliably predict the phenotypic manifestations of the various family members harboring the same mutation(Pitteloud, Acierno et al. 2005) (Pitteloud, Acierno et al. 2006; Pitteloud, Meysing et al. 2006). Subsequently, several case reports of KS/nIHH individuals carrying two gene defects have been published (Pitteloud, Quinton et al. 2007; Pitteloud, Durrani et al. 2010). Subsequently, nearly 400 GnRH deficient patients were studied systematically for the known IHH loci demonstrating that oligogenicity is as common as homozygosity/compound heterozygosity in human GnRH deficiency (Sykiotis, Plummer et

al. 2010). Notably, the major player identified in digenic or oligogenic mutations was *FGFR1*, supporting the central role of FGF signaling in human GnRH deficiency. Further, these reports raise the question whether heterozygous *FGFR1* mutations per se can cause GnRH deficiency or whether additional gene defects and/or environmental cues are required.

Future directions and conclusions

During the last decade, human and murine models have demonstrated a critical role for FGF signaling in GnRH ontogeny. Studying *FGFR1/FGF8* mutations in KS/nIHH has been critical in challenging the traditional monogenic model of these disorders and pointing to a role for complex genetics. However, the precise molecular mechanism underlying the effect of loss-of-function FGF8/FGFR1 mutations on GnRH ontogeny remain largely unknown and further biologic investigation is required to decipher the precise role of this signaling system in human reproduction.

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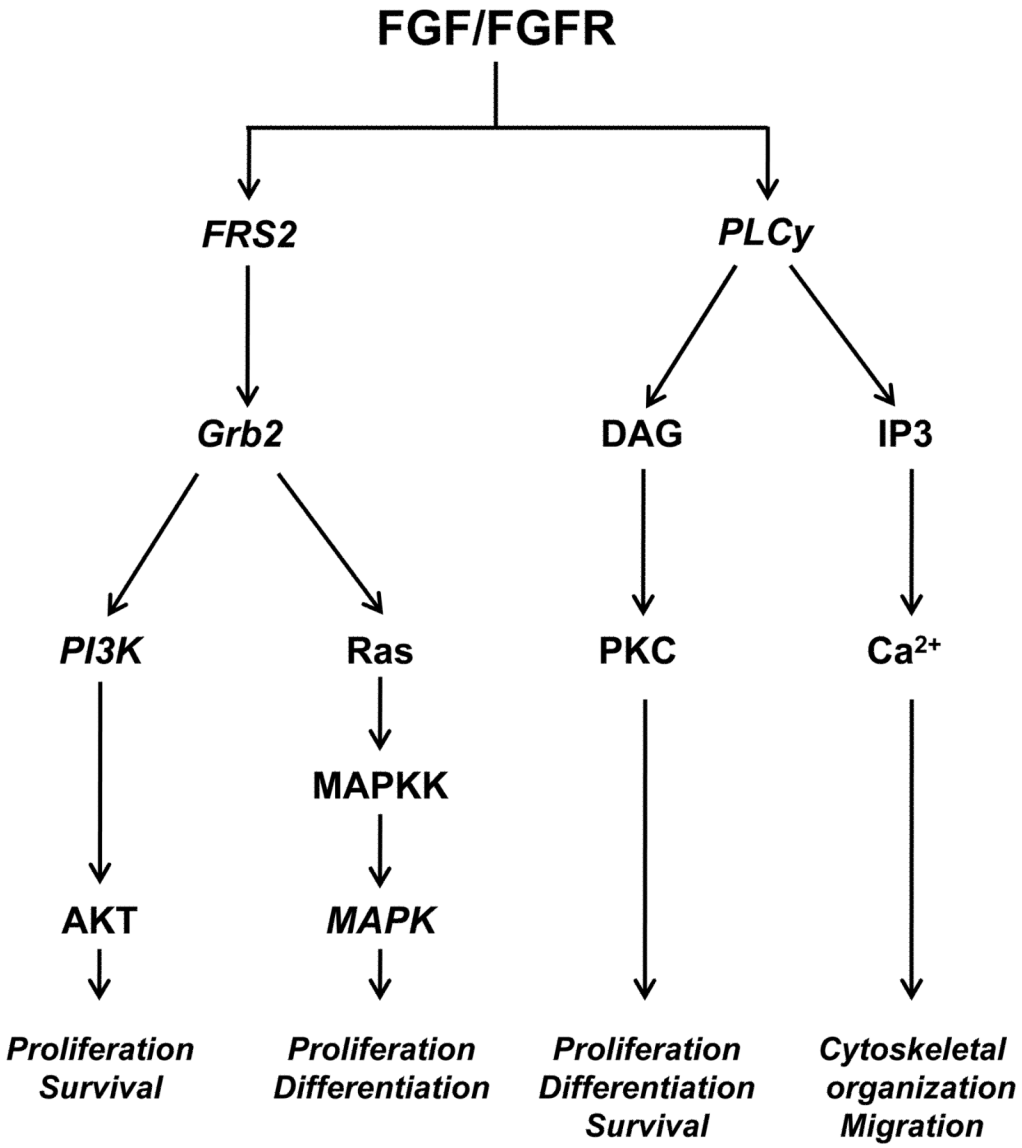

Figure 1. Pathways downstream of FGFR signaling

FGF/FGFR binding leads to activation of several signal transduction pathways including phospholipase Cγ (PLCγ), mitogen-activated protein kinases (MAPK), and phosphatidylinositol 3-kinase (PI3K). FGF signaling cascades are implicated in the control of several cellular processes including cell proliferation, differentiation, and survival in multiple tissues and cell lines.

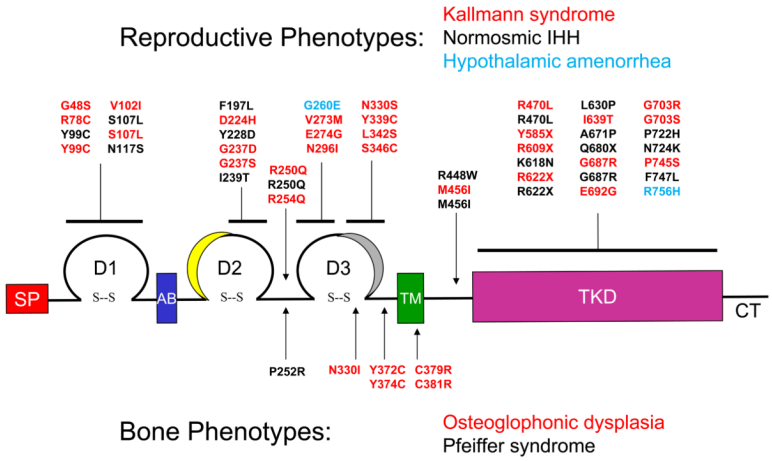

Figure 2. Schematic representing the structural domains of FGFR1 protein with identified human mutations (GnRH deficiency and bone phenotypes)

Signal peptide (SP), acidic box (AB), immunoglobulin like domains (D 1–3), heparan sulfate (yellow crescent), 2nd half of D3 ([gray crescent], determines FGFR1 c or b isoform), transmenbrane domain (TM), tyrosine kinase domains (TKD), and C-terminal tail (CT) are shown. Human FGFR1 mutations exhibiting a reproductive phenotype (GnRH deficiency) are identified above the schematic while bone phenotypes are depicted below.

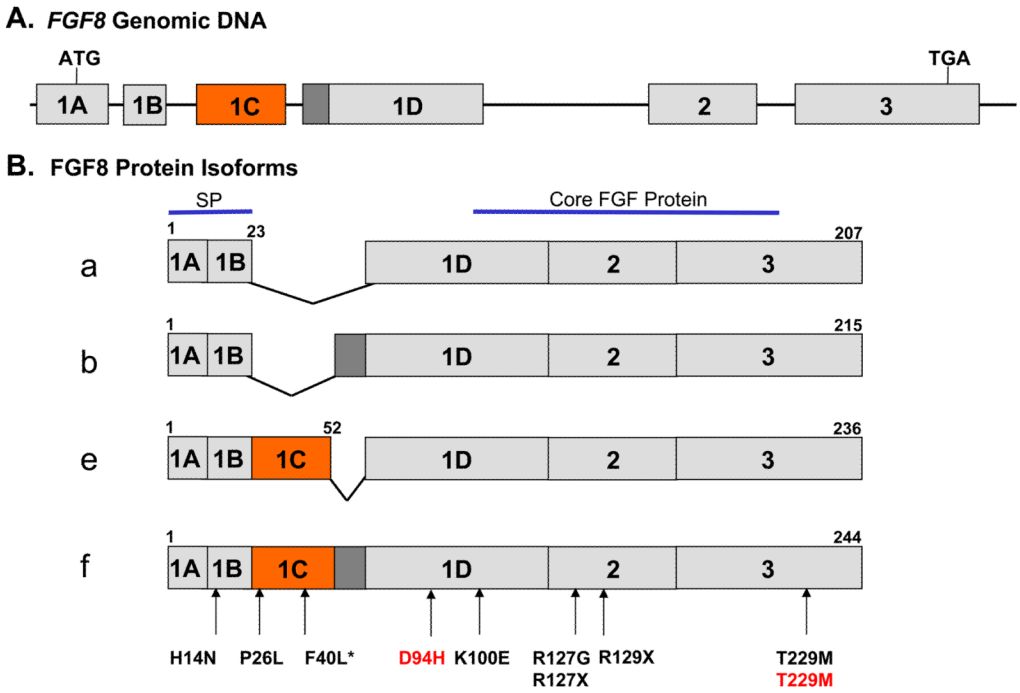

Figure 3. Schematic of genomic structure and differential splicing of the human *FGF8* gene with human mutations identified to date (GnRH deficiency and midline defects)

(A) Structure of the *FGF8* gene: Boxes denote exons; lines denote introns. (B) Schematic of the 4 FGF8 isoforms identified in humans, which differ with regard to the inclusion of exon 1C and part of exon 1D. Most of the conserved FGF core is encoded by exons 2 and 3. Numbers above exons denote the amino acid numbering for each isoform. The mutations identified to date are indicated by arrows and are numbered according to the FGF8f protein isoform. The two mutations in red denote midline defects (D94H [D73H in FGF8b numbering] = nonsyndromic cleft lip/palate (Riley, Mansilla et al. 2007); T229M = holoprosencephaly (Arauz, Solomon et al. 2010)). Asterisk denotes the homozygous change (adapted from Falardeau et. al. (Falardeau, Chung et al. 2008)).

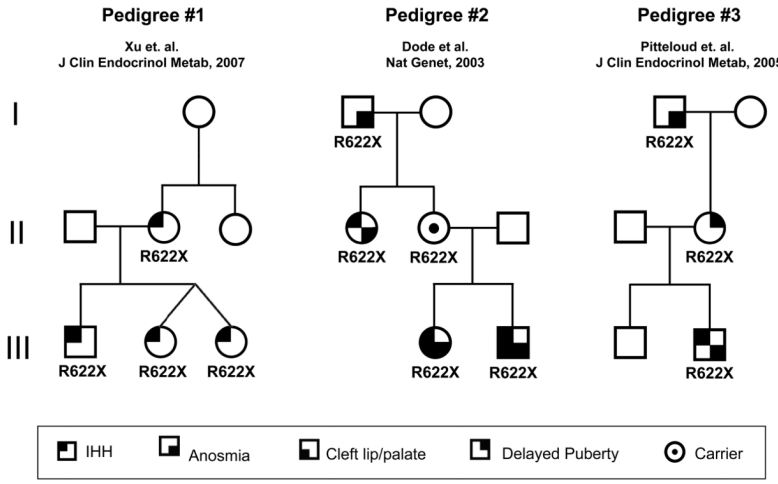

Figure 4. Variable expressivity in three kindreds harboring the identical R622X *FGFR1* mutation

A single genotype cannot reliable predict the phenotype: The identical mutation presents as fully penetrant normosmic IHH in pedigree 1(Xu, Qin et al. 2007). Pedigree 2 shows both mild and severe phenotypes (asymptomatic carrier and Kallmann syndrome [KS] with cleft lip/palate respectively) (Dode, Levilliers et al. 2003). Pedigree 3 displays variable phenotypes of R622X including anosmia only, delayed puberty, and KS. Notably, the KS subject exhibited a reversal (Pitteloud, Acierno et al. 2005).

Table 1

FGFR1 mutations in human GnRH deficiency: associated non-reproductive phenotypes

Skeletal Phenotypes	Other Phenotypes
Cleft lip/palate [1–5,7,9]	synkinesia [1, 4, 7]
dental agenesis [1–3, 5–7, 10]	corpus callosum agenesis [1]
absent nasal cartilage [1]	frontal bossing [8]
external ear hypoplasia/agenesis [5]	hypertelorism [5]
mandibular hypoplasia [5]	iris coloboma [1]
thoracic dystrophia [5]	hearing loss [1]
member length asymmetry [5]	epilepsy [4]
cubitus valgus [4]	sleep disorder [4]
syndactyly [1,5]	obesity [4]
clinodactyly [8]	mental deficiency [4]
osteopenia/osteoporosis [8]	

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Table 2

Functional and phenotypic relationship of FGFR1 mutations in human GnRH deficiency

Mutation	Domain	Structural prediction	Overall protein expression	Protein maturation	Cell surface expression	Transcription reporter activity	Kinase activity	Diagnosis	Degree of pubertal development
Y99C	D1	Disrupts D1 folding	=	↓↓↓	↓↓↓	↓↓↓	ND	nIHH	Partial
N117S	D1	Elimates glycosylation site	=	=	↓	=	ND	nIHH	Absent
Y228D	D2	Disrupts D2 ligand binding site	=	↓↓↓	↓↓↓	↓↓↓	ND	nIHH	Absent
I239T	D2	Destabilizes D2 folding	=	↓↓	↓↓	↓↓↓	ND	nIHH	Absent
R250Q	D2-D3 link	Disrupts ligand binding	=	=	=	↓↓	ND	nIHH/KS	Absent/Partial
L342S	D3	Disrupts FGF8b binding	ND	ND	ND	↓↓↓	ND	KS	Absent
G260E	D3	ND	=	ND	=	↓↓	ND	HA	Full
R470L	TK	Disrupts juxtamembrane-kinase region folding	ND	ND	ND	=	↓↓↓	nIHH	Absent
K618N	TK	Disrupts kinase A-loop	↓	=	=	=	↓	nIHH	Absent
A671P	TK	Disrupts kinase A-loop	=	=	↑	=	↓↓↓	KS	Absent
Q680X	TK	Eliminates C-ter portion including catalytic domain	↓↓	=	↓↓	↓↓↓	ND	nIHH	Absent
R756H	TK	ND	=	ND	=	↓↓	ND	HA	Full

D1 : domain 1, D2 : domain 2, D3 : domain 3, TK : tyrosine kinase, decrease

nIHH : normosmic idiopathic hypogonadotropic hypogonadism, KS = Kallmann syndrome, HA = hypothalamic amenorrhea

= represents equal to wild-type, ND : not determined;↑ : mild increase, ↓: mild decrease, ↓↓: moderate decrease, ↓↓↓ : severe decrease