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An update on the genetic causes of central precocious puberty

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Central precocious puberty (CPP) is caused by the premature reactivation of the hypothalamic-pituitary-gonadal axis. Genetic, nutritional, and environmental factors play a crucial role in determining pubertal timing. Recently mutations in kisspeptin (*KISS1*), kisspeptin receptor (*KISS1R*), and makorin RING finger protein 3 (*MKRN3*) genes have been identified as genetic causes of CPP. In particular, the *MKRN3* gene is known to affect pubertal initiation. The *MKRN3* gene is located on chromosome 15q11-q13 in the Prader-Willi syndrome (PWS) critical region. MKRN3 deficiency, due to a loss of function mutation, leads to the withdrawal of hypothalamic inhibition and prompts pulsatile gonadotropin-releasing hormone secretion, resulting in precocious puberty. The exact functions of these genes associated with CPP are still not well understood. Larger studies are required to discover the mechanisms involved in pubertal development.

Keywords: Central precocious puberty, Kisspeptins, MKRN3 gene, Mutation

Introduction

Gonadotropin-releasing hormone (GnRH) secretion is active in infancy and then becomes quiescent in childhood. At the onset of puberty, the reactivation of pulsatile GnRH secretion leads to an increase in the secretion of the gonadotropins and consequent gonadal stimulation[1]. Central precocious puberty (CPP) is caused by the premature reactivation of the hypothalamic-pituitary-gonadal axis and is usually defined by the development of secondary sexual characteristics before the age of 8 in girls and 9 in boys[2,3].

Complex interactions with genetic, nutritional and environmental factors play a crucial role in determining pubertal timing[4]. Genetic factors are have been considered to have a strong influence on pubertal initiation[5]. CPP is usually regarded to be idiopathic. de Vries et al.[6] mentioned that familial cases accounted for 27.5% (43 out of 156 children) of CPP, and segregation analysis suggested an autosomal dominant transmission with incomplete sex-dependent penetrance.

Numerous studies have been conducted to explore the genetic causes for CPP. The *GABRA1*, *NPY-Y1R*, *LIN28B*, *TAC3* and *TACR3* genes were considered regarded as potential the cause of CPP, but no mutations associated with CPP were found in these genes[7-10]. Recently, kisspeptin (*KISS1*), kisspeptin receptor (*KISS1R*), and makorin RING finger protein 3 (*MKRN3*) genes were found to be responsible for CPP, but a few cases of CPP with these mutations have been reported to date[11-13].

KISS1 and *KISS1R* gene

Kisspeptin and its receptor have been considered essential components in pubertal onset. *KISS1* encodes kisspeptin, which is a natural ligand that binds to the KiSS-1 receptor (KISS1R), a G-protein coupled receptor[14]. Several studies have demonstrated that loss of

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function mutations in *KISS1R* were detected in idiopathic hypogonadotropic hypogonadism patients and it was suggested that this receptor is a regulator of GnRH secretion[15,16]. Kisspeptin is shown to activate hypothalamic GnRH secretion, after binding KISS1R in hypothalamic GnRH-neurons[14]. KISS1 and KISS1R expressions are increase at the onset of puberty[14].

In 2008, Teles et al.[11] detected a gain-of-function mutation in the *KISS1R* gene in a girl with CPP. They identified an autosomal dominant p.Arg386Pro mutation. This mutation prolongs the activation of kisspeptin responsive to intracellular signaling and reduces the rate of normal KISS1R desensitization[11]. In response to kisspeptin stimulation, pulsatile of GnRH secretion increases and induces the initiation of puberty[17]. Silveira et al.[12] reported the p.P74S mutation in *KISS1* gene in a boy with very early pubertal development at 12 months of age, and suggested this mutation was associated with higher kisspeptin resistance to degradation, leading to an increased availability of bioactive kisspeptin. However, so far, *KISS1* and *KISS1R* mutation have been very rarely found in patients with CPP[18].

MKRN3 gene

In 2013, through whole-exome sequencing analysis, Abreu et al.[13] detected *MKRN3* gene mutations in 5 of 15 families with CPP. They found that three frameshift mutations (Arg213Glyfs*73, Tyr391*, and Ala162Glyfs*14) were predicted to encode truncated proteins and one missense mutation (Arg365Ser) predicted to disrupt protein function in 5 families originated from North America, Brazil, and Belgium.

The *MKRN3* gene is located on chromosome 15q11-q13 in the Prader-Willi syndrome (PWS) critical region[19]. While studying a PWS critical region in 1999, Jong et al.[19] discovered *MKRN3* gene. This gene is methylated on the maternal allele, but is unmethylated on the paternal allele. Therefore, the maternal imprinted *MKRN3* gene is expressed only from the paternal allele and si silenced from the maternal allele. All affected patients with familial CPP inherited the *MKRN3* mutations from their father[19]. PWS patients usually have delayed or incomplete puberty despite *MKRN3* gene deletion. However, rare cases with CPP in PWS have been reported[20,21]. There is a needs to evaluate genetic factors in 15q11-13 PWS critical region as related to pubertal timing.

The MKRN3 protein has 2 N-terminal C3H zinc finger motifs, 1 MKRN specific Cys-His domain, 1 C3HC4 RING zinc finger motif, and 1 C-terminal C3H zinc finger motif[19]. Until now, 21 *MKRN3* mutations have been described including 8 frameshift mutations, 10 missense mutations and 3 nonsense mutations[13,22-29] (Fig. 1). Abreu et al.[13] suggested that the function of *MKRN3* gene relevant to pubertal initiation include an inhibiting effect on the pubertal pulsatile GnRH secretion. Their study showed that hypothalamic Mkrn3 mRNA levels were increased in the arcuate nucleus of male and female mice at a young age and decreased immediately before puberty. They suggested they mentioned the Mkrn3 mRNA expression pattern is associated with an inhibitory effect on onset of puberty. Ojeda and Lomniczi[30] also suggested that MKRN3 inhibits the downstream activators of hypothalamic GnRH secretion, such as KISS1. MKRN3 deficiency due to a loss of function mutation leads to the withdrawal of hypothalamic inhibition, which releases and pulsatile GnRH secretion, and therefore precipitates the early onset of puberty[22]. In a study by Hagen et al.[31], the authors ascertained undetectable or low MKRN3 levels in patients with early onset of puberty, and MKRN3 levels were negatively correlated with gonadotropins in serum from prepubertal girls.

Settas et al.[22] demonstrated that a novel heterozygous missense *MKRN3* mutation (p.Cys340Gly) detected in 2 affected Greek sibling. The p.Cys340Gly mutation was predicted to disrupt the protein function in silico analysis. These 2 patients, a girl with CPP and a boy with early puberty, had inherited the mutated *MKRN3* gene from their asymptomatic carrier father and paternal grandmother. Macedo et al.[23] reported

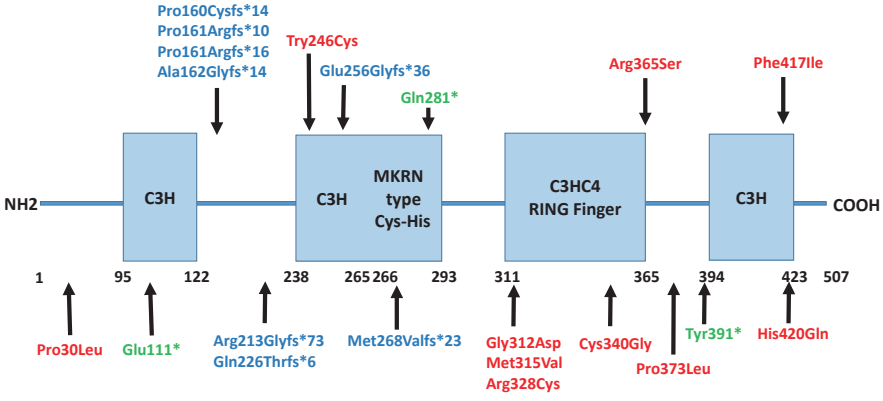

Fig. 1. MKRN3 domains (3 C3H zinc finger motifs, 1 C3HC4 RING zinc finger motif, and 1 MKRN specific Cys-His domain) and *MKRN3* mutations identified in patients with central precocious puberty. The numbers correspond to the amino acid positions in the protein. 8 frameshift mutations (blue), 10 missense mutations (red) and 3 nonsense mutations (green) are shown.

five novel heterozygous mutations in eight unrelated Brazilian patients with sporadic CPP. These mutations were composed of 4 frameshift mutations, predicted to encode truncated proteins, and 1 missense mutation (p.Phe417Ile), which were all informed of paternally inheritance in segregation analysis. de Vries et al.[24] identified a novel missense mutation (p.His420Gln) predicted to disturb RNA binding in the *MKRN3* gene. Schreiner et al.[25] identified 2 heterozygous mutations (a previous reported variant, p.Ala162Glyfs*14 and a novel mutation, p.Glu111*) in the *MKRN3* gene in 2 German families with CPP.

All patients with loss of function mutations in *MKRN3* gene show have typical clinical and hormonal finding of CPP, including breast or testicular enlargement, advanced bone age, accelerated growth velocity, and stimulated luteinizing hormone levels elevation[13,22,23]. Very few patients with *MKRN3* mutations had mild syndromic features. Two related patients had esotropia[13] and a girl had mild nonspecific features, including a high arched palate, clinodactyly, dental abnormalities and hyperlordosis[23]. Apart from these, no other signs were evident in CPP patients with *MKRN3* mutations including features of PWS[13,23]. *MKRN3* mutations affect both genders equally but seem to affect girls more severely in the onset age for puberty[13,22]. The reason for this gender difference is not yet clear. Between CPP patients with *MKRN3* mutation and those without *MKRN3* mutation, the age of pubertal initiation does not differ significantly[23]. However, another study has reported the girls with *MKRN3* mutations are significantly younger at puberty onset than those without mutations[27]. Response to treatment with depot GnRH agonists are good in CPP patients with *MKRN3* defects[13,23,27].

Conclusions

Pubertal timing is determined by interaction between inhibitory effects and stimulatory effects of hypothalamic-pituitary-gonadal axis. It is generally accepted that the *MKRN3* gene is the most frequently known genetic cause of pubertal initiation. However, the exact mechanism involved in pubertal development are still not well understood. Larger studies on the clinical features of CPP patients with *MKRN3* mutations are required and an ongoing effort to find other factors associated with the puberty should be maintained.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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