Rev Esp Endocrinol Pediatr 2023; 14 (Suppl 2)
10.3266/RevEspEndocrinolPediatr.pre2023.Apr.805

Deciphering the genetic basis of central precocious puberty

Descifrando la base genética de la pubertad precoz central

Ana Claudia Latronico, MD, PhD

Internal Medicine Department. Endocrinology and Metabolism Discipline
Sao Paulo Medical School. Sao Paulo University. Sao Paulo. Brazil

Introduction

The premature activation of pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion leads to central precocious puberty (CPP), the most common form of premature sexual development in children. The etiology of CPP is multiple and heterogeneous, including congenital and acquired causes that can be associated with structural or functional brain alterations[1]. The activation of excitatory factors or suppression of inhibitory factors during childhood represent the two major mechanisms of CPP, revealing a delicate balance of these opposing neuronal pathways. The importance of genetic and/or epigenetic factors in the underlying mechanisms of CPP has grown significantly in the last decade, as demonstrated by the evidence of genetic abnormalities in hypothalamic structural lesions (e.g., hamartomas, gliomas), syndromic disorders associated with CPP (Temple, Prader-Willi, Silver-Russell, and Rett syndromes), and isolated CPP due to monogenic defects (MKRN3 and DLK1 loss-of-function mutations)[1,2].

Monogenic causes of CPP

In 2008, a very rare heterozygous activating mutation of KISS1R (p.Arg386Pro) was identified in a girl with CPP[3]. This mutation, located in the C-terminal tail of the receptor, led to prolonged activation of intracellular signaling pathways in response to kisspeptin in mammalian cells. One rare kisspeptin variant, p.Pro74Ser, was later identified in the heterozygous state in a boy who developed sporadic CPP at age 1 year[4]. The capacity to stimulate signal transduction was significantly greater for p.Pro74Ser mutant than for the wild type, suggesting that this variant might be more resistant to degradation.

Makorin Ring Finger Protein 3 (MKRN3) is an important neuroendocrine player in the control of pubertal timing and upstream inhibitor of GnRH secretion[5-9]. The role of MKRN3 in the pathogenesis of CPP was first demonstrated in 2013, when whole exome sequence analysis was performed in several families with CPP[5]. Fifteen individuals (including 8 girls, and 7 boys) from 5 unrelated families carried loss-of-function MKRN3 mutations, characterizing a monogenic familial CPP with an autosomal dominant inheritance and exclusive paternal transmition[5]. To date, approximately 59 different mutations in the MKRN3 were identified in children with CPP[6,7]. A systematic review and meta-analysis demonstrated a prevalence of 9.0% among children with familial or sporadic CPP[6]. Interestingly, a higher prevalence was identified in males, familial cases, and in non-Asian countries. More recently, a multiethnic cohort of 716 children with CPP revealed 71 of them with different types of loss-of-function MKRN3 mutations[7]. Patients with severe MKRN3 mutations (frameshift, nonsense, promoter mutations) had a greater bone age advancement and higher basal LH levels at the time of presentation compared to patients with missense mutations. CPP due to loss-of-function mutations of MKRN3 is clinically indistinct from ICPP, however, the type of genetic defect may affect the severity of the phenotype[7].

In mice, MKRN3 mRNA levels are elevated before puberty in arcuate nucleus, suggesting a potential suppressor on GnRH secretion effect[5]. Abreu et al.[8] showed that Mkrn3 is expressed in Kiss1 neurons of the mouse hypothalamic arcuate nucleus and it repressed promoter activity of KISS1 and TAC3 genes. In addition, MKRN3 has ubiquitinase activity that can be reduced by mutations affecting the RING finger domain of the protein.

In 2017, a complex genetic defect (14 kb deletion associated with 269 bp insertion) involving another imprinted gene, Delta-like homolog 1 (DLK1 located at chromosome 14q), was identified in a family with CPP[9]. Lately, new rare frameshift mutations of DLK1 in female patients with CPP or precocious menarche (< 9 years) were identified. In all reported cases, familial segregation analysis was consistent with the maternal imprinting of DLK1[9-11]. To date 7 distinct deleterious defects in the DLK1 were identified in CPP cases, all located in the extracellular region that contains EGF-like domains. Notably, metabolic abnormalities, such as overweight/obesity, and insulin resistance, were more prevalent in the DLK1 mutated individuals when compared to the idiopathic treated CPP group, suggesting that DLK1 is a new link factor between reproduction and metabolism[10].

A large cohort of Spanish children with idiopathic CPP and their close relatives (444 individuals, Spanish PUBERE Registry) was evaluated as part of a scientific collaboration study between Brazil and Spain that aims understanding the clinical and genetic aspects of human precocious puberty. A rare allelic deletion (c.401_404 + 8del) in the splice site junction of DLK1 was identified in a Spanish girl with sporadic CPP[11]. Familial segregation analysis showed that the DLK1 deletion was de novo in the affected child. Serum DLK1 levels were undetectable (<0.4 ng/mL), indicating that the deletion led to complete lack of DLK1 production. DLK1 is a noncanonical ligand of a Delta-Notch pathway, an evolutionarily conserved signaling pathway which controls a broad range of developmental processes including cell fate determination, terminal differentiation and proliferation. Notably, the potential mechanism(s) of DLK1 deficiency leading to human CPP remains unknown.

Familial CPP

Familial CPP can be defined by diagnosis or clinical history of early sexual development in one or more first-, second-, or third-degree family member of a confirmed CPP case. Recently, we estimated a prevalence of familial CPP in 22% of a large multiethnic cohort, with a similar frequency of maternal and paternal transmission[12]. Pedigree analyses of families with maternal transmission suggested an autosomal dominant inheritance in this recent study. Clinical and hormonal features, as well as treatment response to GnRH analogs, were similar among patients with different forms of transmission of familial CPP. MKRN3 loss-of-function mutations were the most prevalent cause of familial CPP, followed by DLK1 loss-of-function mutations, affecting, respectively, 22% and 4% of the studied families; both affecting exclusively families with paternal transmission[12].

Syndromic CPP

CPP without brain lesions is mostly frequently described as an isolated entity, but it may also present combined with other signs and symptoms, encompassing a syndromic form. To date, few studies have contributed to identifying patients with syndromic disorders among large CPP cohorts[1]. In this setting, a promising translational study investigated 36 selected patients with CPP associated with multiple anomalies through (epi)genetic studies[13]. Rare genetic abnormalities were identified in 12 (33%) of them, including genetic defects in *loci* known to be involved with CPP (14q32.2 and 7q11.23) or candidate chromosomal regions or genes.

The premature activation of the reproductive axis has been described as a possible component of imprinting disorders, a group of congenital diseases caused by disturbances in imprinted genes affecting growth, development, and metabolism. Temple syndrome (OMIM 616222) is a rare imprinting disorder marked by precocious puberty in 80% to 90% of cases. Additionally, patients characteristically present with prenatal and postnatal growth failure, hypotonia, small hands and/or feet, and obesity. It is caused by the disruption of the chromosome 14q32.2, a chromosomal region carrying a cluster of imprinted genes, including DLK1 and its primary imprinting control center, the DLK1/MEG3: intergenic-differentially methylated region (DLK1/MEG3:IG-DMR). Three main 14q32.2 molecular abnormalities can underlie Temple syndrome phenotype: maternal uniparental disomy of chromosome 14, hypomethylation of the DLK1/MEG3:IG-DMR on the paternal allele (epimutation), and paternal deletion of the DLK1/MEG3 domain. These 3 mechanisms harbor in common the lack of expression of the paternal copy of DLK1 gene and clinically may manifest CPP. Based on these lines of evidence, it has been postulated that DLK1 deficiency is probably the leading cause of premature pubertal development in Temple syndrome patients[9].

Prader-Willi syndrome (OMIM 176270) is a classic imprinting disorder, mostly characterized by hypotonia, obesity, growth failure, cognitive disabilities, and hypogonadism, but it has also been associated with precocious puberty albeit infrequently (about 4%). This syndrome occurs from an absence of the paternally expressed imprinted genes at chromosome 15q11-q13. The MKRN3 gene, the most prevalent factor associated with familial CPP, is located at the

boundary of this critical region. It has been postulated that the low frequency of early puberty in Prader-Willi syndrome patients was most likely from concomitant disturbances leading to hypogonadism.

Silver-Russell syndrome (OMIM 180860) is a clinically and (epi)genetically heterogeneous imprinting disorder, mainly characterized by prenatal and postnatal growth retardation. The most common mechanisms are hypomethylation of the IGF2/H19:IG-DMR and maternal uniparental disomy of chromosome 7 (UPD(7) mat). Interestingly, precocious puberty was described in some of the first cases reported in the historical cohorts of Silver-Russell syndrome. More frequently, patients develop early puberty, characterized by age at puberty onset at the younger limit of the normal range. Children with UPD(7)mat are likely to develop puberty at younger ages, possibly from still unknown pubertal influencing factors located in this chromosome. Interestingly, another well-known chromosome 7 abnormality (Williams-Beuren syndrome) can present with premature sexual development. Williams-Beuren syndrome (also called Williams syndrome; OMIM 194050) is a multisystem disorder caused by hemizygous 7q11.23 deletion, leading to a contiguous gene syndrome with clinical heterogeneity. The main clinical features are distinct craniofacial appearance, cardiovascular disease, short stature, intellectual disability, and hypersociability. Affected children may present an early puberty (up to 50%) or CPP (3%-8%). Syndromic girls had menarche approximately 2 years earlier than control girls. Putative genotype-phenotype correlations for genes within the 7q11.23 deletion have been described. However, the exact gene or mechanism involved in this premature puberty phenotype remains unknown. Remarkably, an enriched signal for association with age at menarche within the critical region of Williams syndrome was identified in a large genome-wide association study, increasing the likelihood for this chromosome to carry a potential pubertal influencing factor.

The putative role of genes on the X chromosome in the genetic architecture of human pubertal timing may also be suspected by the description of rare cases of defects in the X-linked gene methyl-CpG-binding protein 2 (MECP2) presenting with precocious puberty. Loss-of-function mutations in MECP2 are associated with neurodevelopmental disorders, mainly with Rett syndrome (OMIM 312750), an X-linked dominant disorder occurring mostly in females. Remarkably, CPP has been described in atypical or rare cases of girls with Rett syndrome. Interestingly, precocious puberty was also described in up to 13% of girls with dominant de novo mutations in the X-linked gene dead-box helicase 3 X-linked (chromosome Xp11.4), which causes an X-linked intellectual development disorder (OMIM 300958).

Conclusions and Perspectives

Genetic and epigenetic abnormal findings associated with human CPP phenotype revealed that this endocrine pediatric condition has a strongly influence of epigenetic mechanisms (especially, methylation modifications) as demonstrated by identification of loss-of-mutations in two imprinted genes (MKRN3, DLK1) and its potential association with epigenetic syndromes (Temple syndrome, Prader-Willi syndrome and Rett syndromes). The discoveries involving the etiology of CPP have had influence on the diagnosis and familial counseling providing bases for potential prevention of premature sexual development and new treatment targets in the future.

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