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Commentary

Taming Idiopathic Central Precocious Puberty: High Frequency of Imprinting Disorders in Familial Forms

Lourdes Correa Brito[1] **and Rodolfo A. Rey**[1,2]

[1]Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE), CONICET – FEI – División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, C1425EFD Buenos Aires, Argentina
[2]Universidad de Buenos Aires, Facultad de Medicina, Departamento de Histología, Embriología, Biología Celular y Genética, C1121ABG Buenos Aires, Argentina

Correspondence: Lourdes Correa Brito, Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE), CONICET – FEI – División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, C1425EFD Buenos Aires, Argentina. Email: lcorrea@cedie.org.ar; or Rodolfo A. Rey, Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE), CONICET – FEI – División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, C1425EFD Buenos Aires, Argentina.
Email: rodolforey@cedie.org.ar.

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Abbreviation: CPP, central precocious puberty.

Central precocious puberty (CPP) results from the abnormally early reactivation of the hypothalamic-pituitary-gonadal axis, leading to the appearance of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys. The incidence of precocious puberty varies according to population, sex, and age at presentation (1), reaching 80/100 000 in girls between 5 and 9 years (2), but 10- to 25-fold lower in boys (1, 2). The etiologies of CPP include lesions of the central nervous system, such as congenital malformations, tumors or other insults (eg, infections, trauma, cranial radiotherapy, cerebral palsy), or conditions without organic lesions (3). The latter include early and chronic exposure to estrogens or androgens resulting in secondary CPP (eg, poorly controlled congenital adrenal hyperplasia), social exposures (eg, international adoption), and genetic disorders. Overall, an overt etiology is identified in 30% to 75% of boys and only 10% of girls (1, 3). Therefore, given that CPP is far more frequent in females, the majority of patients have traditionally been classified as having "idiopathic" CPP, meaning "unexplained" CPP. As usual, the term "idiopathic" has vague boundaries in medicine and, in the case of CPP, although organic lesions are always carefully ruled out, genetic studies have been performed erratically probably leading to an overestimation of the frequency of "idiopathic" CPP.

CPP can be sporadic, or familial, when there is more than 1 affected family member among first-, second-, or third-degree relatives (4). Familial CPP suggests an underlying genetic etiology, and "idiopathic" forms are relatively less frequent in this group. An autosomal dominant mode of inheritance has predominantly been observed in familial CPP, with incomplete and sex-dependent penetrance (4-6). Why does the phenotype not appear in all generations although the trait is dominant and why is there a sex-skewed presentation?

The variants in *KISS1* and *KISS1R* initially described in patients with CPP have shown an extremely low prevalence and cannot answer this previous question. The large, multiethnic study by Tinano and colleagues (7) provides a major contribution to the elucidation of the genetic etiologies of familial CPP considering the modes of transmission. Using stringent criteria, the authors established that familial CPP has a prevalence of 22%, confirming previous estimations of 25% to 27.5% (4, 5), with a similar frequency of maternal and paternal transmission. Interestingly, in families with paternal transmission, a genetic etiology could be established in 67% of the cases: *MKRN3* mutations in 57% and *DLK1* mutations in 10%. Low-cost Sanger sequencing can easily identify the etiology in these cases. Conversely, in families with maternal transmission, the genetic cause could be defined in less than 5% of the cases despite the large number of patients studied using next-generation sequencing technologies.

The low efficiency to identify a genetic cause in patients with maternally transmitted familial CPP in the large cohort studied by Tinano et al (7) may be due to the existence of mechanisms not addressed in this work, involving: (1) copy number variation or single nucleotide variation located in regulatory regions not covered by whole exome sequencing; (2) oligogenic forms; (3) epigenetic mechanisms; or (4) mitochondrial DNA mutations.

That *MKRN3* and *DLK1* variants explain a large proportion of paternally transmitted CPP but are absent in maternally transmitted cases is due to maternal imprinting (7). Sex-biased imprinting is usually not considered among the most elementary concepts of Mendelian genetics, leading to the classification of a dominant or receive mode of inheritance. *MKRN3* and *DLK1* are expressed exclusively from the paternal allele and have an inhibitory role in the complex network of the hypothalamic-pituitary-gonadal axis regulatory

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signals. Loss-of-function mutations trigger an early onset of pubertal development when inherited from the father, but remain unnoticed when inherited from the mother, whose allele is naturally silenced by imprinting. Nonetheless, unaffected males carrying a mutated maternal allele can transmit it, now without imprinting, to their offspring following a classic autosomal dominant mode. Consequently, 1 generation is skipped from a phenotypic standpoint. Here, sex-biased imprinting is the underlying biological mechanism to explain an incomplete penetrance.

In conclusion, carefully defining the mode of transmission of the phenotype in familial cases is essential to guide the genetic diagnosis approach. When one knows what to look for and in which case, the diagnostic efficiency increases, and the "idiopathic" label is assigned sparingly. The advancement of sequencing technologies along with the knowledge of the underlying causes of genetic diseases increase the effectiveness of the etiological diagnosis, especially in those following nonclassic modes of transmission, in which complex mechanisms lead to the phenotype.

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Disclosures

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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