A NCOA5 gene variant in a pedigree with maternally inherited precocious puberty

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The authors declare no conflicts of interests.

Background

1. Mechanisms implicated in pubertal timing regulation are poorly understood.
2. Central precocious puberty (CPP) commonly occurs in families, particularly having maternal inheritance pattern.1
3. The major genetic causes of familial CPP identified to date. Makorin RING-finger protein 3 (MRKRN3) and Delta-like homolog 1 (DLK1) deficiencies, are paternally inherited.2-3 Exceedingly rare patients with CPP carry mutations in kisspeptin system.4,5
4. The CPP genes are also associated with the age at menarche in the population as demonstrated by genome-wide association studies (GWAS).6
5. Nuclear Receptor Coactivator 5 (NCOA5) is a coregulator for the alpha and beta estrogen receptors and is associated with the age at menarche by GWAS.6,7
6. NCOA5 can also form complexes with estrogen receptor alpha (ERα) and ERβ in vitro and enhances ERα transcriptional activity in the presence of estradiol.7

Aim: To identify genetic causes of maternally inherited CPP.

Patients and methods

• Patients with idiopathic central precocious puberty
• Whole genome sequencing
  • 14 family trios affected with maternally inherited CPP + additional proband affected with familial CPP
  • demonstrating maternal (10 pedigrees) or paternal / recessive inheritance pattern 5 pedigrees
• Bioinformatic analysis
  • Genetic variants with coverage >10x were retained and analysed with Variant Studio 3.0 software
  • MAF<0,2%
  • Synomimous changes filtered
• Targeted analysis - 398 genes associated with the age at menarche6
• Whole exome sequencing
  • 13 probands with maternally inherited CPP
  • 5 sporadic boys with CPP
  • 20 sporadic girls with CPP (puberty onset before 7 years)
• Identified candidate variants and their family segregation were verified by Sanger sequencing.
• Coding variants in the MRKRN3 gene were pre-screened and excluded by Sanger sequencing in all probands without obvious dominant maternal inheritance.

<table>
<thead>
<tr>
<th>NCOA5 variants</th>
<th>Gene</th>
<th>Name</th>
<th>Exonic variant</th>
<th>Score</th>
<th>Polyphen2</th>
<th>SIFT</th>
<th>GERP</th>
<th>CADD</th>
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<tr>
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<td>GNMAD</td>
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</tbody>
</table>

Table 2: NCOA5 variants

Results

• p.R70W variant in NCOA5
  • Total allele count in GnomAD database 4/251462
  • in silico predicted to be pathogenic
  • Segregates with CPP
  • A pedigree with maternal inheritance

• p.Q564X truncating variant in NCOA5
  • Novel variant
  • in silico predicted to be pathogenic
  • Sporadic girl

• No other NCOA5 coding variants were identified in the rest of the cohort.

Conclusions

1. Two rare variants predicted pathogenic in a gene implicated in the regulation of estrogen receptors, NCOA5, were identified, one in a pedigree with maternally inherited CPP, the second in a sporadic girl.

References


Funding

This work was supported by the ESPE Research Unit Grant 2016 - 2018, and the University Medical Centre Ljubljana Terciary project (grant number 20170064).