MKRN3 gene mutations in a cohort of patients with central precocious puberty

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Results

• Previously reported heterozygous MKRN3 mutation (c.482dupC, p.Ala162GlyfsTer15) 1 in 10 patients (5 pedigrees ) with familial CPP (Figure 2)
• A novel missense variant (p.Met297Val) in 1 pedigree - paternally inherited CPP
• In silico predicted pathogenic
• Segregated with CPP
• No MKRN3 mutations in sporadic patients.
• No methylation defect or large deletions identified in tested probands in MKRN3 or DLK1 (Figure 3).

The course of puberty in p.Ala162GlyfsTer15 MKRN3 carriers
• Estimated average age at puberty beginning in females 6.3 years (range 5.3-8 years)
• 2 girls untreated with GnRH analag - menarche at 7 and 9 years
• 2 male carriers growth spurt at 9 years

The course of puberty in p.Met297Val MKRN3 carriers
• Proband
  • Presented with CPP at 7.5 y (Pub.stage B2-3, basal LH 0.3 IU/L, peak LH 8.6 IU/L, BA +1.4 SD)
  • Father reported shaving at 13 y
  • Aunt menarche at 10 y

The course of puberty in patients without MKRN3 mutations
• Estimated average age at puberty beginning in boys 5.8 years (range 1.5-8.5 years) and in 41 girls 5.9 years (range 1-8 years)
• 4 untreated girls presented with menarche at 7.9 y, 8.5 y, 9.0 y and 9.7 y

Conclusions

1. We demonstrated a high frequency (50%) of MKRN3 mutations in patients with familial CPP, but not in sporadic cases.
2. The results expand the spectrum of mutations implicated in CPP, with a novel missense mutation, that clinically presented with a less early CPP.
3. Although MKRN3 is one of the gatekeepers of the postnatal activation of the gonadotropin axis, other inhibiting factors are yet to be discovered.

Background

MKRN3 gene (encoding Makorin Ring Finger protein 3):
• a maternally imprinted gene located at a Prader-Willi syndrome region on chromosome 15q11.13.
• Deleterious mutations of MKRN3 gene - a common cause of paternally inherited central precocious puberty (CPP).
• 33-46% of familial cases and in about 5% and 40% of apparently sporadic female and male cases, respectively.

Aim: To evaluate the presence of mutations, deletions and methylation abnormalities in MKRN3 gene in a cohort of patients with CPP.

Patients and background

• 12 pedigrees with familial CPP (Figure 1.2)
• Paternal inheritance 14 subjects with CPP
• Recessive inheritance 10 subjects with CPP
• Their unaffected relatives (n=9)
• 41 sporadic patients (5 males, 36 females) with idiopathic CPP
• MKRN3 gene analysis by Sanger sequencing
• MKRN3 and DLK1 deletion and methylation analysis by commercially available methylation- specific MLPA in sporadic boys and probands with familial CPP without MKRN3 mutation.
• SALSAR®MLPA® - A probemix ME028-C1 Prader-Willi/ Angelman
• SALSAR®MLPA® - A probemix ME32-A1 UPD 7UPD 14, LOT: A1-0814 (MRC Holland)

Figure 1: Study cohort and design

Figure 2: Pedigrees with familial CPP

Figure 3: A normal MS-MLPA PWS region result

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References