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

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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)[1],
- 33-46% of familial cases and in about 5% and 40% of apparently sporadic female and male cases, respectively.[1-4]

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

Patients and methods

- 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:
  - SALSA®MS"MLPA® - A probemix ME028-C1 Prader-Willi/ Angelman
  - SALSA®MS"MLPA® - A probemix ME32-A1 UPD 7/UPD 14, LOT: A1-0814 (MRC Holland)

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 beggining in females 6,3 years (range 5,3-8 years)
  - 2 girls untreated with GnRH analog - 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 beggining in 8 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

Figure 1: Study cohort and design

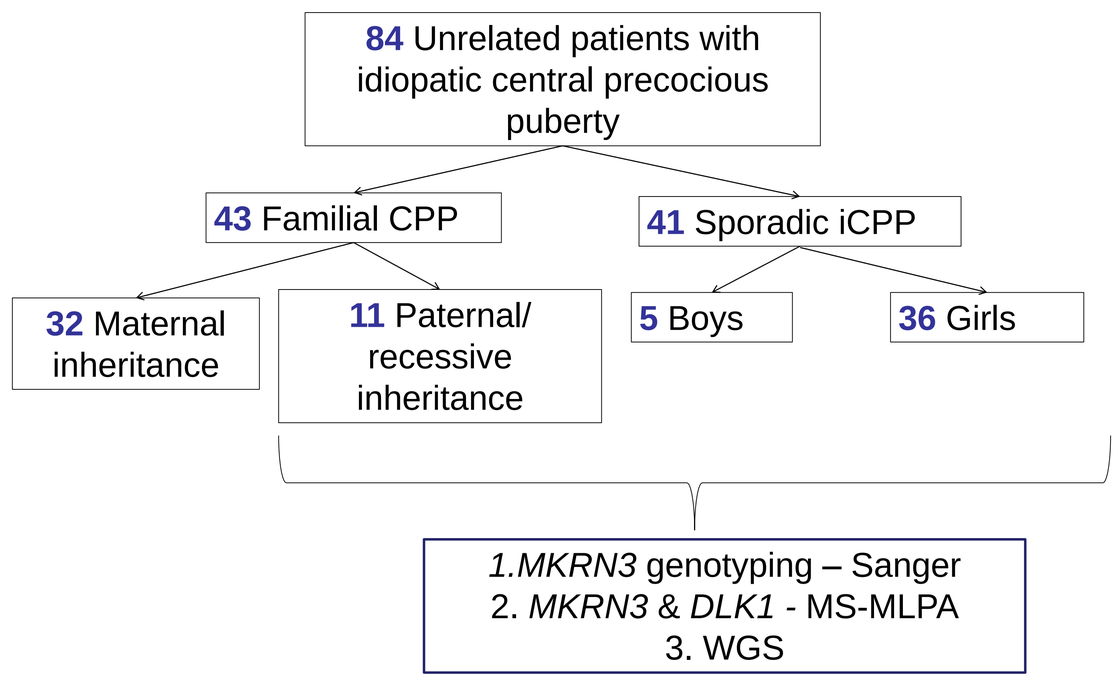


Figure 3: A normal MS-MLPA PWS region result

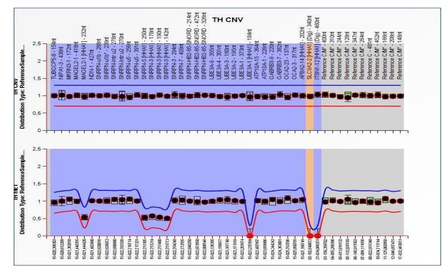
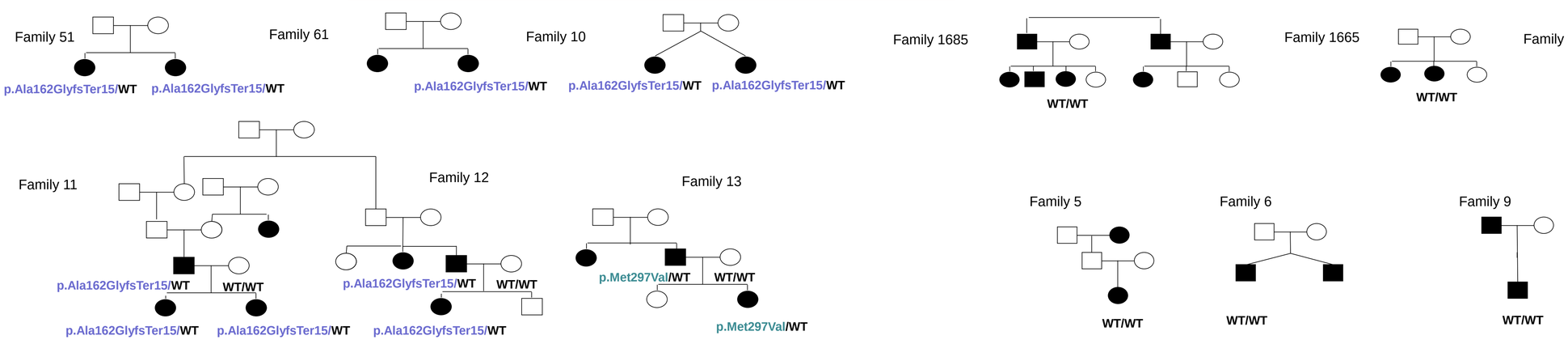


Figure 2: Pedigrees with familial CPP



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 clinicaly presented with a less early CPP.
3. Although MKRN3 is one of the gatekeepers of the postnatal activation of the gonadotropic axis, other inhibiting factors are yet to be discovered.

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