Molecular screening of MKRN3, DLK1 and KCNK9 genes in central precocious puberty

Anna Grandone, Grazia Cirillo, Marcella Sasso, Pierluigi Marzuillo, Adalgisa Festa, Ruggero Coppola, Emanuele Miraglia del Giudice, Laura Perrone

Department of Woman , Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, Naples, Italy.

Background

Central precocious puberty (CPP) is often familial but its genetic cause is largely unknown. Very recently, the makorin RING finger protein 3 (MKRN3) gene has been found mutated for the first time in 5 families with familial precocious puberty. The inheritance pattern is particular being the MKRN3 a maternal imprinted gene. Moreover in a recent genome wide association study common intronic or intragenic variants harbouring this gene and other two imprinted genes, DLK1 and KCNK9, have been associated to age at menarche, demonstrating parent-of-origin-specific associations concordant with known parental expression patterns.

Materials and methods

Here, we investigated mutations in MKRN3, DLK1 and KCNK9 in a cohort of 67 girls with CPP.

Method: We studied 67 Italian children with CPP (all girls, mean age 6.8 ±1.8 years, 25 (37%) familial cases) All patients had pubertal basal and/or GnRH-stimulated LH levels, advanced bone age and normal central nervous system magnetic resonance imaging. The coding regions of MKRN3, DLK1 and KCNK9 were sequenced.

Results

Genetic analysis revealed three mutations in MKRN3, two previously described (Pro160Cysfs*14 and Arg328Cys) and a new one (p.Cys410Ter), in 3 unrelated girls, two with familiar CPP and one apparently sporadic (Figure 1).

The new mutation (p.Cys410Ter) is located in a functional domain (CH3 zinc-finger) and is predicted to be deleterious by prediction software (Polyphen).

No rare variants were found in DLK1 and KCNK9 genes.

Eight Single Nucleotid Polimorphisms (SNPs) in DLK1 were found with a MAF similar to that found in general population (Table 1). One SNP was found in KCNK9 (rs2615374) with MAF 0.65, similar to that reported in literature (0.65).

Table 1: SNPs in DLK1 found in our cohort, with observed and reported minor allele frequency (MAF)

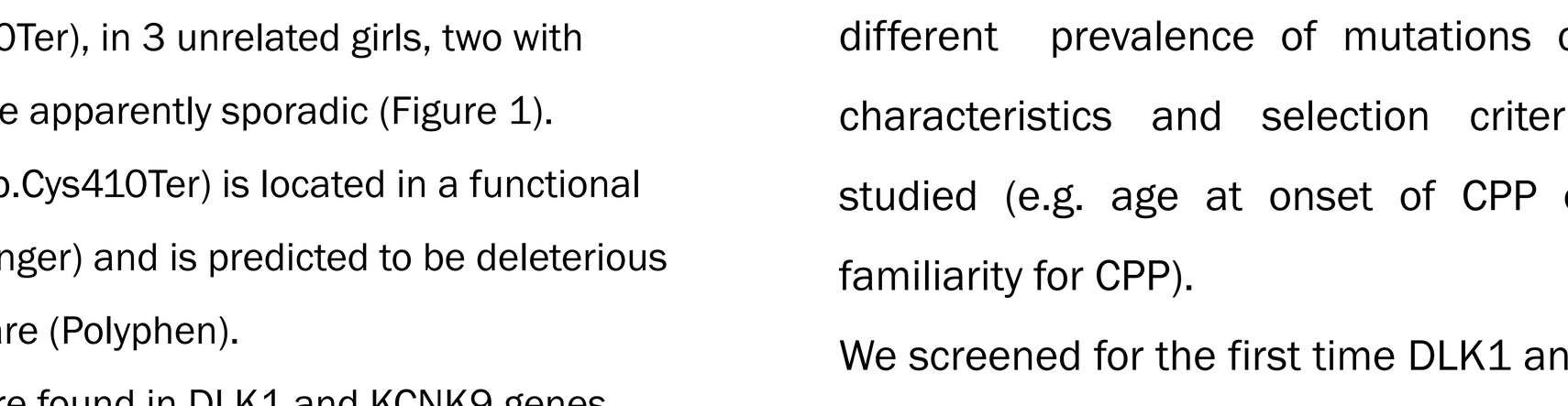
SNPs	Position	MAF in our cohort	Reported MAF in literature
rs17577779	c.405-41T>C	0.46	0.46 (T)
rs1802710	c.564T>C(p.=) p.I188	0.45	0.46 (T)
rs1058009	c.779G>A p.Ser260Asn	0.06 (A)	0.06 (A)
rs7501	c.*40G>T	0.06 (T)	0.06 (T)
rs77235285	c.404+89C>T	0.02 (T)	0.04 (T)
rs114490877	c.67+51T>G	0.06 (G)	0.09 (G)
rs140051660	c.744T>C(p.=) p.Thr248=	0.01 (C)	< 0.01 (C)
rs754825900	c.192T>G(p.=) p.Leu64=	0.01 (G)	< 0.01 (C)

Conclusions

We confirm that MKRN3 gene mutations represent a rather frequent cause of CPP in girls (4.4%), even if different prevalence of mutations can depend on characteristics and selection criteria of patients studied (e.g. age at onset of CPP or definition of familiarity for CPP).

We screened for the first time DLK1 and KCNK9 genes in CPP and our results do not support a role for mutations in their coding region in the etiology of CPP. Involvement of these genes in regulation of pubertal timing in humans warrants further investigation.

Figure 1: MKRN3 domains and mutations identified. The mutation in red has not been previously described



We have no conflicts of interest to declare.

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anna grandone
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