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

Magdalena Avbelj Stefanija[1], Jernej Kovač[2], Galia Gat-Yablonski[3,4,5],Nataša Bratina[1,6], Moshe Phillip[4,5],Tadej Battelino[1,6], Liat de Vries[4,5]

[1] University Medical Centre Ljubljana, University Children's Hospital, Department for Pediatric Endocrinology, diabetes and metabolism, Bohoričeva 20, SI-1000 Ljubljana, Slovenia, [2] University Medical Centre Ljubljana, University Children's Hospital, Unit for special laboratory diagnostics, Vrazov trg 1, Ljubljana, Slovenia,[3] Felsentein Medical Research Center, Petah Tikva,[4] The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel,[5] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv , Israel,[6] Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000 Ljubljana, Slovenia

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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 (MKRN3) 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%
  - Synonimous changes filtered
  - **Targeted analysis -** 398 genes associated with the age at menarche[6]
- **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 *MKRN3* gene were pre-screened and excluded by Sanger sequencing in all probands without obvious dominant maternal inheritance.

Figure 1: Pedigrees with *NCOA5* variants

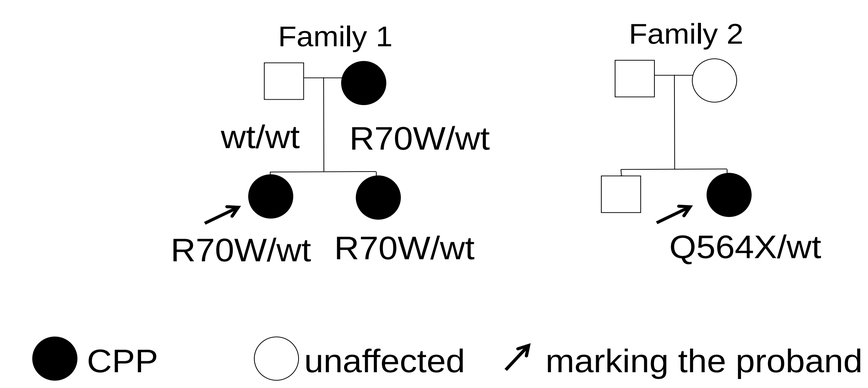

Table 1: Clinical characteristics of *NCOA5* variant carriers

	Proband 1	P1 Sister	Proband 2
Sex	F	F	F
~ age at onset	6	8	6
Age at evaluation	6.85	8.75	6.63
Pubertal stage	B3, P3, A2	B3, P3, A1	B2, P2, A1
Bone age SDS	+3.5	+1.68	+4,5
LH basal [IU/L]	0.35	0.34	0.2
LH peak [IU/L]	30.6	47.1	8.6
Growth spurt	Yes	Yes	No
Height SDS	3.99	1.93	0.38
BMI SDS	1.34	-1.19	1.28
Maternal menarche	10	10	12
Paternal puberty	normal	normal	normal
MRI brain	NA	NA	Arnold Chiari malformation type 1

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

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- **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.

***Table 2: NCOA5 v*ariants**

Gene	Constraint score (GnomAD)	Nucleotid variant (NM_020967)	Amino acid variant (Q9HCD5)	Rs#	CADD score	Polyphen	SIFT	GnomAD EU MAF (%)	Proband #
NCOA5	0.21	c.208C>T	p.R70W	rs756677429	26.6	unknown	deleterious	0.0009	1
NCOA5	0.21	c.1690C>T	p.Q564X	/	37			/	2

Conclusions

1. Two rare variants predicted pathogenic in a gene implicated in the regulation of estrogene receptors, *NCOA5*, were identified, one in a pedigree with maternally inherited CPP, the second in a sporadic girl.
2. The implication of identified variants on *NCOA5* function and CPP phenotype remains to be determined.

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