Next Generation Sequencing in Precocious Puberty: a new diagnostic challenge to identify the molecular basis of complex diseases.

Introduction and Objectives

Precocious puberty is defined as pubertal development at an earlier age than expected. The hypothalamic-pituitary-gonadal (HPG) axis controls puberty and reproduction and is tightly regulated by a complex network of genetic, metabolic, and environmental factors. Earlier puberty timing may be generally associated with higher risks for adverse health outcomes, and the global declines in average ages of puberty onset have important relevance for health. Genetic background plays a critical role in regulating the variation of pubertal onset, however the identification of genes involved in this process is difficult because pubertal timing is a complex genetic trait due to multigenic influences and interactions between genetic variants and environmental exposures. To date only few variants in genes that disrupt the HPG axis have been described as a mirror image of the hypogonadotropic hypogonadism phenotype. Recently, deleterious mutations in *MKRN3* gene were identified using whole-exome sequencing analysis in five families with central precocious puberty (CPP).

Materials and Methods

Targeted resequencing in a cohort of 27 unrelated patients affected by precocious puberty with a panel of 34 genes:

Disease associated genes

Gene	Phenotype	OMIM	Inheritance
KISS1R	Precocious puberty, central, 1	604161	AD
MKRN3	Precocious puberty, central, 2	615346	AD
LHCGR	Precocious puberty, male	176410	AD
GNAS	McCune Albright Syndrome, somatic, mosaic	174800	-

Candidate genes associated with pubertal timing in animal models and highly expressed in the HPG axis:

GNRH1, GNRHR, LHB, FSHB, ESR1, KISS1, TAC3, TACR3, ERMP1, LIN28B, IGF1, IGF1R, LEP, LEPR, SHBG, PRL, IGFALS, AMH, POMC, NR0B1/DAX1, PRLR, PRLH, PRLHR, AMHR2, NPY, DMRT1, SRDA5A2, CGA

Results

Case	Sex	Gene	Variant ID	Transcript Change	Protein Change	Consequence	EXAC MAF %	Predictions of Pathogenicity		References
1	F	*PRLR*	-	c.271G>A	p.Gln91*	Stop codon	-	-	-	-
2	F	*ERMP1*	rs142615324	c.1517T>C	p.Ile506Thr	missense	0.004	deleterious	benign	Cisternino et al 2013
		IGFALS	rs200380381	c.1592G>A	p.Arg531His	missense	0.07	tolerated	Possibly damaging	-
3	F	*KISS1*	rs12998	c.58G>A	p.Glu20Lys	missense	4.8	deleterious	Possibly damaging	Mazaheri et al 2015
		ESR1	rs142712646	c.805C>T	p.Arg269Cys	missense	0.1	deleterious	benign	-
		IGFALS	-	c.1634G>A	p.Arg545Gln	missense	-	tolerated	benign	-
4	F	*ESR1*	rs149308960	c.478G>T	p.Gly160Cys	missense	0.19	deleterious	possibly damaging	-
		AR	-	c.1369_1398del30+c.1369_1398del30	-	del_5'UTR	-	-	-	-
5	F	*NPY*	rs16139	c.20T>C	p.Leu7Pro	missense	3	tolerated	probably damaging	-
6	F	*LHB*	-	c.421C>T	p.Leu141Phe	missense	-	tolerated	possibly damaging	-
		AR	rs201934623	c.1174C>T	p.Pro392Ser	missense	0.8	deleterious	benign	Hiort et al. 2000
7	F	*SHBG*	-	c.1165A>G	p.Ser389Gly	missense	-	deleterious	probably damaging	-
8	M	*LHCGR*	rs544579784	c.-391_-390insT	-	5'UTR	-	-	-	-
		LHCGR	rs185085809	c.308+55G>A	-	5'UTR	-	-	-	-

Conclusions

Targeted resequencing showed different heterozygous variations in different genes involved in pubertal development: 10 non-synonymous variants, 1 stop gain, and 1 deletion were identified, some of which we speculate could contribute to patients' phenotypes. Although the interpretation of these variants may be not univocal, we suggest that also those classified as not pathogenic by *in silico* data or present with low frequency in the population, could have an impact on pubertal onset, considering the complexity of interactions in the modulation of HPG pathway. In particular, an interesting gene could be *ERMP1*. In fact, the protein is required for the organization of somatic cells and oocytes into discrete follicular structures, as observed in animal model experiments. Additional functional studies, as well as enlargement of our cohort, may be useful to demonstrate the pathogenicity of the variants .

NGS is the only strategy that may provide additional diagnostic potential, mostly when are studied complex genetic traits, for genetic counseling and may help clinical decision making in a fast and cost-efficient manner.

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55ESPE 12--3-RFC

Neuroendocrinology

Stefano Stagi

DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS