Prevalence of parental consanguinity in children with precocious puberty and kisspeptin gene polymorphisms

Mahin Hashemipour[1], Silva Hovsepian[1], Ali Mazaheri[1], Mansour Salehi[2]

1Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran 2Department of Genetics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

OBJECTIVES

Puberty is considered as a complex network of coordinated biological process with multiple level of neuroendocrine and genetic regulations. Timing of puberty could influence by different environmental and genetic factors. Precocious puberty (PP) is one of its variations which defines as appearance of physical signs of sexual development in a child prior to the earliest accepted age of sexual maturation, 7 years in girls and 9 years in boy. The exact mechanisms and genetic background of PP are not well understood. It is suggested that the kisspeptin neuropeptide ,encoded by the KISS1 gene, could have role in this regard. Considering the higher rate of parental consanguinity among Iranian population and its possible role in the occurrence of PP, the aim of current study was to determine the mutation of kisspeptine gene (KISS1) among a group of patients with PP and role of parental consanguinity in this regard.

METHODS

In this case control study, a group of children with diagnosed PP and a group of healthy children were selected. Bone age of patients with PP was evaluated and MRI and pelvic ultrasonography was performed. Stage of puberty was determined using Tanner staging method. Selected patients had advanced bone age (Greulich and Pyle method), and normal central nervous system (CNS) MRI.Genomic DNA was extracted from peripheral blood of selected population by salting out method. Occurrence of any mutation or polymorphism in KISS1gene was investigated using PCR method. The rate of parental consanguinity was determined in patients with and without KISS1gene polymorphism/mutation.

Table1: Characteristics of patients with precocious puberty and control group

	Patients with precocious puberty n=33	Control group n=30	P value
Age(years)	10.42 +/- 3.6	10.8+/- 4.1	0.72
Sex(female/male)	15/18	16/14	0.69
Age of puberty	6.88 +/- 1.51	9.76+/- 1.8	0.02

Table2: Allelic variants identification in the KISS1 gene of patients with precocious puberty

Location	nucleotide	Amino acid change	number
5'URT	c.-148 T>A	-	NOT REPORTED
5'URT	c.-145 del T	-	rs5780218 del
5URT	c.-89G>A	-	rs3924587
EXON2	c.58 G>A	E20k	rs12998

RESULTS

In these study 33 patients with idiopathic PP and 30 control age and sex matched children were studied(Table1). Genetic analysis indicated that there was not any polymorphism or mutation in studied participants of control group .Among patients with PP, 4 SNPs within the promoter and coding regions of KISS1 gene were determined in 9 patients (5 boys and 4 girls)(Table2). Among them the c.-148 T>A was novel variant. Patogenecity of these variants is predicted by inSilico prediction softwares e.g.polyphen2, phylop and mutationtaster. As only 3 exons of these genes were sequenced, presence of mutations outside these regions, not included in our study. There was not any case of familiar PP as well as any case with parental consanguinity among patients with detected polymorphism.

CONCLUSIONS

The findings of current study identified one novel polymorphism and three reported polymorphism in KISS1gene among patients with PP in Iran. Considering that parental consanguinity was not associated with reported polymorphism of KISS1gene, it is suggested that it could not have important role in the occurrence of PP in Iranian population. Studying other related genes as well as further epigenetic studies is recommended. Moreover, designing studies for evaluating the interaction of different environmental and nutritional factors with detected polymorphisms in the is necessary for better understanding of the disease pathogenesis.

References

1. Styne DM, Grumbach MM. Puberty: ontogeny, neuroendocrinology, physiology, and disorders. In: Kronenberg HM, Melmed, S, Polonsky KS, Larsen PR, eds. *Williams Textbook of Endocrinology* . 12th ed. Philadelphia, Pa: Elsevier Saunders; 2011: chap 25. 24.
2. Gajdos ZK, Hirschhorn JN, Palmert MR. What controls the timing of puberty? An update on progress from genetic investigation. Curr Opin Endocrinol Diabetes Obes 2009;16:16-24.
3.. Silveira LG, Noel SD, Silveira-Neto AP, Abreu AP, Brito VN, Santos MG, et al. Mutations of the KISS1 gene in disorders of puberty. J Clin Endocrinol Metab 2010;95:2276-80.
4. Cho SG, Li D, Tan K, Siwko SK, Liu M. KiSS1 and its G-protein-coupled receptor GPR54 in cancer development and metastasis. Cancer Metastasis Rev. 2012;31:585-91.
5. Pinilla L, Aguilar E, Dieguez C, Millar RP, Tena-Sempere M. Kisspeptins and Reproduction:Physiological Roles and Regulatory Mechanisms.Physiol Rev 2012; 92:1235-316.
6. Krstevska-Konstantinova M, Jovanovska J, Tasic VB, Montenegro LR, Beneduzzi D,Silveira LF, Gucev ZS. Mutational analysis of KISS1 and KISS1R in idiopathic central precocious puberty. J Pediatr Endocrinol Metab. 2014;27:199-201.
7. Ko JM, Lee HS, Hwang JS. KISS1 gene analysis in Korean girls with central precocious puberty: a polymorphism, p.P110T, suggested to exert a protective effect. Endocr J. 2010; 57:701–709.
8. Luan X, Zhou Y, Wang W, Yu H, Li P, Gan X, Wei D, Xiao J. Association study of the polymorphisms in the KISS1 gene with central precocious puberty in Chinese girls. Eur J Endocrinol 2007;157:113–118.
9. Ghaemi N, Noorozi Asl S, Abbaszadegan MR, Ghahraman M, Vakili R.GPR54 Gene Mutations in Iranian Girls with Central Familial Precocious Puberty. Iranian J Obstetrics,Gynecology & Infertilit 2012;15:1-8

ESPE 2015 1152--P3

Puberty

Mahin Hashemipour

DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: ESPE 2015 BARCELONA European Society for Paediatric Endocrinology

PosterSessionOnline.com