Clinical and Genetics Approaches to Hypogonadotropic Hypogonadism

Ali Kemal Topaloğlu

Çukurova University Faculty of Medicine, Department of Pediatric Endocrinology, Adana, Turkey

Idiopathic hypogonadotropic hypogonadism (IHH) is often defined when a girl or a boy reaches the age 13 and 14 respectively, with a bone age of at least 11, who lack secondary sexual characteristics in the presence of low serum sex steroids as well as low gonadotropins. In an individual with pubertal delay, to establish a diagnosis of IHH frequently requires a battery of tests and a long follow-up period. Increasingly popular use of whole exome sequencing made extremely important contributions in making timely diagnosis of IHH and understanding the human reproductive biology.

Key words: Idiopathic hypogonadotropic hypogonadism, clinical and genetics approach

Genetics in Pituitary Short Stature

Z. Oya Uyguner

İstanbul University İstanbul Faculty of Medicine, Department of Medical Genetics, İstanbul, Turkey

Studies on animal model about the developmental phases of pituitary gland have contributed to the understanding of the functional roles of the signal molecules responsible for the embryologic changes, development, growth and maturation and the transcription factors interacting with these molecules. The genes related to congenital pituitary deficiencies are evaluated in two groups according to their temporal and spatial expression during the developmental phases. The mutations of genes taking place in the early phase of development (*GLI2, HESX1, FGF8, FGF1, PROK2, PROKR2, OTX2, SOX2, SOX3, PITX2, ARNT2, LHX3, LHX4*) result in more complex and heterogeneous phenotypes such as pituitary anomalies, various craniofacial and limb malformations in addition to pituitary hormone deficiencies. On the other hand, mutations of genes playing a role in the late development (*PROP1* and *POU1F1*) are usually associated with multiple pituitary hormone deficiency (MPHD) phenotype. In 1992, the *POU1F1* gene has been described. It is the human homologue of the mapped *PIT1* gene identified in 1990 in dwarf mouse models and it has been screened in MPHD cases; the mutations have been shown and in this way, the first gene related to the phenotype has been described. In 1996, the human homologue of the *PROP1* gene mapped in dwarf mouse model has been reported and *PROP1* gene mutations have been shown by which the second gene of the disease has been determined. The first development of pituitary gland starts with the external stimulus. These are signal proteins like SHH, BMP, FGF, WNT and SHH, which function at early stages and even though they do not have any direct role in the development of Rathke's pouch, they are important for the development of midline, forebrain, brain lobes and eyes. SHH plays a role in the expression of GLI factors, which are expressed in the early stages of pituitary development. It has been shown that the heterozygous mutations in *GLI2* gene are related to pituitary hormone deficiency as well as to holoprosencephaly, ectopic hypophysis, hypophyseal hypoplasia, mild hypophyseal anomalies, polydactyly and corpus callosum agenesis. *HESX1*, the first pituitary transcriptional factor during embryologic development, has influence on expression of other transcriptional factors (LHX1, LHX2, LHX3) together with the formation of midline and Rathke's pouch. In the developing hypophysis, the *HESX1* expression should be decreased in order to express *PROP1* firstly and then *PIT1* at the right time. The essential clinical finding for *HESX1* mutations, showing both autosomal dominant and