Gonadotropin-releasing hormone receptor gene mutation: a new cause of hereditary hypogonadism and another mutated G-protein-coupled receptor

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The list of activating and inactivating mutations of the G-protein-coupled receptors with seven transmembrane domains involved in endocrine diseases is increasing rapidly. Two reports (1, 2) have recently added inactivating mutations of the gonadotropin-releasing hormone receptor (GnRHR) to the list. Hereditary hypogonadotropic hypogonadism (HH) is genetically heterogeneous, and so far only some forms of X-linked recessive inheritance have been explained. The well-known X-linked form of HH associated with anosmia is Kallmann's syndrome due to mutations of the KALIG-1 gene located to chromosome Xp22.3 (3, 4). Mutation of the chromosome Xp21-located gene of the transcription factor DAX (DSS-AHC critical region of the X chromosome, gene 1) causes congenital adrenal hypoplasia and HH (5). Nevertheless, these two genetic defects do not explain all the cases of familial HH and this disease is not always linked to the X chromosome. Therefore, it was tempting to search for other candidates. Since gonadotropin-releasing hormone (GnRH) plays a major role in the central control of the gonadotropic axis, it was a possible candidate. Indeed mutation of the GnRH gene was first reported in the hypogonadal mouse more than 10 years ago (6), but a similar mutation has never been reported in humans (7).

GnRHR is a member of the family of G-protein-coupled receptors with seven transmembrane domains. Binding of GnRH to its receptor stimulates the activity of phospholipase C and intracellular calcium through Gq/G11 proteins (see refs (1, 2) for reviews). The human GnRHR gene is located on chromosome 4 and comprises three exons. As the response to exogenous GnRH is quite variable among patients with HH, it was tempting to postulate a GnRHR defect in some patients. Layman *et al.* (2) have screened 46 unrelated patients with HH (32 males and 14 females) without anosmia and have identified two GnRHR gene mutations in one patient. As in the family presenting with HH reported by De Roux *et al.* (1), the affected siblings are compound heterozygotes for GnRHR gene mutation. In both families, females as well as males are affected, in keeping with the chromosomal localization of the GnRH gene. This is the first genetic explanation for an autosomal form of familial HH in humans. Three missense mutations of the GnRHR gene are reported in these two families. One mutation led to a Q106R substitution in the first extracellular loop of the

receptor, leading to a dramatic reduction in GnRH binding (1). A second mutation is present in both families and causes a R262Q substitution in the third intracellular loop, leading to a decrease in inositol phosphate production in response to GnRH stimulation (1, 2). The last mutation is responsible for a Y284C substitution in the sixth transmembrane region, also altering the signal transduction of the mutant GnRHR (2).

Interestingly, basal plasma levels of follicle-stimulating hormone (FSH) or luteinizing hormone (LH) are not always low and are even reported in the normal range in some affected siblings presenting with HH from these two families. The FSH and LH response to exogenous GnRH is not decreased, suggesting that the receptor defect is only partial and could be masked by a supraphysiological dose of GnRH used for the stimulation tests. Furthermore, LH pulsatility studied in one of these patients showed a dramatic reduction in pulse amplitude despite a normal pulse frequency (1). This last observation might be in keeping with a partial defect of the GnRH mutant receptors. It will therefore be difficult for the clinician to select patients for a GnRHR gene study only on the basis of the gonadotropin basal or stimulated plasma levels.

The determination of the prevalence of GnRHR mutations in patients with HH will be important. According to the first screening performed by Layman *et al.* (2), GnRHR mutation would occur in 2.2% of patients with idiopathic HH, but this rate will increase to 7.1% when only families with an affected female are considered (2).

References

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