GENETICS

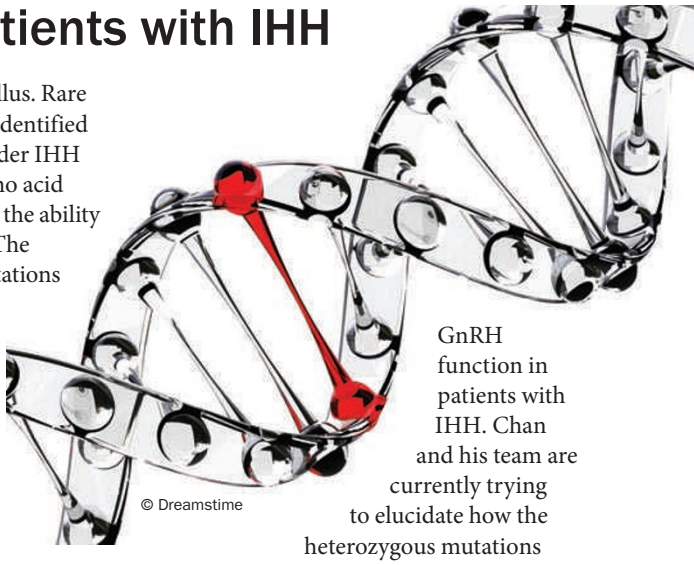
# *GNRH1* mutations identified in patients with IHH

Idiopathic hypogonadotropic hypogonadism (IHH) is a condition characterized by the failure to undergo puberty in association with low levels of gonadotropins and sex steroids. Mutations in numerous genes that regulate reproduction have been described in patients with IHH, including genes involved in the production, secretion and downstream signaling of gonadotropin-releasing hormone (GnRH), known as the master molecule of the reproductive system. Now, for the first time, two research groups have identified mutations in *GNRH1*, which codes for the hormone precursor of GnRH. "Together, our work fills a long-standing gap in the genetics of IHH," states Yee-Ming Chan from the Reproductive Endocrine Unit at Massachusetts General Hospital, lead author of the study published in *PNAS*.

Chan and colleagues screened 310 patients with IHH and identified 5 individuals with mutations in the *GNRH1* gene. A homozygous frameshift mutation, causing truncation of GnRH in a region essential for its function, was found in a teenage boy with severe IHH exhibiting cryptorchidism and microphallus. Rare heterozygous mutations were identified in four other patients with milder IHH phenotypes, including an amino acid substitution that might reduce the ability of GnRH to bind its receptor. The discovery of heterozygous mutations in affected patients suggests they may act in a dominant fashion to cause IHH.

The other research group, lead by Jacques Young at the Service d'Endocrinologie et des Maladies de la Reproduction in France, also identified a homozygous frameshift mutation in *GNRH1* using a candidate gene approach. In this case, the N-terminal portion of GnRH is deleted, producing a nonfunctional protein. The mutation was detected in a teenage brother and sister who both display complete hypogonadism and sexual infantilism. Their unaffected parents and sister were found to be heterozygous.

Further characterization of these mutations will reveal how they affect GnRH function in patients with IHH. Chan and his team are currently trying to elucidate how the heterozygous mutations they identified might exert a dominant effect. "By doing so, we hope to uncover new molecular mechanisms that underlie IHH," he says.



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**Original articles** Bouligand, J. *et al.* Isolated familial hypogonadotropic hypogonadism and a *GNRH1* mutation. *N. Engl. J. Med.* **360**, 2742–2748 (2009).
Chan, Y. M. *et al. GNRH1* mutations in patients with idiopathic hypogonadotropic hypogonadism. *Proc. Natl Acad. Sci. USA* **106**, 11703–11708 (2009).