

## Silent Mutation in *KISS1* and *KISS1R* and Unexplained Infertility

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### Dear Editor,

Kisspeptin (KP) is a set of peptides coded by the *KISS1* gene that is a metastasis suppressor gene located on chromosome 1q32. It plays an important role in regulation of hypothalamic-pituitary-gonadal axis (1). The association of KP with the disruption of hypothalamic-pituitary-gonadal axis, can be exemplified by high concordance of the phenotypes between analogous mutations in gonadotropin releasing hormone (GnRH) receptor, follicle stimulating hormone (FSH), luteinizing hormone (LH), FSH receptor or LH receptor in mice and humans (2). Its receptor, *KISS1R*, is a G protein coupled receptor 54 (GPR54) located on various hypothalamic nuclei (3). Loss-of-function mutations in *KISS1R* result in down regulation of pulsatile GnRH secretion and infertility, whereas activating mutations in *KISS1R* prevent desensitization of the *KISS1-KISS1R* pathway and lead to precocious puberty. This pathway seems to be central to the initiation of puberty and the negative feedback of steroids on GnRH pulsatility in mammals. Thus, this pathway represents a primary transducer of cues from internal and external environments that ultimately regulate the neuroendocrine reproductive axis.

*KISS1* is 6151 base pairs in length and has four exons. The first exon remains untranslated while exons 2 and 3 are coding exons (4). At least 294 single nucleotide polymorphisms (SNPs) have been reported in the *KISS1* gene, out of which 42 correspond to mutations located in untranslated regions (UTR), 30 in exon and 222 in intron regions (5, 6). We hypothesized that mutation in the UTR regions might be associated with unexplained infertility as their odds ratio has been reported as 0.5 / 0.5 in the normal group as well as Ovarian Hypothalamic Pituitary (OHP) axis. We believe that these mutations cause some alterations in the protein function of KP, GnRH, FSH or LH, conferring susceptibility of an individual to develop infertility. The polymorphism introduces a

substitution of an amino acid, which is yet to be identified; however, the change would not seriously affect the bioavailability of the peptide. Thus, on one hand the hormonal levels are normal in the serum yet on the other hand they remain unsuccessful in either assisting in normal development of oocyte, its fertilization or implantation in healthy endometrium. Regarding bioactivity, no reports are available which confer the role of this mutation in unexplained infertility. Future studies are required to identify the relationship between the two. Perhaps this might be the case in unexplained male infertility as well.

**Hypothesis:** a deletion/insertion (rs5780 218; A/K) mutation in Exon 1 of the *KISS1* gene may lead to unexplained infertility in females.

**Plan of action:** the mutations occurring in the untranslated exon 1 on *KISS1* gene and their relationship with unexplained infertility needs to be explored. The evaluation of reproductive hormones in these patients may further reveal the effect of KP deficiency on HPO axis.

**Recommendations:** genetic studies should be conducted on the samples of couples with unexplained infertility. This might pave the way to an improved diagnosis of the cause of yet unexplained infertility. As KP administration is under clinical trials, we are confident that patients with identified mutations might benefit, leading to successful results of fertility treatment.

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