Mutations and polymorphisms in FSH receptor: functional implications in human reproduction

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Abstract

FSH brings about its physiological actions by activating a specific receptor located on target cells. Normal functioning of the FSH receptor (FSHR) is crucial for follicular development and estradiol production in females and for the regulation of Sertoli cell function and spermatogenesis in males. In the last two decades, the number of inactivating and activating mutations, single nucleotide polymorphisms, and spliced variants of FSHR gene has been identified in selected infertile cases. Information on genotype–phenotype correlation and in vitro functional characterization of the mutants has helped in understanding the possible genetic cause for female infertility in affected individuals. The information is also being used to dissect various extracellular and intracellular events involved in hormone–receptor interaction by studying the differences in the properties of the mutant receptor when compared with WT receptor. Studies on polymorphisms in the FSHR gene have shown variability in clinical outcome among women treated with FSH. These observations are being explored to develop molecular markers to predict the optimum dose of FSH required for controlled ovarian hyperstimulation. Pharmacogenetics is an emerging field in this area that aims at designing individual treatment protocols for reproductive abnormalities based on FSHR gene polymorphisms. The present review discusses the current knowledge of various genetic alterations in FSHR and their impact on receptor function in the female reproductive system.


Introduction

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH) are glycoproteins secreted by the anterior pituitary. They are heterodimers comprising a common α-subunit and a hormone-specific β-subunit that contributes to receptor-binding specificity (Pierce & Parsons 1981). FSH and LH are under the regulation of gonadotropin-releasing hormone (GNRH) and in turn regulate gonadal functions in males and females by activating their cognate receptors. FSH receptors (FSHR) along with other glycoprotein hormone receptors (LH/CGR and TSHR) form a subgroup of G-protein-coupled receptors (GPCR). FSH binds to its receptors expressed on the membrane of granulosa cells (GCs) in the ovary and Sertoli cells in the testis to bring about folliculogenesis (Richards & Midgley 1976) and spermatogenesis (Niebel & Nieschlag 1999) respectively.

Sprengel et al. (1990) cloned the cDNA of FSHR from rat testicular cells. Later, the mapping of FSHR gene on the chromosome number 2p21 in human was reported (Rousseau-Merck et al. 1993). The FSHR gene is 192 kb in size and comprises ten exons and nine introns (Gromoll et al. 1994). The first nine exons encode the N-terminal part of the extracellular domain (ECD). Exon 10 is large and encodes the C-terminal part of the ECD (hinge region), the transmembrane domain (TMD), and the intracellular domain (ICD) of the receptor. The TMD comprises seven α-helices, interconnected through three extracellular (ELs) and three intracellular loops (ILs). The ICD is predominantly coupled to a Gs protein that is responsible for initiating a cascade of intracellular events leading to specific biological effects of the ligand. The X-ray crystal structures of FSH complexed with the ECD of FSHR (Fan & Hendrickson 2005, Jiang et al. 2012) have immensely contributed to understanding the interaction of FSH with its receptor at the molecular level. However, it does not provide information on ligand-induced activation of the receptor leading to steroidogenesis.

Fshb gene (Kumar et al. 1997) and Fshr gene (Dierich et al. 1998) knockout female mice were found to be infertile with thin uteri and streak ovaries. But in both cases the male mice were fertile, although there was a decrease in testicular size and partial spermatogenic failure. These observations clearly indicate that FSH is absolutely essential for female fertility. In recent years, naturally occurring mutations in the FSH and FSHR genes have been reported. In vitro functional characterization
of these mutants has provided valuable information with respect to genotype–phenotype correlation in the case of both FSH and FSHR. Studies of FSHR mutants also provide an opportunity to understand the extracellular and intracellular events, such as hormone binding, signal transduction, and receptor trafficking, in response to FSH action. The FSHR gene is highly polymorphic in nature and three single nucleotide polymorphisms (SNPs) at positions −29, 307, and 680 have been extensively studied by various investigators using different ethnic populations both in males and females. Currently, FSH is used as a therapeutic in reproductive medicine, and published data on SNPs of FSHR has provided a new dimension with an emphasis on ‘pharmacogenetics of FSH action’ (Laan et al. 2012). Alternatively spliced variants of the FSHR gene have been reported and some of them affect fertility, mainly in females (Song et al. 2002, Gerasimova et al. 2010).

Our group is working on understanding the structure–function relationship of FSHR and one of the approaches employed toward this is studying the naturally occurring mutations, SNPs, and spliced variants of FSHR in women enrolled in IVF and infertility clinics. In the present review, we have made an attempt to provide an update on FSHR gene mutations and their effect on hormone–receptor interaction and signal transduction. We have also reviewed the usefulness of studying FSHR polymorphisms in developing a molecular marker for predicting ovarian response in women who are treated with FSH. Toward the end, the available information on the spliced variants of FSHR is also included.

Naturally occurring mutations of the FSHR gene

The presence of naturally occurring inactivating/activating mutations in the FSHR gene has been found to be a rare phenomenon when compared with the occurrence of mutations in the LHR and TSHR genes (Dufau et al. 1995). Studies suggest that the probable reason for the rare occurrence of the FSHR gene mutations could be due to the virtual absence of disease characterized by the deficiency or hypersecretion of FSH. Moreover, the FSHR mutations leading to severe forms of phenotype causing infertility are not inherited by the next generation. Therefore, screening of subjects with the phenotypes related to lack or hypersecretion of the FSH might remain unnoticed. The loss-of-function mutations in FSHR have been found in women with ovarian dysgenesis (ODG), primary amenorrhea, and secondary amenorrhea. Such mutations are also reported in men with small testes and impaired spermatogenesis (Table 1). On the other hand, gain-of-function mutations have been identified in women with ovarian hyperstimulation syndrome (OHSS) and in a single case of a hypophysectomized man (Table 2). The positions of the mutations reported so far in the ECD and TMD of FSHR have been shown in Fig. 1. For depicting the mutations in the ECD, the X-ray crystal structure of FSH complexed with ECD-FSHR (Jiang et al. 2012) is used. Whereas, for depicting the mutations in the TMD, the homology model generated for TMD-FSHR based on the rhodopsin receptor structure is used (Okada et al. 2004).

FSH action on its target cells involves initial binding of hormone to the receptor followed by signal transduction. These two events of hormone binding and signal transduction are generally studied by *in vitro* experiments while characterizing the naturally occurring mutations of FSHR.

Inactivating mutations

Identification of an inactivating mutation in the FSHR gene was first reported by Aittomäki et al. (1995) in women with ODG. In Finland, a large genetic survey of women with ODG was carried out. ODG is characterized by elevated gonadotropin levels and primary amenorrhea with normal karyotype. By genetic analysis, the locus segregating the disease was mapped on chromosome number 2p, which corresponds to the locus for both FSHR and LHR. As the males in these families were unaffected and their androgen levels were found to be normal, the mutation screening for only the FSHR gene was carried out. The observed mutation was at position 189 substituting Ala to Val in the ECD of FSHR. This mutation was found to be homozygous in affected women. *In vitro* functional studies with the mutant receptor expressed in MSC-1 cells showed reduced ligand-binding ability probably due to reduced expression on the cell membrane. However, the ligand-binding affinity was not affected. FSH-induced cAMP was abolished in the mutant receptor when compared with the WT receptor. Amino acids from 189 to 193 (AFNGT) in FSHR are conserved across all the glycoprotein hormone receptors and also across all the species. N191 is the proposed glycosylation site and the mutations at position 189 may have an effect on glycosylation and probably on trafficking of mature receptor onto the membrane (Davis et al. 1995).

Although this mutation in a homozygous condition has impaired fertility in females, the affected male siblings homozygous for this mutation showed a variable degree of spermatogenic failure. None of the five men investigated was found to be azoospermic. Only one was infertile, while two of them had fathered children (Tapanainen et al. 1997). The phenotype observed in women and men was similar to the one shown by *Fshr* knockout female and male mice respectively. Another mutation in the ‘AFNGT’ motif (Asn191He) was reported in a healthy woman in a heterozygous condition (Gromoll et al. 1996). *In vitro* studies with this mutation showed impairment in FSH-induced cAMP production and this defect could also be due to lack of glycosylation,
### Table 1 Inactivating mutations of FSHR in men and women: phenotype of the affected individual and findings from *in vitro* functional studies with mutants when compared with WT receptor.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Nucleotide change (exon number)</th>
<th>Amino acid change (region)</th>
<th>Phenotype of subjects</th>
<th>Cell surface expression of FSHR</th>
<th>FSH binding</th>
<th>FSH-induced cAMP</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>c.479C&gt;T (exon 6) Heterozygous mutation with inherited/de novo microdeletion or de novo gene conversion</td>
<td>p.Ile^{160}Thr (ECD)</td>
<td>Secondary amenorrhea with increased serum FSH levels</td>
<td>Affected</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Beau et al. (1998)</td>
</tr>
<tr>
<td>5</td>
<td>c.1717C&gt;T (exon 10) Compound heterozygous carrier of both mutations</td>
<td>p.Arg^{573}Cys (IL3)</td>
<td>ND</td>
<td>Similar</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Touraine et al. (1999)</td>
</tr>
<tr>
<td>6</td>
<td>c.671A&gt;T (exon 7) Compound heterozygous carrier of both mutations c.1801C&gt;G (exon 10)</td>
<td>p.Asp^{226}Val (ECD)</td>
<td>Primary amenorrhea with increased serum FSH levels</td>
<td>Affected</td>
<td>Decreased</td>
<td>Abolished</td>
<td>Doherty et al. (2002)</td>
</tr>
<tr>
<td>7</td>
<td>c.566C&gt;T (exon 7) Compound heterozygous carrier of both mutations c.1255G&gt;A (exon 10)</td>
<td>p.Ala^{180}Val (ECD)</td>
<td>Primary amenorrhea with increased serum FSH levels</td>
<td>Affected</td>
<td>Decreased</td>
<td>Abolished</td>
<td>Orio et al. (2006)</td>
</tr>
<tr>
<td>8</td>
<td>c.1555C&gt;A (exon 10) Homozygous mutation</td>
<td>p.Pro^{519}Thr (EL2)</td>
<td>Primary ovarian failure with FSH levels</td>
<td>Affected</td>
<td>Minimal</td>
<td>Abolished</td>
<td>Meduri et al. (2003)</td>
</tr>
<tr>
<td>9</td>
<td>c.1231A&gt;T (exon 10) Heterozygous mutation</td>
<td>p.Ile^{411}Asn (TMD helix 2)</td>
<td>PCOS</td>
<td>ND</td>
<td>ND</td>
<td>Similar</td>
<td>Kuechler et al. (2010)</td>
</tr>
<tr>
<td>10</td>
<td>c.1760C&gt;A (exon 10) Mutation on single allele with unbalanced translocation c.1723C&gt;T (exon 10) Heterozygous mutation</td>
<td>p.Pro^{580}His (TMD helix 6)</td>
<td>Primary amenorrhea</td>
<td>ND</td>
<td>ND</td>
<td>Abolished</td>
<td>Kuechler et al. (2010)</td>
</tr>
</tbody>
</table>

ECD, extracellular domain; EL, extracellular loops; IL, intracellular loops; ND, not determined; TMD, transmembrane domain.
Table 2 Activating mutations of FSHR in men and women: phenotypes of the affected individuals and findings from *in vitro* functional studies with mutants when compared with WT receptor.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Nucleotide change (exon number)</th>
<th>Amino acid change (region)</th>
<th>Phenotype of subjects</th>
<th>Cell surface expression of FSHR</th>
<th>FSH binding</th>
<th>cAMP levels</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c.1700A&gt;G (exon 10) Heterozygous mutation</td>
<td>p.Asp567Gly (IL3)</td>
<td>Hypophysectomized man with undetectable amount of serum FSH</td>
<td>ND</td>
<td>ND</td>
<td>1.5-fold higher</td>
<td>Similar upon FSH stimulation</td>
</tr>
<tr>
<td>2</td>
<td>c.1699G&gt;A (exon 10) Heterozygous mutation</td>
<td>p.Asp567Asn (IL3)</td>
<td>Women with sOHSS</td>
<td>Decreased cell surface expression</td>
<td>Similar</td>
<td>Threelfold higher</td>
<td>Similar upon FSH stimulation, increase upon hCG and TSH stimulation</td>
</tr>
<tr>
<td>3</td>
<td>c.1292A&gt;T (exon 10) Heterozygous mutation</td>
<td>p.Asn431Ile (EL1)</td>
<td>Normal spermatogenesis, suppressed serum FSH</td>
<td>Reduction cell surface expression</td>
<td>Decreased</td>
<td>Lower</td>
<td>Higher upon FSH stimulated when receptor expression is normalized</td>
</tr>
<tr>
<td>4</td>
<td>c.1346C&gt;T (exon 10) Heterozygous mutation</td>
<td>p.Thr449Ile (TMD helix 3)</td>
<td>Women with sOHSS</td>
<td>Similar</td>
<td>Similar</td>
<td>Similar</td>
<td>Similar upon FSH stimulation, increase in hCG stimulation, no effect by TSH</td>
</tr>
<tr>
<td>5</td>
<td>c.1345A&gt;G (exon 10) Heterozygous mutation</td>
<td>p.Thr449Ala (TMD helix 3)</td>
<td>Women with sOHSS</td>
<td>Twofold increase receptor expression</td>
<td>ND</td>
<td>2.5-fold higher</td>
<td>Similar upon FSH stimulation, increase in response to hCG and TSH</td>
</tr>
<tr>
<td>6</td>
<td>c.1634T&gt;C (exon 10) Heterozygous mutation</td>
<td>p.Ile545Thr (TMD helix 5)</td>
<td>Women with sOHSS</td>
<td>77% cell surface expression</td>
<td>Similar</td>
<td>130% increase</td>
<td>Increase upon FSH, hCG, and TSH stimulation</td>
</tr>
<tr>
<td>7</td>
<td>c.383C&gt;A (exon 5) Heterozygous mutation</td>
<td>p.Ser128Tyr (ECD)</td>
<td>Women with sOHSS</td>
<td>36% cell surface expression</td>
<td>ND</td>
<td>Similar</td>
<td>Increased sensitivity to hCG, no response upon TSH stimulation</td>
</tr>
</tbody>
</table>

ECD, extracellular domain; EL, extracellular loops; IL, intracellular loops; ND, not determined; sOHSS, spontaneous ovarian hyperstimulation syndrome; TMD, transmembrane domain.
resulting in a poor surface expression of the receptor (Gromoll et al. 2002). Recently, it has been reported that the 'AFNGT' motif plays an important role in maintaining the structural integrity of the receptor (Casas-Gonzalez et al. 2012). α- and β-subunits of FSH are shown in yellow and green color respectively. ECD of FSHR (in slate blue) shows the presence of leucine-rich repeats. Inset shows hydrophobic interaction of V221 of FSHR with P42 and A43 of α-subunit of FSH. (B) Homology model of TMD of FSHR constructed based on the crystal structure of bovine rhodopsin receptor (PDB ID: 1U19; Okada et al. 2004). H1–H7 are the helices that are interconnected by extracellular and intracellular loops. In both A and B, amino acids shown in orange and red correspond to inactivating and activating mutations of FSHR respectively.

Figure 1 Positions of naturally occurring activating and inactivating mutations in FSHR (A) X-ray crystal structure of human FSH complexed with ECD of human FSH (PDB ID: 4ay9; Jiang et al. 2012). α- and β-subunits of FSH are shown in yellow and green color respectively. ECD of FSHR (in slate blue) shows the presence of leucine-rich repeats. Inset shows hydrophobic interaction of V221 of FSHR with P42 and A43 of β-subunit of FSH. (B) Homology model of TMD of FSHR constructed based on the crystal structure of bovine rhodopsin receptor (PDB ID: 1U19; Okada et al. 2004). H1–H7 are the helices that are interconnected by extracellular and intracellular loops. In both A and B, amino acids shown in orange and red correspond to inactivating and activating mutations of FSHR respectively.

women. In a woman with secondary amenorrhea, mutations at Ile160Thr and Arg573Cys positions were detected. The other two cases were of primary amenorrhea where the mutation reported was at Asp224Val, Leu601Val, Ala199Val and Ala419Thr. Both these women developed high plasma gonadotropin levels, contrasting with normal-sized ovaries and the presence of antral follicles. Functional studies revealed that mutations located in the ECD affect receptor trafficking, thereby affecting ligand binding and subsequent signaling, whereas mutations at Arg573Cys, Leu601Val, and Ala419Thr did not impact greatly on the ligand-binding ability of the receptor but did, however, show reduced cAMP production (Beau et al. 1998, Touraine et al. 1999, Doherty et al. 2002). But, when Arg573 was replaced by Ala, the plasma membrane expression was observed to be severely affected, suggesting that the nature of amino acid substitution and location of the mutation are important and are observed to be independent determinants of FSHR function (Zarinan et al. 2010).

Meduri et al. (2003) reported a novel mutation in the EL2 of FSHR at the position Pro519Thr. This mutation has been observed in a homozygous condition in women with primary amenorrhea. Histological studies revealed a markedly enhanced number of (24.2 ± 4.6) primary follicles in the small ovaries. This mutation completely abolished the ligand binding and cAMP production in vitro, due to the defect in the trafficking of the receptor. Therefore, it can be concluded that Pro519 is probably a prerequisite for the FSHR trafficking and receptor function. Thus, along with ECD, ELs also seem to play an important role in ligand binding and receptor trafficking.

Apart from inactivating mutations identified in the ECD, a number of mutations in the helices of the TMD have also been reported so far. A mutation at Ile411Asn position was detected in women with polycystic ovary syndrome (PCOS; Orio et al. 2006). On the other hand, the mutations at Pro587His and Ala575Val were observed to lead to more adverse phenotypes such as primary amenorrhea (Achrekar et al. 2010, Kuechler et al. 2010). However, in vitro studies on the effect of the mutations in TMD on receptor trafficking have not yet been reported so far.

Genotype–phenotype association studies and in vitro functional characterization of these inactivating mutations of FSHR have provided valuable information about the contribution of the mutated residues and the corresponding region in hormone receptor interaction and signal transduction. In case of certain mutations, the defect is at the level of maturation of the receptor which is responsible for its trafficking onto the cell surface. Recently, efforts have been made to rescue the trafficking defective mutation to the cell surface using a pharmacorone (Org41841) by Janovick et al. (2009). This drug was observed to bind to the FSHR at a site other than the FSH binding site and it increased the membrane
expression of mutant FSHR (A189V) associated with misrouting and endoplasmic reticulum retention. Such studies need to be undertaken in future, which will form the basis for developing treatment modalities in some cases of reproductive abnormalities due to non-functioning of the receptor.

**Activating mutations**

Activating or gain-of-function mutations in the FSHR gene have been reported in both men and women. However, the number of cases reported is few when compared with the incidences and severity of the phenotype reported with activating mutations of the LHR gene (Meehan & Narayan 2007).

The first activating mutation was reported in a hypophysectomized, hypogonadotropic man (Gromoll et al. 1996). Although the serum gonadotropin levels were undetectable, he had normal testis volume and semen parameters. He had also fathered three children with testosterone treatment. The mutation was identified at Asp567Gly position in the IL3 of FSHR. This mutant exhibited ligand-independent constitutive activity when tested in vitro. It was reported that Asp567 is conserved across other glycoprotein receptors. The mutation in the corresponding residues in TSHR and LHR has also been reported. A mutation at Asp519Gly in TSHR was tested in cases with thyroid hyperfunctioning adenoma (Russo et al. 1996) and Asp564Gly in LHR was reported in cases of pseudoprecocious puberty (Laue et al. 1995). Interestingly, the first activating mutation in a female was identified at the same residue (567) of FSHR. The Asp567 was found to be mutated to Asn in a woman with spontaneous OHSS (sOHSS). The mutant receptor displayed threefold higher constitutive activity when studied in vitro and also responded to hCG and TSH treatment (Smits et al. 2003). Apart from Asp567Gly mutation, there is another activating mutation at Asn128Ile reported in an asymptomatic man (Casas-González et al. 2012). In vitro experiments demonstrated decreased cell surface expression of the mutant receptor. Further, the agonist-induced desensitization and internalization were found to be markedly altered.

All the activating mutations reported in women till date are associated with sOHSS. There are two cases of sOHSS where the Thr449 in the TMD was substituted. In one case, the mutation was at Thr449Ile (Vasseur et al. 2003) and in the second case it was Thr449Ala (Montanelli et al. 2004). Both the mutations were heterozygous in condition and displayed decreased hormone binding specificity of the receptor as these mutant receptors also responded to hCG. Substitution of Thr to Ala was observed to give constitutive activity to the receptor and was also observed to be nonspecifically responding to both hCG and TSH, whereas in the case of mutation at Thr449Ile, no constitutive activity was observed and the mutant receptor was not responding to TSH.

The mutation at Ile545Thr, also from the TMD, was detected in a woman with sOHSS. When tested, this mutation was found to cause cross-sensitivity of the receptor to both hCG and TSH together. The mutant receptor was also observed to be constitutively active. It was interesting to note that the symptoms of sOHSS were observed in this patient in the first trimester of pregnancy with normal hCG levels. The examination of an other seven women with sOHSS and high hCG or TSH levels indicated the presence of normal FSHR genotype. This suggests that, for these seven patients, sOHSS results from the natural promiscuous stimulation of WT FSHR by very high levels of hCG or TSH (De-Leener et al. 2006). It is worth noting that most of the germ line mutations in FSHR causing sOHSS were identified in the TMD (remote to the hormone binding site) of the FSHR. These mutations were observed to cause a non-specific response to hCG and TSH while displaying constitutive activity.

So far, there is only one report on an activating mutation (Ser128Tyr) from the ECD observed in a case of sOHSS (De-Leener et al. 2008). In contrast to the other mutations, this mutation in the ECD did not show any constitutive activity but exhibited higher affinity and sensitivity toward hCG but not to TSH. Subsequently, the extensive site-directed mutagenesis study at position 128 demonstrated that the increase in the sensitivity to hCG selectively is not a consequence of the loss of serine residue, as some substitutions were found to be neutral (Ser to Ala/His), whereas some substitutions were observed to be sensitive to both hCG and TSH (e.g. Ser to Ile/Val).

In general, it is observed that the gain-of-function mutations in the FSHR gene can cause a phenotype even when present in the heterozygous condition with dominant inheritance whereas the loss-of-function mutations are mostly transmitted recessively and give a phenotype only when present in the homozygous or compound heterozygous condition. Although studies were carried out to detect mutation in diseases such as ovarian tumors, megalotestes, precocious puberty, and twin pregnancies, no change in the FSHR gene was observed. This suggests that the phenotypes associated with the activating mutations of FSHR are still unclear in both men and women.

**SNPs of the FSHR gene**

Various SNPs in the coding and non-coding region (>1300 SNPs) of the FSHR gene have been identified in diverse populations. Of the total of eight polymorphisms present in the coding region, six are non-symptomatic and the other two polymorphisms present at position p.Thr307Ala (rs6165) and p.Asn660Ser (rs6166) are most extensively studied to assess the response of the receptor to FSH stimulation. The polymorphism at position 307 is located in the hinge region of the ECD whereas the polymorphism at position 680 is present in the ICD of the FSHR gene.
As the frequency distribution in various populations revealed that the Thr<sup>307</sup>-Asn<sup>680</sup> and Ala<sup>307</sup>-Ser<sup>680</sup> isoforms are predominant, most of the association studies focused on the polymorphism at position 680 alone. These two isoforms were believed to be present as potential glycosylation/phosphorylation sites of FSHR as Asn<sup>680</sup> introduces a consensus sequence for glycosylation which in turn may play a role in receptor trafficking and Ser<sup>680</sup> may contribute as a phosphorylation site, which might be involved in receptor turnover (Davis et al. 1995). Other than the polymorphisms in the coding region, Wunsch et al. identified the two polymorphisms at positions −29 and −114 in the 5′ UTR of the FSHR gene. These two polymorphisms are also linked due to their close proximity with each other. SNP in the −29 position (rs1394205) has been observed to be present in the viral E26 transformation-specific sequence (c-ETS-1) transcription factor binding site (Wunsch et al. 2005).

### Association of FSHR gene polymorphisms with ovarian response

As FSH plays a central role in stimulating follicular growth, it is used for controlled ovarian stimulation during IVF protocol and for various other infertility treatments in both females and males. Although similar stimulation protocols are used in IVF, the ovarian response to exogenous FSH varies widely ranging from poor to hyper-responsive. Many parameters, such as age and diminished ovarian reserve (Klingman & Rosenwaks 2001) and serum AMH levels (Nardo et al. 2009), have been used as a marker to predict the ovarian response. However, determining the dose of FSH to attain optimum response is one of the ongoing challenges in the field of infertility management in IVF clinics. By far, polymorphisms in the FSHR gene are most studied in relation to ovarian response in various populations and findings are summarized in Table 3.

Perez-Mayorga et al. (2000) demonstrated for the first time the association of higher serum FSH levels with the Ser<sup>680</sup> allele in women undergoing IVF. This paper served as a real breakthrough in signifying the role of FSHR gene polymorphisms as a genetic marker to predict ovarian response. Studies on the functional characteristics of these two isoforms were reported by various investigators. The in vitro functional analysis of the Thr<sup>307</sup>-Asn<sup>680</sup> and Ala<sup>307</sup>-Ser<sup>680</sup> isoforms suggested that the FSH binding and cAMP production are similar for both these isoforms (Tilly et al. 1992, Minegishi et al. 1994, Simoni et al. 1999, Sudo et al. 2002). Response of these isoforms to TSH stimulation was also characterized in HEK-293 cells and was observed to be alike (Ryan et al. 2007). Therefore, the molecular mechanism by which both these polymorphisms might be altering the ovarian response is still unclear. Significantly higher basal FSH levels and lower estradiol production upon hCG stimulation were associated with Ser<sup>680</sup> allele in studies conducted in different ethnic groups (Sudo et al. 2002, de-Castro et al. 2004, Behre et al. 2005, Greb et al. 2005). Recently, a meta-analysis carried out by Morón & Ruiz (2010), Aultman et al. (2011), and Yao et al. (2011) suggested that the Ser<sup>680</sup> allele is the only promising marker available to be used in clinical setup to predict the ovarian response to FSH stimulation.

Nevertheless, in the above studies, the significant associations of Ser/Ser genotype with total amount of FSH administered, number of follicles, and mature oocytes were not observed when compared with Asn/Asn genotype alone or in combination with Asn/Ser genotype at position 680. In a study reported by de-Castro et al. (2004), although the percent of poor responders were significantly higher in women with Ser/Ser genotype, the other clinical parameters, such as peak E<sub>2</sub> levels, number of follicles and oocytes, and amount of exogenous FSH, were observed to be similar in all the three genotypes at position 680 of FSHR. Additionally, it was noted that in a systematic randomized control study, women with either Ser/Ser or Asn/Asn genotype with 150 or 225 IU/day of FSH dose resulted in a similar number of follicles and retrieved oocytes, fertilization rate, and clinical pregnancy (Behre et al. 2005). Furthermore, there are reports from different ethnic origins from The Netherlands (Laven et al. 2003, Klinkert et al. 2006) and UK (Mohiyiddeen et al. 2012), which did not report any association of the polymorphism at position 680 with poor ovarian response.

On the other hand, in the study by Greb et al. (2005), the number of antral follicles was observed to be significantly greater in women with Ser/Ser genotype (22.6 ± 1.3) when compared with Asn/Asn genotype (17.8 ± 1.1). Similarly, the systematic study of subjects with ODG, poor responders, and good responders demonstrated that subjects with Ser/Ser genotype generate a significantly higher amount of estradiol and higher number of follicles and oocytes when compared with subjects with Asn/Asn genotype (Loutradis et al. 2006). Daelemans et al. (2004) also reported that women with the Ser<sup>680</sup> allele were at risk of showing hyper-response when compared with the Asn<sup>680</sup> allele. Similarly, our group has observed that although not significant, 50% of the subjects (three of six subjects) with p.Ser<sup>680</sup>Ser genotype developed OHSS (Achrekar et al. 2009a).

The association of polymorphism at position 307 with ovarian hyper-response was reported in an Indian population. Almost 85% of the subjects (six of seven subjects) with Ala<sup>307</sup>Ala genotype were found to be significantly associated with iatrogenic OHSS. These subjects developed OHSS when stimulated with significantly lower amount of exogenous FSH and demonstrated significantly higher levels of estradiol before and on the day of hCG stimulation (Achrekar et al. 2009a). As mentioned earlier, Ala at 307 is linked with the Ser<sup>680</sup>
allele. Thus, it is more likely that the Ser<sup>680</sup> allele along with the Ala<sup>307</sup> allele may be associated with hyper-response to FSH stimulation.

The rate of pregnancy in an IVF cycle is very important as it is considered as a measure to determine the IVF outcome. Klinkert <em>et al.</em> (2006) reported that the Ser<sup>680</sup> allele is more likely to give a higher pregnancy rate when compared with the Asn<sup>680</sup> allele. Recently, a genome-wide analysis carried out by Boudjenah <em>et al.</em> (2012) reported that women with Ser/Ser genotype were more likely to have a higher response than women with Asn/Asn genotype at position 680 (24 vs 12% respectively, <i>P</i> = 0.013). These observations suggest that there is a lack of consistency in the outcome of these association studies and there is a need for clarity in defining the poor ovarian response. Various attempts have been made to study the impact of the polymorphism at position 680 on FSHR activity using GCs. GCs obtained from women with three different genotypes at position 680 were cultured for a short time (<i>6–7</i> days) and were used to study the response of FSH stimulation. Results revealed that the amount of cAMP production and estrogen and progesterone synthesis was similar in GCs obtained from all three genotypes at position 680. Although the basal estradiol levels in GCs with Ser/Ser genotype were significantly lower, the estrogen production upon FSH stimulation was not significantly different among the three genotypes. The peak estradiol levels, number of follicles, and oocytes were similar in all three genotypes.

### Table 3: Studies on association of the polymorphism in the FSHR gene with ovarian response in women undergoing the IVF program.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Subjects screened (n)</th>
<th>Outcome of the studies</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Asn&lt;sup&gt;680&lt;/sup&gt;Ser</td>
<td>161</td>
<td>Women with Ser/Ser and Asn/Ser genotype showed significantly higher basal FSH levels and required significantly higher FSH dose for ovarian stimulation when compared with Asn/Asn genotype</td>
<td>Perez-Mayorga &lt;em&gt;et al.&lt;/em&gt; (2000)</td>
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<tr>
<td></td>
<td></td>
<td>Peak estradiol levels, number of follicles, and oocytes were similar in women with all three genotypes</td>
<td></td>
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<tr>
<td></td>
<td>58</td>
<td>Women with Ser/Ser genotype were significantly associated with increased exogenous FSH and decreased estradiol levels on the day of hCG administration</td>
<td>Sudo &lt;em&gt;et al.&lt;/em&gt; (2002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The number of oocytes retrieved was similar in all three genotypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>102</td>
<td>Ser/Ser genotype displayed significantly higher basal FSH levels and higher number of IVF cycles</td>
<td>de-Castro &lt;em&gt;et al.&lt;/em&gt; (2004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The peak estradiol levels, number of follicles, and oocytes were similar in all three genotypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>Women with Ser/Ser genotype required higher total FSH dose (225 U/day) for ovarian stimulation when compared with women with Asn/Asn genotype (who received 150 U/day) to attain similar ovarian response</td>
<td>Behre &lt;em&gt;et al.&lt;/em&gt; (2005)</td>
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<tr>
<td></td>
<td></td>
<td>Basal FSH, number of follicles, oocytes, and pregnancy rate was not different among Ser/Ser (150 U/day), Ser/Ser (250 U/day), and Asn/Asn (150 U/day) groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>148</td>
<td>Women with Ser/Ser genotype displayed significantly higher basal FSH levels, but the peak estradiol levels, exogenous FSH levels, number of follicles, and oocytes were similar when compared with women with Asn/Asn and Asn/Ser genotype</td>
<td>Klinkert &lt;em&gt;et al.&lt;/em&gt; (2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women with Ser/Ser genotype associated with hyper-response than women with Asn/Asn genotype (24 vs 12% respectively, &lt;i&gt;P&lt;/i&gt; = 0.013). These observations suggest that there is a lack of consistency in the outcome of these association studies and there is a need for clarity in defining the poor ovarian response. Various attempts have been made to study the impact of the polymorphism at position 680 on FSHR activity using GCs. GCs obtained from women with three different genotypes at position 680 were cultured for a short time (&lt;i&gt;6–7&lt;/i&gt; days) and were used to study the response of FSH stimulation. Results revealed that the amount of cAMP production and estrogen and progesterone synthesis was similar in GCs obtained from all three genotypes at position 680. Although the basal estradiol levels in GCs with Ser/Ser genotype were significantly lower, the estrogen production upon FSH stimulation was not significantly different among the three genotypes. The peak estradiol levels, number of follicles, and oocytes were similar in all three genotypes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>105</td>
<td>Women with Ser/Ser genotype had implantation and pregnancy rate significantly higher than women with Asn/Asn genotype</td>
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<tr>
<td></td>
<td>421</td>
<td>The total amount of FSH stimulated and the number of oocytes retrieved were similar in all three genotypes</td>
<td>Mohiyiddeen &lt;em&gt;et al.&lt;/em&gt; (2012)</td>
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<tr>
<td></td>
<td>64</td>
<td>Women with Ser/Ser genotype were associated with higher ovarian threshold to FSH, decreased negative feedback of luteal secretion, longer menstrual cycles but displayed significantly higher number of antral follicles</td>
<td>Greb &lt;em&gt;et al.&lt;/em&gt; (2005)</td>
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<td></td>
<td>Peak estradiol levels, inhibin B, and growth velocities of dominant follicles were not significantly different among the three genotypes</td>
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<tr>
<td></td>
<td>79</td>
<td>Women with Asn/Ser genotype generate a significantly higher amount of estradiol and higher number of follicles and oocytes when compared with women with Ser/Ser and Asn/Asn genotype</td>
<td>Loutradis &lt;em&gt;et al.&lt;/em&gt; (2006)</td>
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<td></td>
<td>37</td>
<td>Ser&lt;sup&gt;680&lt;/sup&gt; allele present more risk of giving iatrogenic OHSS when compared with Asn&lt;sup&gt;680&lt;/sup&gt; allele, but the Asn&lt;sup&gt;680&lt;/sup&gt; allele was significantly associated with severity of iatrogenic OHSS</td>
<td>Daelemans &lt;em&gt;et al.&lt;/em&gt; (2004)</td>
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<td></td>
<td>427</td>
<td>Women with Ser/Ser genotype were more likely to have hyper-response than women with Asn/Asn genotype</td>
<td>Boudjenah &lt;em&gt;et al.&lt;/em&gt; (2012)</td>
</tr>
<tr>
<td>p.Thr&lt;sup&gt;307&lt;/sup&gt;Ala</td>
<td>50</td>
<td>Women with Ala&lt;sup&gt;307&lt;/sup&gt;Ala genotype were significantly associated with lower dose of exogenous FSH, higher estradiol levels before and on the day of hCG stimulation</td>
<td>Achrekar &lt;em&gt;et al.&lt;/em&gt; (2009a)</td>
</tr>
<tr>
<td>g.G&gt;A –29</td>
<td>202</td>
<td>85% of the women with Ala/Ala genotype developed OHSS</td>
<td>Wunsch &lt;em&gt;et al.&lt;/em&gt; (2005)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Basal FSH and estradiol levels were not significantly different among the three genotypes at position –29</td>
<td>Achrekar &lt;em&gt;et al.&lt;/em&gt; (2009b)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>Women with AA genotype displayed lower estradiol levels, number of follicles and oocytes, and higher total amount of exogenous FSH administered when compared with women with GG genotype</td>
<td>Desai &lt;em&gt;et al.&lt;/em&gt; (2011)</td>
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</tbody>
</table>

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stimulation did not differ significantly between the three genotypes, suggesting that the probable contribution of polymorphism at position 680 needs further investigation in long-term GC culture system (Nordhoff et al. 2011, Zalewski et al. 2013).

The level of FSHR expression also has an impact on the FSH action. Moreover, the reduced expression of FSHR on GCs has been shown to be associated with poor ovarian response (Cai et al. 2007). The polymorphism at position –29 of the 3′ UTR in the FSHR gene has been studied with respect to its effect on receptor expression as this polymorphism may modulate the cETS-1 transcription factor binding site. In vitro analysis carried out in CHO cells demonstrated that the A−29 allele expressed a significantly lower level of luciferase activity when compared with the G−29 allele of the FSHR gene (Nakayama et al. 2006). Despite the fact that Wunsch et al. (2005) did not observe any association of the polymorphism at position –29 with ovarian response, the clinical parameters considered in this study were limited (basal FSH levels and E2 levels). Recently, we observed that subjects with AA genotype were significantly associated with a reduced number of follicles and retrieved oocytes when compared with subjects with GG genotype. The amount of FSH required for optimum response was also significantly higher in subjects with AA genotype when compared with GG genotype. Almost 66.67% (odds ratio 8.154; 95% CI 2.79 to 23.77; P<0.0001) subjects with AA genotype were poor ovarian responders (Fig. 2; Achrekar et al. 2009b, Desai et al. 2011, 2013). Further, using GCs obtained from women undergoing IVF, we observed that subjects with AA genotype expressed significantly reduced FSHR expression both at transcript and protein level when compared with GG genotype (Desai et al. 2011). This study provides the experimental evidence to suggest that reduced receptor expression observed in subjects with AA genotype could be the probable reason for the poor ovarian response to FSH stimulation observed in them. However, a greater number of subjects from various ethnic populations needs to be analyzed to assess the usefulness of screening this polymorphism, which could be used as a biomarker to predict poor ovarian response.

![Figure 2 Association of AA genotype at position –29 of the FSHR gene with poor ovarian response (A, B, C and D). Amount of (recombinant or urinary) exogenous FSH administered during controlled ovarian hyperstimulation, number of preovulatory follicles, number of retrieved oocytes, and percent poor ovarian responders respectively in women (n = 150) with different genotypes who are undergoing an IVF protocol (Achrekar et al. 2009b, Desai et al. 2011, 2013). The same letter (a or b) indicates statistically significant difference at P≤0.05 among different genotypes.](image-url)

**Association of FSHR gene polymorphisms with PCOS, premature ovarian failure, and amenorrhea**

PCOS represents a clinical condition distinguished by impaired menstrual cycle and formation of multiple cysts in the ovary. In these subjects, LH:FSH ratio is generally increased and there is excessive production of androgen (Goodarzi et al. 2011). So far, a number of polymorphisms has been studied in various candidate genes to predict the risk of developing PCOS. A meta-analysis across the eight studies suggested that the Asp680 allele was associated with lower risk and the Ala307-Ser680 genotype was associated with an increased risk of developing PCOS (Du et al. 2010).

Generally, treatment of infertility in cases with PCOS is based on increasing the level of FSH either by antagonizing the effect of estrogen by clomiphene citrate (CC) or by administering recombinant FSH (rFSH). Recently, it was observed that subjects with Ser/Ser genotype at position 680 exhibited high resistance to CC treatment but showed the most favorable response to rFSH stimulation (Overbeek et al. 2009). Likewise, in a study in PCOS women from Italy, Asn/Thr genotype at position 307 displayed higher response to FSH stimulation when compared with both the homozygous genotypes (Dollin et al. 2011).

Premature ovarian failure (POF) is also referred to as primary ovarian insufficiency (POI) and is characterized by low levels of gonadal hormones (estrogen, inhibins) and elevated levels of FSH with impaired ovarian folliculogenesis. The phenotype of the FSHR knockout mice was observed to be similar as observed in POF (Dierich et al. 1998). Thus, FSHR could serve as a strong candidate gene responsible for the phenotype observed in the females with POF. Although there are no clear associations observed in FSHR gene polymorphism with POF, recently Kim et al. (2011) reported that epistasis between FSHR and CYP19A1 polymorphisms was significantly associated with POF.

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In the case of subjects with amenorrhea, an association with the Ser\textsuperscript{680} allele has been observed (Sudo et al. 2002). Recently, our group has investigated the association of polymorphisms at position −29, 307, and 680 in women with primary and secondary amenorrhea. We observed that in the subjects with primary amenorrhea, AA genotype at position −29 was significantly associated with increased basal serum FSH levels when compared with GG and GA genotype (Achrekar et al. 2010).

Association of FSHR gene polymorphisms with male infertility

In recent years, several studies on the association of the FSHR gene polymorphisms on sperm motility, sperm counts, and testicular volume were carried out. Most of the reports showed no significant association of the polymorphisms at position −29, 307, and 680 with these parameters (Ahdal et al. 2005, Pengo et al. 2006, Li et al. 2011, Lindgren et al. 2012). The recent three meta-analyses that summarized the seven original papers also suggest no association of these polymorphisms with reproductive abnormalities in men (Tüttelmann et al. 2007, Lend et al. 2010, Wu et al. 2012). However, it was interesting to note that subjects with AA genotype at position −29 showed significantly smaller mean testicular volumes when compared with subjects with GG genotype (Lend et al. 2010). Taken together, these studies from different populations suggest that FSHR genotype does not seem to have a significant impact on male reproductive physiology.

Association of FSHR gene polymorphisms with gonadal cancer

There are limited studies on FSHR gene polymorphisms in cases with ovarian or testicular cancer. Contradicting observations with respect to the association of FSHR polymorphisms with low or high risk of forming gonadal cancers have been reported. Ala\textsuperscript{307}/Ser\textsuperscript{680} allele alone or in combination with G\textsuperscript{−29}/T\textsuperscript{−114} allele was observed to be associated with lower risk of developing testicular cancer (Ferlin et al. 2008). On the other hand, homozygous Ala\textsuperscript{307}/Ser\textsuperscript{680} alleles have been associated with higher risk and recurrence of developing ovarian cancer (Ludwig et al. 2009). However, the mechanism by which these alleles could modulate the FSHR function in ovarian or testicular cancer cells is still unknown and holds a great research interest.

Alternatively spliced variants of the FSHR gene

Alternatively spliced variants of the FSHR gene have been identified in various species such as cattle, rat, and sheep. Alternatively spliced variants of the FSHR gene in rat and sheep have been observed to result in the soluble form of the protein or modification of the C-terminal domain of the receptor (Sairam et al. 1996, Yarney et al. 1997). In humans, alternate splicing of exon 9 in normal testicular tissue has been reported, which suggests that this spliced variant does not affect the FSHR function in testis (Gromoll et al. 1992). Deletion of exons 6 and 9 and insertion of part of intron 8 has also been identified in infertile men (Song et al. 2002). Additionally, a number of spliced variants such as del exon 2, 6, and 9 and insertion of 102 bp of intron 8 along with the WT FSHR in the GCs obtained from women undergoing IVF has also been reported. The clinical parameters of these women suggested that deletion of exon 2 was associated with poor ovarian response whereas deletion exon 6 was associated with a high response (Gerasimova et al. 2010). In our study, in subjects undergoing IVF, we observed that out of a total of 20 subjects screened, only one subject was observed to posses insertion of a part of intron 8 (102 bps) along with the WT-FSHR (S S Desai and S D Mahale 2011, unpublished data). However, this spliced variant did not seem to affect the various clinical parameters. Therefore, screening of spliced variants in a greater number of subjects is essential to corroborate their role in ovarian response and female infertility.

Summary and future perspective

Studies reported so far clearly indicate that mutations, polymorphisms, and alternatively spliced variants in FSHR have varied effects on receptor function. The overview of the phenotypes associated with genetic alterations in the FSHR and their functional characterization carried out so far has been summarized in Fig. 3. Identification of different inactivating mutations in the FSHR gene and correlating them with respective phenotypes clearly suggest that receptor function is impaired in women with such mutations, resulting in infertility. However, the affected men had no effect on their fertility. In vitro functional studies undertaken to characterize these mutants have provided valuable information in understanding FSH–FSHR interaction at the molecular level. These mutations are believed to bring about structural change in the receptor, thereby reducing the hormone binding ability or hormone-induced signaling ability. Few of the mutations have shown any defect at the level of trafficking to the cell membrane, probably due to a defect in the maturation of the receptor (Casas-González et al. 2013). Further studies with these mutants will possibly help in understanding the events involved in post-translational modifications of FSHR, its interaction with intracellular adaptor molecules, internalization, recycling, degradation of the activated receptor, etc. In addition, generation of the corresponding mutant animal model will help in developing modalities to rescue the receptor function. Toward this, efforts have been made to use small molecules capable of restoring the receptor function...
Association studies
findings from the analysis of data in women (K
increase the predictive value of the marker. Preliminary
made toward this. It would be interesting to study these
position is not well understood and efforts need to be
of the altered ovarian response with SNP at 307 and 680
response, which is found to be reduced expression
of the receptor both at transcript and protein levels. On
response, which is found to be due to loss of hormone
activating mutations of FSHR gene, the receptor activity
was observed that in most of the
cases, the receptor was activated by hCG or TSH or by
both. In women, such mutations resulted in sOHSS.
The polymorphic nature of the FSHR gene is being
explored to develop molecular markers mainly in the
case of women undergoing controlled ovarian hyper-
stimulation procedure. SNPs at 29, 307, and 680 have been studied in detail by various
investigators in different ethnic populations. Polymorphism at -29 (AA) has been linked to poor ovarian
response, which is found to be due to reduced expression of the receptor both at transcript and protein levels. On
the other hand, mechanisms involved in the association of the altered ovarian response with SNP at 307 and 680
position is not well understood and efforts need to be
made toward this. It would be interesting to study these
SNPs in combination with each other with an aim to
increase the predictive value of the marker. Preliminary
findings from the analysis of data in women (n=150)
suggest that A-29A/Asn680Asn genotype is associated
with poor ovarian response with an odds ratio of 7.92
(P=0.009) (Desai et al. 2013). Thus, studying SNPs of the
FSHR gene is emerging as an important arm of
pharmacogenomics and personalized medicine and
needs to be explored further to optimize the dose of
FSH required for superovulation and also to predict the
ovarian response in women undergoing FSH treatment.

Declaration of interest
The authors declare that there is no conflict of interest
that could be perceived as prejudicing the impartiality of
this review.

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