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Pharmacogenetics of FSH action

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Abstract

Purpose of the review—To review the current knowledge of genetic variants in the two genes affecting the individual responsiveness to follicle-stimulating hormone (FSH) action—the FSH beta-subunit (*FSHB*) and the FSH receptor (*FSHR*), as well as the pharmacogenetic ramifications of the findings.

Recent findings—Four common variants in *FSHB/FSHR* were shown to exhibit significant effect on FSH action: linked *FSHR* variants Thr307Ala and Asn680Ser determining common receptorisoforms, andgene expression affecting polymorphisms *FSHR* –29G/A and *FSHB*–211G/T. In women, the *FSHR* Thr307Ala/Asn680Ser polymorphisms show consistent predictive value for estimating the most optimal rFSH dosage in controlled ovarian hyperstimulation(COH).The same variants exhibit a potential for the pharmacogenetic assessment of the treatment ofPCOS. The *FSHR*–29G/A variant was also shown to contribute to ovarian response to COH. Pilot studies have suggestedthe *FSHB*–211TT-homozygous oligozoospermicmen with genetically determined low concentration of FSH, as potentially the best responders to FSH treatment; furthermore, modulation of this response by *FSHR* polymorphisms is possible.

Summary—Genetic variants in *FSHB/FSHR*exhibit a potential for pharmacogenetic applications in selecting appropriate treatment options (timing and dosage) in male and female conditions requiring or benefitting from FSH therapy.

Keywords

Follicle-Stimulating Hormone; *FSHB*–211G/T SNP; *FSHR*Thr307Ala/Asn680Ser; *FSHR*–29G/A SNP; pharmacogenetics

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Introduction

Follicle-stimulating hormone (FSH) together with the other gonadotrophic hormone, luteinizing hormone (LH), is produced by the anterior pituitary gland, and it acts along the hypothalamic-pituitary-gonadal (HPG) axis to regulate the crucial functions of the ovary (female sex steroid production and follicular maturation) and testis (spermatogenesis) (Fig. 1) [1,2].Today, treatments with recombinant FSH (rFSH)are a mainstay in several areas of reproductive medicine. Knowledge is accumulating that the efficiency of rFSH therapy is modulated by polymorphisms ingenes regulating the dynamics of FSH action.

Function of FSHin women and men

In women, pulsatilegonadotropin-releasing hormone (GnRH) secretion from the hypothalamus maintains similarly pulsatile secretion of FSH andLH from the anterior pituitary, anddrivesin the ovary thehormonal and cellular events that regulate the maturation of Graafian follicles and granulosa cell estrogen production. FSH is also essential to prevent apoptosis and to stimulate proliferation of granulosa cells. Knockoutfemale mice lacking FSHor FSH receptor (FSHR) exhibit infertility, small ovaries, blockage in folliculogenesis, defects in granulosa cell proliferation and function, and suppressed aromatase activity [3,4], and provide accurate phenocopies for similar mutations in women. Outside reproduction, and quite surprisingly, recent studies have suggested a possible extragonadal role of FSH in postmenopausal bone loss[5,6*] and in the neovascularization surrounding malignant tumours [7*]. More data is required to draw the conclusions on extragonadal actions of FSH.

In men, GnRH regulates similarlythe pulsatile secretion of LH and FSH. Lower responsiveness to GnRH pulsatility in men has been explained by androgen exposureduring embryonic developmentleading to different functionality of the hypothalamic GnRH system [8]. In the male,FSHRs are located in testicular Sertoli cells. During fetal, neonatal and pubertal development, FSH activates the proliferation of Sertoli cellsthat is crucial for normal testes development and promotes mitosis in spermatogonia [9*,10*]. In adult men, FSH is important for the maintenance of the metabolic functions of Sertoli cellsthat are essential for the maintenance of qualitatively and quantitatively normal spermatogenesis, germ cell survival and male fertility [11,12]. In male mice, FSH β-subunit or FSHR deficiency did not lead to infertility, although the animals displayed decreased Sertoli cell number, reduced testes size, sperm count and motility [3]. Interestingly, in menthe inactivating *FSHR* mutationsrepresent phenocopies of murine *fshb* and *fshr*knockouts, but thehuman FSHB inactivation induces a more extreme phenotype (azoospermia) compared to male mice, for a so far unknown reason. More information is thus also needed to improve our knowledge on the FSHactions in men.

Key genes involved in FSH action

The efficiency of FSH action is regulated by threemain factors—the intrinsic bioactivity of the hormone, its serum concentration, andthe efficacy of FSHR signal transduction in response to hormonal stimulation. The rate-limiting step in FSH production is the transcription of the FSH beta subunit coding *FSHB*gene [13]. The other component in the biologically active FSH heterodimer, the common alpha subunit, is produced normally in excess and is not known to limit the production of bioactive FSH[14]. Activation of FSH receptor coded by the *FSHR* gene is necessary for the hormonal functioning of FSH[15]. Other genetic variants affecting FSH action may localize in genes involved in the HPG axis either upstream (e.g. *GnRH, INHBA*, *INHBB*) or downstream (e.g. *CYP19A1, ESR1, ESR2*, etc.) of the pituitary level (Fig. 1), but their clinical value in pharmacogenetic applications requires further studies.

Follicle stimulating Hormone beta subunit gene (*FSHB*)

The human *FSHB* gene (MIM: 136530, chr. 11p13, gene 4262 bp, protein 119 amino acids) belongs to the glycoproteinhormone (LH, FSH, TSH) beta gene family (*GtHB*) and is expressed in gonadotroph cells within the anterior pituitary gland [16**].It is characterized by a low number of polymorphisms mostly within noncoding regions and spread as high-frequency alleles in human populations (Fig. 2A). These variants arein strong linkage disequilibrium (LD)with each otherand form two main*FSHB*haplotypes [17].

Only five inactivating *FSHB*mutations (all in exon 3) have been reported in nineindividuals (Fig. 2A)(reviewed in [16**]). These mutations result in premature stop-codon or loss of a cysteine residue affectingproper subunit folding. Homozygous or compound heterozygousfemale patients exhibited impaired pubertal development and primary amenorrhea.Male patients had normal or impaired puberty and azoospermia.

A regulatory SNP within the *FSHB* promoter –211G/T (rs10835638) is the only identified genetic variant with direct major effect on serum FSH concentrations in men. In Estonians, the median serum FSH of TT- compared to GG-genotype carriers was in young men78%[18] and among infertility patients48.5% of control levels [19**].The association of the T-allele with reduced serum FSH was confirmed in a large cohort of Baltic young men [20**], as well as in Italian [21**] and German [22] infertility patients.The reduction incirculating FSH levels wasaccompanied by significantly reduced serum Inhibin B and testosterone, as well asby lower testis size and sperm concentration(Fig. 2B).Genetically determined low concentrationof FSHduring development might affecttesticular cell proliferation and lead to impaired testicular function. Increasedfrequency of theT-allele in Estonian infertility patientssuggesteda possible contribution of the *FSHB* gene position –211G/T to the male reproductive potential.

In addition, the C-allele of an*FSHB*synonymous change (2623T/C, Tyr58Tyr, exon 3, rs6169; Fig. 2A) has been associated with anincreased risk for polycystic ovarian syndrome (PCOS) [23] and with later age at menarche[24].

Follicle stimulating Hormone Receptor gene (*FSHR*)

The human *FSHR* gene (MIM:136435, chr. 2p21, gene 192 kb, protein 695 amino acids) encodes for FSH receptorthat belongstogether with LHR and TSHRto the glycoprotein hormone receptor subfamily of the G-protein coupled receptors (GPCRs)[15]. FSHR is primarily expressed in ovarian granulosa and testicular Sertoli cells, but its expression in endometrium [25], osteoclasts [5] and vascular endothelium surrounding malignant tumours [7*] has recently been reported.Of the >1300 SNPs in the *FSHR* gene, eight (six non-synonymous) locate in the coding region (Fig. 3).

Activating*FSHR*mutationslead toconstitutively activereceptor signalling in the absence of hormone bindingdue to a conformational alteration of the transmembrane domain(Fig. 3; reviewed in [26*]). In the single man found with such a mutation (Asp567Gly), the phenotype was persistent spermatogenesis in the absence of circulating gonadotrophins (after hypophysectomy)[27].This clinical phenotype has been reproduced in transgenic mutant male mice [28,29]. In heterozygous women with such mutations the phenotype ispregnancy-associated ovarian hyperstimulation, mainly due to responsiveness of the mutated receptor to hCG. In female mice, gain-of-function *fshr* mutations lead to distinct pathological changes in ovarian structure and function, e.g. accelerated loss of follicles[30]. Inactivating *FSHR* mutations caused in men impaired spermatogenesis and in womenhypergonadotropic ovarian failure[26*].

Most of the functional studies on *FSHR* polymorphisms have concernedtwo substitutions in exon 10,Thr307Ala (rs6165) and Asn680Ser (rs6166)[31]. These polymorphisms are instrong LD and exhibit almost equal distribution of the two main isoform variants (Thr307-Asn680, Ala307-Ser680) in Europeans.As FSHRisoforms differ in sensitivitytoFSH stimulation, they havea significant effecton female serum FSHconcentration and ovarian FSHRresponse [32,33,34*,35**,36*]. Women with the Ser680/Ser680 genotype exhibit longer menstrual cycles as another sign of reduced ovarian response to FSH [37]. In addition, in Taiwanese women the*FSHR*Asn680 variantwas reported to reducethe risk ofendometriosis [38], andin Italian women the Ala307-Ser680 gene variant homozygosity (least sensitive receptor) was associated with lower risk to Alzheimer disease [39]. In contrast, no effectsof *FSHR* Thr307Ala and Asn680Ser variants on adult male serum FSH and efficiency of spermatogenesis have been proven. Additionally, the carrier status of the*FSHR*isoforms has been suggested to influencethe susceptibility to testicular [34*,40] and ovarian cancer[41-43], but due to a small number of studies no clear-cut associations or definitive conclusions can be drawn.

Anovel *FSHR*polymorphism –29G/A (rs1394205) located in the 5′-UTR was shownto alter the transcriptional activity, and it was associated with female hypertension [44].A recent study demonstrated significantly reduced FSHR at mRNA and protein level in granulosa cells of subjects with *FSHR*–29 minor A-allele homozygosity compared toG-allele homozygotes [45**].The *FSHR*–29 AA-genotype was significantly enriched among Indian women with primary or secondary amenorrhea compared to normally cycling fertile women, and the AA-subjects with primary amenorrhea exhibited increased serum FSH levels consistent with inadequate receptor stimulation [46*].Reduced testis volume and slightly lower sperm counts in*FSHR* –29 A-allele male carriers has also been reported[47].

As*FSHR* is a large gene, it may contain several other functional variants in addition to the few studied SNPs. A recent genome-wide association study (GWAS) pinpointed an*FSHR*intronic SNP (rs2268363) being associated with the development of erectile dysfunction in African-American men after radiotherapy for prostate cancer [48].A significant association of several *FSHR* polymorphisms was detected with preterm birth [49].

Pharmacogenetic potential of *FSHB* and *FSHR* gene variants

Serum FSH level are measured for the assessment of fertility potential and gonadal function. In both sexes, abnormal serum FSH level suggests impaired gonadal function.Low FSH indicates a deficiency in the hypothalamic GnRH secretion or pituitary gonadotrophin synthesis and/or secretion(Fig. 1). Gonadotrophin levels are inadvertently high in primary gonadal failure due to insufficient negative feedback of gonadal sex steroids and/or inhibin. In the clinical diagnostic utility the correct interpretation of estimated serum FSH (as abnormally low or high) is not always straightforward as automated commercial immunoassays exhibit between-method sensitivity and measurement variability [50].An option to treatdeficient gonadotrophin secretion is non-invasive medication by FSH injections or pulsatile GnRH infusions. Another common application of FSH treatment is during ovarian priming for *in vitro fertilization* (IVF) treatment.

Pharmacogenetics of disturbed action of FSH in women

Polycystic ovary syndrome (PCOS)

PCOSrepresents a common clinical condition (6-10% of women) characterized by unbalanced FSH (normal or reduced) levels in relation to LH (increased).It results in increased LH/FSH ratio and excessive ovarian androgen production causing impaired

menstrual cycle,ovulatory dysfunction and symptoms of androgen excess (e.g. hirsutism) [51,52]. Familial disposition to the syndrome suggests a genetic risk [53]. Biological evidence, and candidate gene and genome-wide association studies point to the link between PCOS andpolymorphisms in gonadotrophin and their receptor genes [54,55**,56]. Meta-analysis across eight studies showed significant reductionin PCOS risk in homozygotes for the *FSHR* Asn680/Asn680 major isoform(OR= 0.639; 95%CI: 0.416, 0.980) [57*].

Treatment of infertility ofPCOS patients consists of ovulation induction byclomiphene citrate (CC) and/or rFSH. PCOS patients homozygous for the*FSHR*Ser680 alleleexhibited high resistance to CC [58]. Consistent with the impaired FSH action, anovulatory (46%) compared to oligo-ovulatory (10%) PCOS patients were shown to have a higher chance of pregnancy after ovulation induction with rFSH, whereas CC treatment was less effective [59]. Interestingly, ina recent study in Italian PCOS women the*FSHR*Ala307Thr heterozygotesexhibited a higher ovarian responsiveness to exogenous rFSH than subjects homozygous for FSHR isoforms [60].

Premature ovarian failure/insufficiency(POF, POI)

In 1-2% of women, this is a condition accompanied by elevated FSH levels due to impaired ovarian response to FSH-stimulation [61,62]. There is no clear association or pharmacogenetic perspectivein the conducted studies targeting the *FSHR*Ala680Servariant [34*,57*]. Recently, epistasis between*FSHR*Asn680Ser and polymorphisms in *CYP19A1* (aromatase) was associated with POF [63**].

The pharmacogenetic relevance of the*FSHR*–29G/A and *FSHB*–211G/T polymorphisms in PCOS and POF patients remainsto be studied.

Postmenopausal hormone therapy and osteoporosis

In postmenopausal women, *FSHR* Asn680Ser Asn/Asn-individuals have an increased risk of osteoporosis[64*].Still, the direct effect of FSH on bone must first be confirmed in human before any pharmacogenetic studiesof polymorphisms modulating FSHactionare relevant.

Pharmacogenetics of FSH action in ovulation induction in assisted reproduction

Controlled ovarian hyperstimulation (COH)

Identification of predictive factors of ovarian response is important in order to apply the most optimal schemes of ovulation induction and ovarian stimulation resulting in high rates of good-quality oocyte recovery and pregnancies, withminimalside-complications of the treatment to the patients. Currently, the*FSHR* Thr307Ala, Asn680Serpolymorphisms are the only oneswithreliable consistent predictive value andpotentially applicable in clinical tests for estimating the required rFSH dosage in COH.The Ala307-Ser680 variant is associated with elevated FSH requirement, reduced COH outcome and lower clinical pregnancy rate, whereas Thr307-Asn680 is associated with good response during COH[32,33,34*,45**, 65*]. However, no clear conclusions can yet be drawn from the available data on association of the*FSHR* Asn680Ser and *ovarian hyperstimulation syndrome* (OHSS) affecting up to 5% of patients undergoing IVF [26*,34*,35**,65*,66].

An*FSHR*promoter polymorphism –29G/A (rs1394205) mayalso contribute to ovarian response to COH. A seminal study showed that *FSHR*–29 AA-homozygous women with lower*FSHR*expression required higher dosesof FSH for ovulation induction [67].A follow-up study revealed that almost 72% of subjects with the AA-genotype were poor ovarian responders[45**]. In addition to SNPs, the variability in response to rFSH treatment in COH

may be modulated by *FSHR*variants due to alternative splicing. Deletion of exon 2 was associated with low response to FSH and deletion of exon 6 with high response [68*]. Abnormal FSHR splice variants were identified in 30% of young patients.However, the profiling of splice variants in routine molecular diagnostics and pharmacogenetics applications might be challenging.

No data is available on the role of the*FSHB* –211G/T SNP in determination of the outcome of COH.

Pharmacogenetics of FSH action in men

Idiopathic infertility

It has been claimedthat FSH treatment of male infertility could be performed on selected patients utilizing some predictive parameters able to identify *a priori* responders with high probability [69,70]. For example, elevated plasma levels of FSH have been shown as a negative predictor for the usefulness of FSH treatment. Grigorova *et al.* [19**] suggested that one potential group of responders to the FSH therapy may be men diagnosed with idiopathic infertility, but exhibiting genetically inherited, constitutively lower serum FSH. Determination of the genotype of the *FSHB* promoter polymorphism (–211G/T) could potentiallyallow identification ofthe patients, whose primary cause of the infertility problems may be inadvertentlylow FSH production (Fig.2). The results of the first pilot study following this hypothesisshowed that Italian infertile men carrying the *FSHB*–211 T-allele were the best responders to FSH treatment [21**].All patients (9/9) in the TT-homozygote group responded to FSH treatment positively. Among the GG-homozygotes and GT-heterozygotesthe fraction of men that increased their sperm count after FSH therapy was 34.2% (13/38) and 65.0% (13/20), respectively.

Another pilot pharmacogenetic study has suggested that response to FSH treatment is may be further modulated by FSHR isoforms. Onlythe carriers of *FSHR* Ala307-Ser680allelewere reported withimprovedspermparameters [71**].

Timing of treatment in cases of genetically altered FSH action

Recently, it has been suggested that neonatal gonadotrophin therapy, instead of treatment in adulthood might have additional benefits [72**].As an example, in boys diagnosed with congenital hypogonadotropic hypogonadism at birth, prepubertal treatment had positive effect in testicular endocrine function and on genital development and growth, which could potentially improve the response to spermatogenesis inducing treatments in adulthood [73].

Conclusion

The previously established *FSHR*Thr307Ala/Asn680Ser variant, as well as the other more recently identified polymorphisms (*FSHB*–211G/T, *FSHR*–29G/A) provide convincing evidence for their functional relevance in men and women. These polymorphisms exhibit a potential for pharmacogenetic applications inselecting appropriate treatment options in conditions requiring or benefitting from FSHtherapy.

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Key points

- The efficiency of FSH action is regulated by threemain factors—the serum levels of circulating hormone, its intrinsic bioactivity and the efficacy of FSHR signal transduction in testicular and ovarian target cells
- Four common variants in *FSHB/FSHR* were shown to exhibit significant effect on FSH action: linked *FSHR* variants Thr307Ala and Asn680Ser determining common protein isoforms, andgene expression affectingpolymorphisms *FSHR*–29G/A and*FSHB*–211G/T
- In women, the*FSHR* Thr307Ala/Asn680Serpolymorphisms show consistent predictive value for estimating the most optimal rFSH dosage in COH, and these variants also exhibit a potential for the pharmacogenetic assessmentin PCOS patients
- Recently, the*FSHR*–29G/A polymorphism was shown to modulateto ovarian response to COH
- In men,pilot studieshave demonstrated the *FSHB*–211 TT-homozygotes with genetically determined low FSH aspotentially the best responders to rFSH treatment, and the response may also be modulated by *FSHR*polymorphisms

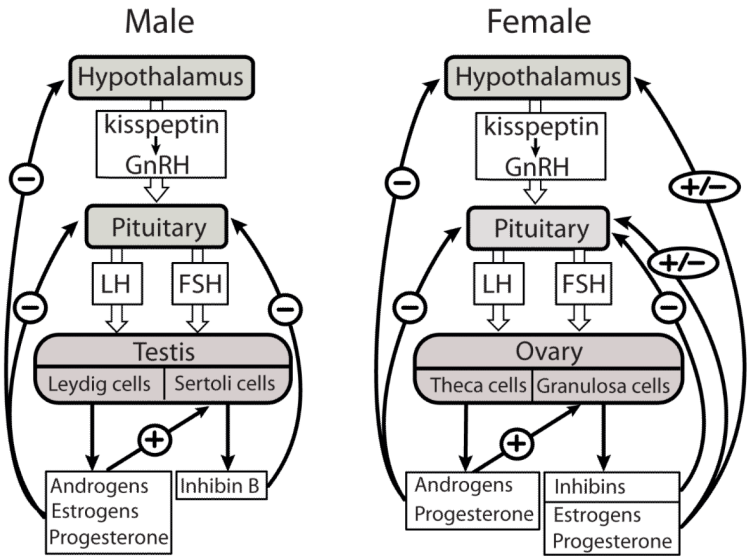

Figure 1.

Schematic feedback control of the human hypothalamic-pituitary-gonadal (HPG) axis. In males and females, kisspeptin-triggeredpulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of pituitary gonadotrophins (FSH and LH). FSH binds to its receptors located in testicular Sertoli and ovarian granulosa cells, and stimulates the secretion of inhibins that suppress FSH production from the pituitary. LH interacts with receptors on testicular Leydig cells and ovarian theca and granulosa cells, thereby stimulating the production of steroid hormones that stimulate their target cells in the reproductive tract.Steroid hormones (androgens, estrogens, progesterone) produced by ovaries and testesexert theirnegative (males) and negativeand positive (females)endocrine feedback to hypothalamic-pituitary levelby regulating thesynthesis and secretion of kisspeptin, GnRH and gonadotrophins.

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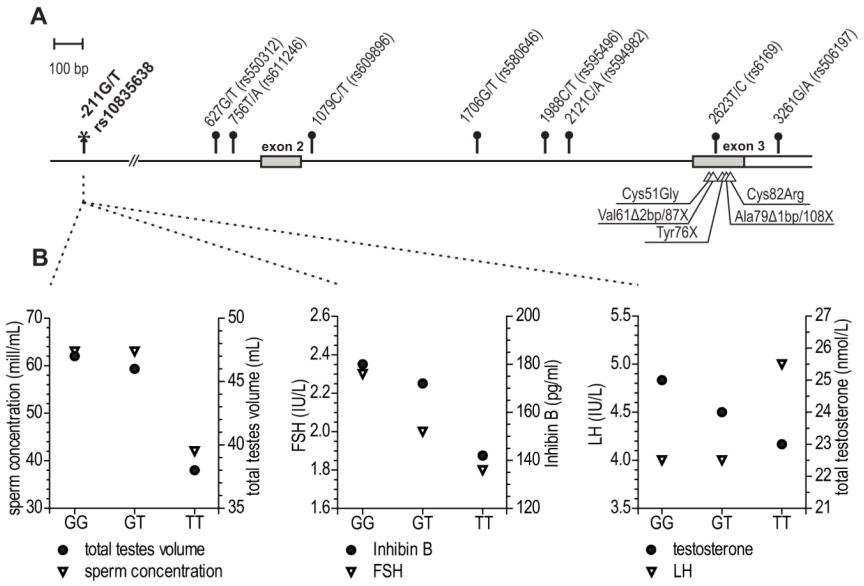

Figure 2.

(A) Genetic variation in the *FSHB* gene**;(B)** Phenotypic effects of the carrier status of alternative genotypes of *FSHB*promoter polymorphism –211G/T (rs10835638) on male reproductive parameters

(A) *FSHB*transcribedregions are indicated by boxes and translated sequencesaredenoted by *grey* areas. Common polymorphisms (minor allele frequency >10%) that form two major gene haplotypes (96.6% of analysed samples[17]) are shown as circle-headed bars and their positionsare denoted relative to the *FSHB* transcription start-site. The *FSHB*–211G/T promoter SNP is indicated by an asterisk. *FSHB* mutations identified in infertile patientsare shown by triangles and their localization in the mature FSH beta peptide is indicated.

(B) Effect of the *FSHB* gene promoter polymorphism –211G/T (rs10835638) on male hormonal and testicular parameters: total testis volume and sperm concentration (*left panel*), serum FSH and Inhibin B levels (*middle panel*), serum LH and total testosterone levels (*right panel*). Individuals are subgrouped according to their *FSHB* promoter position –211G/T genotype. Median values of reproductive parameters are presented based on Grigorova *et al.*[20**].

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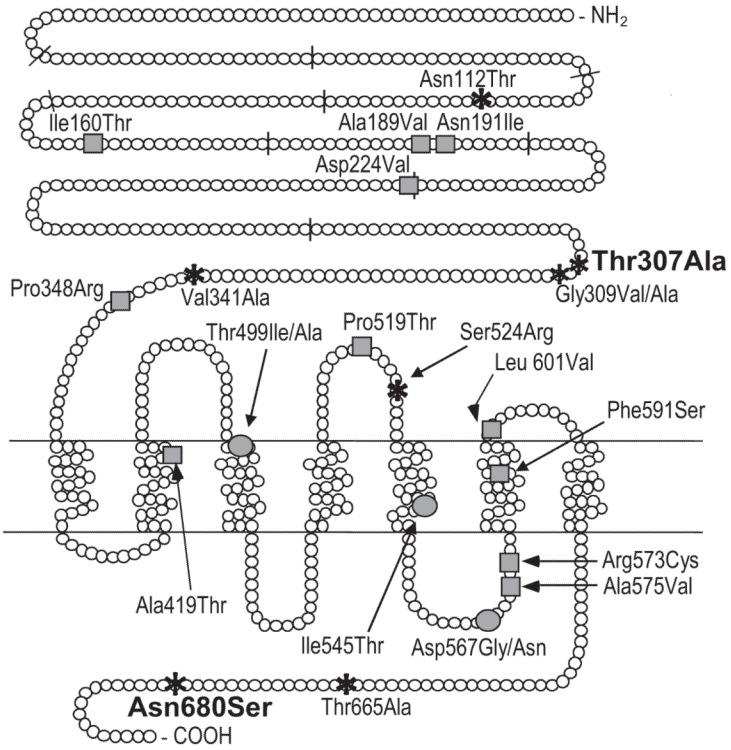

Figure 3.

The distribution of currently known functional polymorphisms, and activating and inactivating mutations across the human *FSHR* gene. The *FSHR* exon boundaries are marked with *short bars* striking through the protein sequence. *Greycircles* depict the activating, *greysquares* inactivating mutations, and the *asterisks* the polymorphisms. The two polymorphisms Thr307Ala and Asn680Ser with currently known pharmacogenetic significance and exhibiting linkage disequilibrium in most populations are marked in bold. An additionalpolymorphism that has been indicated to have pharmacogenetic potential is *FSHR*–29G/A located in 5′-untranslated region and thus, not presented in this figure.