REVIEW ARTICLE

Elucidating the Relationship between Single-nucleotide Polymorphisms and Impaired Fertility

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Abstract

Infertility is a prevalent health issue which affects ~15–20% of couples worldwide. Almost one-half of idiopathic infertility cases have been accepted to be caused by genetic basis, yet the basic causes are obscure. The reason for the present review is to comprehend and acquire information on the current status of examination on the genetics of females and its relationship with infertility.

This article reviews the effects of single-nucleotide polymorphisms (SNPs) present in follicle-stimulating hormone receptor (FSHR), luteinizing hormone/choriogonadotropin receptor (LHCGR), luteinizing hormone subunit beta (LHβ), anti-Mullerian hormone receptor (AMHR), and estrogen receptor (ESR) on female infertility. To investigate the strength of the relationship between SNPs and infertility, 74 articles were studied from multiple sources such as PubMed, Medline, and Google Scholar. Further more, a conclusion can be drawn that SNPs do have an impact on infertility irrespective of ethnicity and more research needs to be done in this area to understand the correlation of polymorphisms and infertility in order to benefit the population affected by it.

Keywords: Infertility, *In vitro* fertilization, Single-nucleotide polymorphism.

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Introduction

Infertility is the inability to conceive after 12 months of consistent unprotected sexual intercourse which can be treated using assisted reproductive technique (ART), *in vitro* fertilization (IVF) being the most common one in which oocytes are gathered after controlled ovarian stimulation (COS) with gonadotropins and then embryos are formed *in vitro* and transferred again inside the female. There are numerous predictive markers of COS outcome including genetic variability. Nearly, 19 million single-nucleotide polymorphisms (SNPs) have been detected in human genome,[1] that is, single-base changes where one nucleotide is substituted by another nucleotide. There are various studies that have shown correlation between polymorphism and infertility which have been reviewed in this paper.[2]

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Materials and Methods

This narrative review was done by analyzing review papers published related to the subject from 1981 to 2022. Articles were taken from various electronic scientific bases, such as PubMed, Medline, and Google Scholar and a summary was drawn based on various ethnicities and the effect of SNPs on fertility. The search included keywords, such as SNPs, luteinizing hormone (LH), follicle-stimulating hormone (FSH), infertility, subfertility, and polymorphisms.

Results and Discussions

Follicle-stimulating Hormone Receptor (FSHR) Polymorphisms

Follicle-stimulating hormone synthesis is regulated by different steroids and proteins of hypothalamic-pituitary gonadal axis (HPG). FSH plays a key part in follicular growth and ovarian steroidogenesis. The National Centre for Biotechnology Information (NCBI) states that nearly, 1900 SNPs are there in FSHR gene, and nearly eight polymorphisms are listed in the coding region but the most frequently observed polymorphism in FSHR is rs6166, also known as Asn680Ser (N680S); rs6165 also known as Ala 307 Thr (T307A) and rs1394205 (–29G > A) (Table 1).

Rs6166 in the FSHR gene is situated in the intracellular part of the receptor and can affect the glycosylation status of intracellular part which in turn causes alteration in the downstream signaling response and receptor activity.[3,4] Loutradis et al. in their study showed that females having Asn/Ser genotype have a higher number of follicles and oocytes in comparison to females having Ser/Ser and Asn/Asn genotype, and females having Ser/Ser genotype have more probability of having hyperresponse in

Table 1: Polymorphisms in FSHR gene and its location

Gene	*refSNP*	*Chromosome*	*DNA nucleotide*	*Protein*
FSHR	rs6166	2	919 G>A	N680S
FSHR	rs6165	2	2039 G>A	T307A
FSHR	rs1394205	2	29 G>A	–

comparison to Asn/Asn genotype[5] whereas Elli Anagnostou stated that Ser allele females had higher number of follicles as compared with other females.[6]

Additionally, in men too, conflicting results have been observed with polymorphism N680S on their reproductive functions. Common frequency of the FSHR N680S was observed in fertile controls and infertile men by a few articles[7–10] as well as in a study by Ahda, it was noted that S680 was more occasional in men who were infertile than in controls, and N680 was more seen in controls than in patients.[11,12]

A significant increase in A307T (rs6165) polymorphism has been noted by Sudo et al. in polycystic ovary syndrome (PCOS) women in Japan; on the other side, there are articles which state that there is no relation between FSH polymorphism with PCOS and chronic anovulation.[13] It has also been noted that females with A307A genotype were linked with less dose of exogeneous FSH before and even at the time of hCG stimulation.[14,15] Laven JSE in his review article summarized the effect of rs6165 polymorphism based on ethnicity. Further, it stated that European, Turkish, and Caucasian women showed no effect on PCOS or various phenotypical features of syndrome.[16]

Both SNPs rs6166 and rs6165 are located in exon 10 causing amino acid exchange; rs6166 exchanges asparagine for serine leading to a phosphorylation site whereas rs6165 replaces threonine (T), that is, polar to a nonpolar alanine (A).

Alain Wunsch et al. state that the newly identified SNPs like –29, –37, –114, –123, and –138 did not impact clinical parameters but influenced the expression of the FSHR by having a switch in transcription factor binding sites.[17] A study was done by Tanni Borgbo to investigate the follicle fluid (FF) concentrations of various hormones in relation to the different genotypes of FSHR –29G > A.[18] The study states that the testosterone levels of the A/A genotype were significantly high in comparison to other two genotypes and reduced rostenedione levels were seen for the G/G genotype (Table 2).

In rs6166, females having Ser/Ser allele are often linked with high number of follicles, mature oocytes, and require higher FSH doses, whereas females with Asn/Asn genotype require less FSH doses and is also linked with poor ovarian reserve (POR), whereas rs6165 females with Ala/Ala genotype are associated with low doses of FSH and linked with PCOS.

Table 2: Effect of single-nucleotide polymorphisms in FSHR gene on various ethnicities

SNP	*Ref*	*Country*	*No. of samples*	*Association*	*Reference*
FSHR	rs6166	Greece	32	Women having Ser allele have high no. of follicles, retrieved oocytes and mature oocytes compared with other females	Anagnostou E et al. (2021)[6]
FSHR	rs6166	South Korea	263	Clinical pregnancy rates were higher in Asn/Asn in comparison to other genotypes	Jun JK et al. 2006)[19]
FSHR	rs6166	Germany	161	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	Perez Mayorga M et al. (2000)[20]
FSHR	rs6166	USA	58	Women with Ser/Ser genotype were significantly associated with increased exogenous FSH and decreased estradiol levels on the day of hCG administration	Sudo S et al. (2002)[13]
FSHR	rs6166	Germany	93	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	Behre H et al. (2002)[21]
FSHR	rs6166	Germany	64	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	Greb RR et al. (2005)[22]
FSHR	rs6166	Greece	79	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	Loutradis D et al. (2006)[5]
FSHR	rs6166	Belgium	37	Ser680 allele present more risk of giving iatrogenic ovarian hyperstimulation syndrome (OHSS) when compared with Asn680 allele, but the Asn680 allele was significantly associated with severity of iatrogenic OHSS	Daelemans C et al. (2004)[23]
FSHR	rs6166	Germany	60	The study showed an association between rs6166 and poor ovarian reserve (POR)	Sindiani AM et al. (2021)[24]
FSHR	rs6166			The review paper stated that females with homozygous N680S S genotype experience 30–40 cycles less compared with N680SS during their reproductive span and experience lower risk of pregnancy risks	Simoni M and Casarin L (2014)[25]
FSHR	rs6166	Spain	308	Rs6166 was negatively associated with recurrent pregnancy loss	Sater MS et al. (2018)[26]
FSHR	rs6166	China	1,250	Basal FSH level and dose of exogeneous FSH were higher in GG (Ser/Ser) poor responders	Hermann and Heckert (2007)[27]
FSHR	rs6166	India	150	A higher frequency of homozygote G (Ser/Ser) mutant, that is, in infertile patients which means polymorphism in rs6166 from asp to ser have a negative impact on fertility of females	Ganesh V et al. (2018)[28]

(Contd...)

Table 2: *(Contd...)*

SNP	*Ref*	*Country*	*No. of samples*	*Association*	*Reference*
FSHR	rs6166	European	148	Normogonadotropic anovulatory infertile patients have a different FSH receptor genotype than do normo-ovulatory controls. Although this characteristic is associated with increased baseline FSH serum levels, altered ovarian sensitivity to exogenous FSH during ovulation induction could not be established	Laven JS et al. (2003)[29]
FSHR	rs6166	European	193	The frequency distribution of the 680-polymorphism was 26% (Asn/Asn), 50% (Asn/Ser) and 24% (Ser/Ser). Significantly more patients with Ser/Ser-polymorphism were resistant to CC (28%) compared with Asn/Ser (14%) and Asn/Asn group (15%), with an odds ratio for ovulation of 0.44 (95% CI, 0.21–0.97)	Overbeek A et al. (2009)[30]
FSHR	Rs6165	India	50	Women with Ala307Ala genotype were significantly associated with lower dose of exogenous FSH, higher estradiol levels before and on the day of hCG stimulation. 85% of the women with Ala/Ala genotype developed OHSS	Achrekar SK et al. (2009)[31]
		Iran	198	FSHR rs6165 showed a strong association with ovarian response to ART ($p < 0.05$)	Kaviani M et al. (2017)[32]
		South Korea	377	Findings of this study suggest a significant association between FSHR gene Thr307Ala or Asn680Ser coding sequence change and PCOS. The variants homozygote genotype results in a higher risk of PCOS	Kim JJ et al. (2017)[33]
			677	More oocytes were retrieved from FSHR (rs6165) Ala/Ala homozygotes than from Thr/Thr homozygotes and Ala/Thr heterozygotes	Alviggi C et al. (2018)[34]
FSHR	Rs1394205	India	50	In India females with AA (Ala/Ala) require low dose of FSH for COS and are at higher risk of OHSS	Achrekar SK et al. (2009)[31]
		Iran	30	A/A (Ala/Ala) genotype at position –29 is associated with POR to FSH so that subjects with A/A genotype at the –29 position may require higher doses of exogenous FSH for ovulation induction during IVF process	Bonyadi K et al. (2017)[35]

Table 3: Polymorphisms in LHβ, LHCGR gene and its location

Gene	*refSNP*	*Chromosome*	*DNA nucleotide*	*Protein*
LHβ	rs1800447	19	82T>C	Trp28Arg
LHβ	rs34349826	19	104T>C	Ile35Th
LHβ	rs1056917	19	1502 G>A	Gly1502Ala
LHCGR	rs4539842	2	An insertion of two amino acids [leucine (L) and glutamine (Q)] in the signal peptide of the LHCGR	18insLQ
LHCGR	rs2293275	2	935G>A	Ser312Asn
LHCGR	rs12470652	2	827A>G	Asn 291Ser

LH Polymorphisms

Luteinizing hormone is a hetero-dimeric glycoprotein and is secreted by the anterior pituitary gland. The beta-subunit has 120 amino acids. The receptor comprises of enormous ectodomain that ties the hormone having 10 exons and tandom repeats of leucine-rich recurrent designs framing a concave surface of short beta-turns with cysteine-rich domain on either sides.[36] In LH receptor, ~ 282 polymorphisms have been recognized and the majority of these SNPs are situated in large introns. The LH receptor (LHCGR) is a G-protein coupled receptor that is expressed on the cells of the ovary, as well as on the cells of granulosa and cumulus.[37,38] The LH receptor gene is located on chromosome 2p21. Some common polymorphisms in LHR are rs12470652, also known as Asn 291Ser (291NS) and rs2293275, also known as Ser312Asn (312 SN) and rs4539842 (insLQ). These three polymorphisms are linked with breast cancer, OHSS and PCOS (Table 3).

Within a cluster of seven highly homologous sequences is the LHß gene subunit situated, that is, LHß in chromosome 19q13.3. LHß changes hamper the construction and capability of LH by one or the other enacting or inactivating its bioactivity. This change might prompt anovulation, amenorrhea, and PCOS.[20]

Most studied LHβ polymorphisms are rs34349826, also known as Ile35Th (I35T); rs1056917, also known as Gly102Ala (G102A); and rs1800447, also known as Trp28Arg (W28R), whereas the most common LHCGR polymorphisms are rs4539842, also known as 18 insLQ; rs2293275, also known as Ser312Asn (S312N); and rs12470652, also known as Asn291Ser (N291S) (Table 4).

Table 4: The effect of single-nucleotide polymorphisms present in LHβ, LHCGR gene on various ethnicities

SNP	*Ref*	*Country*	*No. of samples*	*Association*	*Reference*
LHCGR	rs12470652	Iraq	100	The study showed that the prevalence of LHR (rs12470652) polymorphisms had no significant difference in the infertile patients' groups when compared with the fertile control group.	Mahmoud STM et al. (2020)[39]
LHCGR	rs4539842	Brazil	67	Prevalence of rs4539842 was shown to be higher in patients suffering from endometriosis and infertile compared with fertile patients.	Cunha Filho et al. (2015)[40]
LHβ	rs1056917 rs149579838	Turkey	69	The study stated that females having GG genotype for rs149579838 and AG genotype for rs1056917 were under the high risk of primary infertility.	Yılmaz E et al. (2020)[41]
LHβ	rs1056917	China	315	Study stated that LH G1052A polymorphism might influence PCOS susceptibility and phenotypes.	Liu N et al. (2012)[42]
LHβ	rs1056917	India	50	LHβ TC and CC genotypes were significantly associated with PCOS risk.	Deswal R et al. (2019)[43]
LHCGR	rs2293275	India	193	A connection was found between LHCGR polymorphism rs2293275 and the necessity of r-hLH in COS protocols and their pregnancy result.	GA R et al. (2021)[44]
LHCGR	rs2293275	Sweden	384	The paper stated that ladies homozygous for S allele in both the polymorphisms, i.e., N312S and N680S had 4-crease higher possibilities of pregnancy.	Lindgren I et al. (2016)[45]
LHCGR	rs4539842 rs2293275			rs4539842 is linked with PCOS but AA genotype at rs2293275 in LHCGR is connected with higher dangers of PCOS in Caucasians female.	Zou J et al. (2018)[46]
LHβ	rs1056917	Egypt		LH G1502A polymorphism in Egyptian females is linked with PCOS and had a huge positive connection with higher risk of PCOS.	El-Shal AS et al. (2016)[47]
LHβ	rs1800447/ rs34349826	Brazil	130	A modulatory effect of LHB polymorphisms on hyper-androgenemia phenotype of PCOS was seen.	Batista MCP et al. (2014)[48]
LHCR	rs4539842 and rs2293275	Iran	100	rs4539842 and rs2293275 were related with the outcome of IVF in Iranian infertile women.	Javadi-Arjmand M et al. (2019)[49]

Table 5: Polymorphisms in AMHR gene and its location

Gene	*refSNP*	*Chromosome*	*DNA nucleotide*
AMH	rs10407022	19	146 T > G
AMHR	rs2002555	12	–482 A > G

Both the receptor as well as the subunit of LH have shown to be linked with polymorphisms related to infertility. Polymorphisms in receptors are linked with endometriosis and polymorphisms in beta-subunit are associated with PCOS.

AMH Polymorphisms

Anti-Mullerian hormone (AMH), otherwise called Mullerian inhibiting substance, is a part of the transforming growth factor-beta (TGF-β) superfamily. Anti-Mullerian hormone is produced in females by granulosa cells in the ovary which encompasses preantral and little antral follicles.[50] Anti-Mullerian hormone decreases FSH sensitivity. A review by Iliodromiti S revealed that AMH is a decent mark of ovarian reaction in ladies going through COH for IVF.[51] Anti-Mullerian hormone is unequivocally connected with ovarian reaction and oocyte yield that is a known determinant of pregnancy, results in IVF cycles (Table 5).[52,53]

The molecular function or signaling transduction of AMH is dependent on the AMH receptors. There are two types of AMH receptors, out of which the AMH type II receptor (AMHRII) is profoundly specific, while the characteristics and capability of the AMH type I receptor are not known.

Most dissected AMH polymorphisms are AMH 146 T > G (rs10407022) and AMHR II –482 A> G. Kevenaar et al. broke down the genetic variety in AMH/AMHRII and showed that the AMH 146 T > G and the AMHR II –482 A > G SNPs are associated with an increase in follicular stage estradiol levels in normo-ovulatory ladies.[54] Another imminent review expressed that G/G genotypes of the AMH 146 T > G polymorphism basal FSH levels were higher in those with essentially two past IVF failure.[55] Peluso et al. have shown that both the AMH and AMHRII polymorphisms were related to the count of embryos formed; however, no affiliation was found with pregnancy rates in 186 infertile females in Brazil (Table 6).[56]

The above studies show a correlation between AMH polymorphisms and infertility. Anti- Mullerian hormone polymorphism has been linked with the age of menopause, PCOS, as well as being a reason for poor responders in stimulated cycles. The above studies show a correlation between AMH polymorphisms and infertility. AMH polymorphism has been linked with the age of menopause, PCOS as well as being a reason for poor responders in stimulated cycles.

Table 6: The effect of single-nucleotide polymorphisms present in AMHR gene on various ethnicities

SNP	*Ref*	*Country*	*No. of samples*	*Association*	*Reference*
AMH	rs10407022	China	635	The AMH 146 T >G G/G genotype in women was linked with a lower rate of clinical pregnancy.	Wu CH et al. (2019)[53]
AMHRII	rs2002555	Greece	151	Females with a wild type for the AMHRII polymorphism had a greater number of follicles.	Karagiorga I et al. ((2015)[55]
AMHRII	rs2002555	Greece	300	AMHRII −482 A > G was linked with the ovarian response to gonadotropin stimulation, but no association was seen regarding clinical. Pregnancy rates.	Lazaros L et al. (2016)[53]
AMH AMHRII	rs10407022 rs2002555	UK	603	No notable links were found between the AMH 146 T > G and AMHRII −482 A > G with ovarian response regarding. No. of oocytes and live birth rates.	Cerra C et al. (2016)[57]
AMHRII	rs2002555	Japan	635	This polymorphism was linked with follicular development and poor responders in IVF cycles.	Yoshida Y et al. (2014)[58]
AMH	rs10406324	Netherlands	655	Polymorphism rs10406324 was linked with serum AMH levels in all PCOS.	Moolhuijsen LME et al. (2022)[59]
AMH	rs10417628	UK	7,049	Genetic correlation analyses indicated a strong positive correlation among SNPs for AMH levels and for age at menopause.	Verdiesen RMG et al. (2022)[60]

Table 7: Polymorphisms in ESR gene and its location

Gene	*refSNP*	*Chromosome*	*DNA nucleotide*
ESR	rs2234693	6	−397T>C
ESR	rs9340799	6	−351A>G

Estrogen Receptors (ESRs) Polymorphisms

Estrogen is an endocrine hormone and is responsible for the overwhelming majority jobs in females, such as ovulation, implantation, pregnancy upkeep, and lactation.[61,62] Estrogen flagging is interceded by restricting to ligand-dependent transcription factors, that is, ESRs (Table 7).

ERa and ERb are two types of ESRs coded by ESR1 and ESR2 genes. The 140 kb ESR1 is present on chromosome 6q and has eight exons with its two polymorphisms PvuII (T/C) and XbaI (A/G) present in its intron. These two SNPs have been linked with spontaneous abortions and infertility (Table 8).[63]

The above studies show that ESR mediates estrogen effects on follicular growth, oocyte maturation, and implantation. PvuII and Xba1 polymorphisms are linked with endometriosis as well as RPL, and these polymorphisms need to be analyzed more for better ART results.

Summary

There are various factors affecting female fertility, and single-nucleotide polymorphism is suspected to be one such factor. A few studies have shown a link between various factors of infertility, such as PCOS, endometriosis, recurrent pregnancy loss, menstrual disorders, and lower clinical pregnancy rates with FSH, LH, AMH, and ESR polymorphisms,[59] whereas few studies reported no difference in control and sample size.[39,57]

Follicle-stimulating hormone stimulates follicular development, granulosa cells in females, and Sertoli cells function in males. Mutations and polymorphisms in its receptors or subunits can lead to infertility. Follicle-stimulating hormone receptor and FSHβ polymorphisms are highly linked with PCOS and endometriosis. Simoni's group stated that females with rs6165 and rs6166 are less sensitive to FSH and require more amount of FSH for ovarian hyperstimulation.[20] If proper understanding of FSH polymorphisms is carried out, it can help in defining the number of dosages of FSH, number of follicles, and time to conceive in such patients.

Luteinizing hormone subunit beta as well as LHCGR too has been linked with PCOS, endometriosis, and primary infertility in few studies while on the contrary, few articles do not support this theory. Disputable findings in various populations with respect to the impact of LHCGR polymorphisms on fertility and its IVF achievement require additional examination at a sub-atomic level and in different populations. Moreover, combined evaluations including LHCGR and FSHR polymorphisms must be done in various populations including the Indian population.

Anti-Mullerian hormones and estrogen also play an important role in female fertility and polymorphisms in their receptors and may lead to endometriosis and also affect a number of oocytes retrieved.

A rising number of research dynamically clarify how polymorphic variations of gonadotropins, and their receptor qualities affect the human reproductive function and health. Top-to-bottom investigation of polymorphisms connected with fertility might help in strengthening the downfall of fertility in the current society in which parenthood attempts are relegated in very less time.

Strengths and Limitations

A total of 74 studies have been added in the manuscript showing us the effect of these hormonal problems on different ethnicities; however, these studies are not enough to give a conclusion about the effect of polymorphisms and relationship with hormonal dosages, number of oocytes retrieved, mature oocytes, etc. and not many studies have been done on the Asian population.

Table 8: Effect of single-nucleotide polymorphisms present in ESR gene on various ethnicities

SNP	*Ref*	*Country*	*No. of samples*	*Association*	*Reference*
ESR1	rs9340799	Turkey	211	A significant correlation was observed in XbaI polymorphism and chances of having infertility.	Ayvaz OU et al. (2009)[64]
ESR1	rs9340799	India	114	Xba I heterozygote genotype had higher frequency in the controls when compared with the cases showing a possible protective effect.	Swaminathan M et al. (2016)[65]
ESR1	rs2234693 rs9340799	Taiwan	328	The study stated that XbaI G and PvuII-C alleles were related with higher chances of endometriosis.	Hsieh YY et al. (2007)[66]
ESR1	rs2234693		5,948	PvuII was associated with endometriosis and showed a positive correlation.	Zhao L et al. (2016)[67]
ESR1	rs9340799	China	214	Study stated that XbaI was linked with endometriosis.	Xie J et al. (2009)[68]
ESR1	rs2234693	Tunisia	444	The research confirmed a notable association of rs2234693 with an increased risk of RPL.	Bahia W et al. (2020)[69]
ESR1	rs2234693 rs9340799			The systemic review concluded that re2234693 and rs9340799 played a significant role in RPL.	Jalilvand A et al. (2022)[70]
ESR1	rs2234693 rs9340799	Iran	244	The study shows that polymorphisms in ESR1gene are not linked with an increased chance of RPL.	Mahdavipour M et al. (2014)[71]
ESR1	rs9340799	Brazil	213	The study states a link between rs9340799 polymorphism and endometriosis.	Paskulin DD et al. (2013)[72]
ESR1	rs2234693			The review study states that ESR1 (rs2234693) variant might play an important role in the potential of females' fertility based on ethnic backgrounds.	Asgari (2021)[73]

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