

Association of Follicle Stimulating Hormone Receptor Single Nucleotide Polymorphisms with Fertility in Greek men.

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OBJECTIVES

Although several epidemiological studies have been conducted, the impact of Follicle Stimulating Hormone Receptor (FSHR) polymorphisms on male infertility remains unclear. The aim of this study was to investigate the prevalence of specific FSHR Single Nucleotide Polymorphisms (SNPs) in the Greek population and associate the latter with the clinical phenotype.

METHODS

Our cross-sectional, single-center study prospectively enrolled 96 subjects. Men with idiopathic non-obstructive azoospermia (n=78) were compared with a control group with fertile men (n=18) for SNPs in FSHR in the promoter at position -29 (G-29A, rs1394205), in the coding region at position 566 (566 C/T, Ala189Val, rs121909658), position 919 (919A/G, Thr307Ala, rs6165), position 2039 (2039A/G, Asn680Ser, rs6166). The SNP in position 566 was assessed by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) and the other three SNPs' (-29, 919, 2039) with Single Strand Conformation Polymorphism (SSCP); All of them were validated with DNA sequence.

Graphs and tables

Association of hormonal and semen parameters with 680 and 566 SNPs.

	2039 SNP 2	2039 SNP 3	566 SNP 2
Testis (R)	0.039	0.008	0.585
Testis (L)	0.192	0.588	0.581
FSH	0.660	0.380	0.327
LH	0.479	0.363	0.456
Prolactin	0.869	0.379	0.374
T	0.455	0.517	0.674
Inhibin B	0.322	0.054	1.000
AMH	0.908	0.419	0.569
Semen volume	0.450	0.343	0.794
Sperm count	0.822	0.149	0.839
Sperm motility	0.900	0.707	0.119
Sperm morphology	0.960	0.316	0.227

2039 SNP 1 vs. 2039 SNP 2, 3, in P value: 0.550; 566 SNP 1 vs. 566 SNP 2, in P value: 0.481; 0.106

RESULTS

No SNPs were detected in positions -29 and 919. The heterozygous SNP (AG) at position 2039 (680) was associated with different size of the right testis ($p = 0.080$). There was no association between the 566 SNPs polymorphism and hormonal or semen parameters. The combination SNP 2039 AA with 566 CT revealed significant association with FSH and LH concentrations.

2039 and 566 SNP distribution.

	Fertile	Infertile
AA ¹	5 (28%)	21 (27%)
AG ¹	4 (22%)	39 (50%)
GG ¹	9 (50%)	18 (23%)
566C ²	4 (22%)	19 (24%)

¹ Chi-square, AA vs. AG and GG, $p = 0.14$ (78%) squared = 59 (56%) vs. 566T, $p = 0.848$.

CONCLUSIONS

The prevalence of 566CT polymorphism of the FSHR gene was high in the Greek population, yet no association was found with male infertility. The present study, showed no association between FSHR SNPs and male infertility, in the Greek population.

In conclusion, our study indicates that despite the ethnic differences in FSHR, SNPs do not appear to play any specific role in male infertility. Further studies with larger populations may be required to confirm our findings in a more definitive fashion.

References

- Hadda Y, Gromoll J, Wunsch A, et al. Follicle-stimulating hormone receptor gene haplotype distribution in normozoospermic and azoospermic men. *J Androl* 2005; 26:494-499.
- Ghirelli-Filho M, Peluso C, Christofolini DM, et al. Variants in follicle-stimulating hormone receptor gene in infertile Brazilian men and the correlation to FSH serum levels and sperm count. *Reprod Sci*. 2012; 19(7):733-9.
- Grigorova M, Punab M, Poolamets O, et al. Study in 1790 Baltic men: FSHR Asn680Ser polymorphism affects total testes volume. *Andrology*. 2013 ;1(2):293-300.
- Lend AK, Belousova A, Haller-Kikkatalo K, et al. Follicle-stimulating hormone receptor gene haplotypes and male infertility in estonian population and meta-analysis. *Syst Biol Reprod Med*. 2010;56(1):84-90.
- Safarinejad MR, Shafiei N, Safarinejad S. Evaluating the role of the FSH receptor gene Thr307-Ala and Asn680-Ser polymorphisms in male infertility and their association with semen quality and reproductive hormones. *BJU Int*. 2011 ;108(2 Pt 2):E117-25.
- Wu XQ, Xu SM, Wang YQ, et al. FSHR gene Thr307Ala and Asn680Ser polymorphisms in infertile men: an association study in North China and meta-analysis. *Genet Mol Res*. 2015 25;14(2):5592-601