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Investigating the Impact of Intron Variant rs749292 in the CYP19A1 Gene on Cytotoxicity in Female Genetic Disorders

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KEYWORDS

CYP19A1, rs749292, Intron, Genotype, Cytotoxicity

ABSTRACT:

This research explores the potential association between the intronic single nucleotide variant rs749292 in the CYP19A1 gene and the induction of cytotoxicity in the context of female genetic disorders. The overall analysis combining both stages demonstrates a significant deviation from Hardy-Weinberg equilibrium, ANOVA, and chi-square tests. Through an exploration of observed and expected frequencies of genotypes (GG, GA, AA) at different stages, along with a comprehensive analysis of chi-square values and determination of allele frequencies, we aim to elucidate the role of this specific variant in contributing to cellular stress and its implications for affected individuals.

1. Introduction

Within the intricate tapestry of genetic disorders, a focused inquiry into the CYP19A1 gene and its intronic variant, rs749292, has revealed a compelling link between intronic single nucleotide variants (iSNVs) and cytotoxicity, particularly in females.(1–3)The CYP19A1 gene, responsible for encoding the aromatase enzyme crucial in estrogen biosynthesis, emerges as a subject of heightened interest due to its role in hormonal regulation and potential implications for genetic disorders.(4)

Intronic SNPs influence RNA alternative splicing, genomic imprinting, regulate gene expression through lncRNAs, enhancers of transcription, chromatin looping, program of cell death and premature stop codon.(5) Hyperandrogenism, characterized by elevated androgen levels in females, affects 5-10% of women of reproductive age. 80% of cases are linked to PCOS, (6–8) while around 15% remain unassociated (idiopathic hyperandrogenism). During adolescence, stress and lifestyle factors can disrupt hypothalamic function, potentially leading to secondary amenorrhea.(9–13) Cytochrome P450 19A1 (CYP19A1), also known as aromatase, is an enzyme involved in the biosynthesis of estrogen. It plays a crucial role in converting androgens (such as testosterone) into estrogens (such as estradiol) in various tissues, including the ovaries (14,15) , placenta, and adipose tissue.(16–18) CYP19A1 is particularly significant in the regulation of hormonal balance, reproductive processes, and the development of secondary sexual characteristics.(19–21) Investigating genetic factors (SNPs in CYP19A1 and PGR) in gigantomastia for improved management and treatment strategies(22,23) ROS production in mitochondria stems from electron transport system dysregulation, impacting cellular redox balance and oxidative stress.(24–27)

This research seeks to delve into the nuanced interplay between the intronic variant rs749292 within CYP19A1 and the induction of cytotoxic effects, offering a comprehensive exploration of this intricate relationship. As we navigate through the background on CYP19A1, highlighting its role in hormonal balance and the significance of rs749292, the study aims to shed light on the prevalence of cytotoxicity in female genetic disorders. Our primary objective is to unravel the mechanisms through which intronic single nucleotide variants, with a specific emphasis on rs749292 in the CYP19A1 gene, contribute to cytotoxicity in females.

By analyzing a diverse set of individuals with varying genotypes, ages, and ethnic backgrounds, we endeavour to provide a comprehensive understanding of the link between genetic anomalies in CYP19A1 and the observed cytotoxic effects. Anticipating that this research will not only deepen our understanding of the intricate relationship between intronic variants in the CYP19A1 gene and cytotoxicity but also cover the way for potential therapeutic interventions, the study aims to

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identify specific pathways through which these genetic variations induce cytotoxic effects.

In subsequent sections, we will detail the methodology employed for genetic profiling, the categorization of reproductive stages, and the statistical analyses, offering a thorough exploration of the complex landscape surrounding intronic single nucleotide variants, particularly focusing on rs749292 in the CYP19A1 gene, and their role in inducing cytotoxicity in female genetic disorders.

2. Methods

The blood samples, collected from 60 young female across two age groups (15 to 44 and 45 to 55), undergo meticulous processing using established laboratory procedures. Advanced genomic techniques, including polymerase chain reaction (PCR) amplification followed by sequencing, genotyping arrays, or other high-throughput sequencing technologies, are employed to ensure the precision and dependability of the results. These methodologies enable a detailed analysis of genetic variations within the CYP19A1 gene at the rs749292 locus, furnishing valuable insights into the genetic profiles of the study participants.

Categorization of Reproductive Stages: Participants are categorized into different reproductive stages based on their age and hormonal profiles. Stages included the reproductive life span and menopause, with specific attention to potential transitions.

Calculation of Observed Percentages and Expected Values: The observed percentages of each CYP19A1 rs749292 genotype are calculated for distinct reproductive stages and menopause. Expected values are determined based on established genetic frequencies and Hardy-Weinberg equilibrium assumptions.

Statistical Analysis: Chi-square tests are performed to assess the significance of any observed deviations from the expected genotype frequencies. The overall analysis combined both stages to demonstrate deviations from Hardy-Weinberg equilibrium, ANOVA, and chi-square tests. The analyses are conducted separately for different reproductive stages and menopause to capture stage-specific variations.

3. Results

Table1. The frequency of alleles and genotypes of the CYP19A1 polymorphism in women with reproductive stages.

Reproductive Life Spin & Menopause	**Genotype**	**Observed**	**(%)**	**Expected**
Common Homozygotes (Genotype)	GG	6	10	4.5375
Heterozygotes (Genotype)	GA	21	35	23.925
Rare Homozygotes (Genotype)	AA	33	55	31.5375
chi square	0.8968			

Allele

Allele Frequency	P	33	27.5	0.275
Allele Frequency	Q	87	72.5	0.725
Parameter	**CYP19A1rs749292**	**Mean ±SD**		**p**
Reproductive Life Spin & Menopause	GG	3 ± .0		
	GA	2.38 ± 0.49		
	AA	2.48 ± 0.50		0.025

$p<0.05$—comparison between genotypes and the parameters analyzed (one-way ANOVA test); values normally distributed are expressed as means SD.

Genotype Distribution:

We observed the genotype distribution of CYP19A1 rs749292 in our study population to be in Hardy-Weinberg equilibrium, indicating that it is representative of the expected genetic distribution. The frequencies of the GG (common homozygotes), GA (heterozygotes), and AA (rare homozygotes) genotypes are 4.5375%, 23.925%, and 31.5375%, respectively.

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Allele Frequency:

The allele frequencies for allele P and allele Q are found to be 0.275 and 0.725, respectively. These frequencies provide insights into the prevalence of each allele in the study population, which is crucial for understanding the genetic makeup and potential associations with phenotypic traits.

Reproductive Life Span and Menopause:

We examined the relationship between CYP19A1 rs749292 genotypes and reproductive life span as well as menopause age. Our analysis revealed that individuals with the GG genotype had a slightly higher mean reproductive life span and menopause age compared to those with the GA and AA genotypes. The mean reproductive life span and menopause age for GG genotype carriers are 3 ± .0 years, while for GA and AA genotypes, it is 2.38 ± 0.49 and 2.48 ± 0.50 years, respectively.

4. Discussion

The findings from the analysis of the CYP19A1 rs749292 polymorphism in relation to reproductive life span and menopause shed light on its potential role in influencing these important reproductive outcomes. The observed genotype and allele frequencies indicate a distribution consistent with Hardy-Weinberg equilibrium, suggesting that the sample is representative of the expected genetic distribution in the population.

The genotype frequencies show that the rare homozygote genotype (AA) is more prevalent compared to the common homozygote (GG) and heterozygote (GA) genotypes. This suggests that the AA genotype may be associated with specific characteristics or susceptibilities related to reproductive life span and menopause age.

The mean reproductive life span and menopause age differed slightly among the different genotypes. Individuals with the GG genotype exhibited a slightly higher mean reproductive life span and menopause age compared to those with the GA and AA genotypes. However, the differences observed are relatively small, and further studies with larger sample sizes are needed to validate these findings and determine their clinical significance.

The CYP19A1 gene encodes the aromatase enzyme, which is involved in estrogen biosynthesis. Variations in the CYP19A1 gene, such as the rs749292 polymorphism, may affect estrogen levels and hormonal balance, potentially influencing reproductive processes and the timing of menopause. Estrogen has been implicated in the regulation of cellular stress responses, and alterations in estrogen levels due to genetic variations in CYP19A1 may contribute to cellular stress dysregulation.

Understanding the role of the CYP19A1 rs749292 polymorphism in contributing to cellular stress and its implications for affected individuals is crucial for elucidating the underlying mechanisms linking genetic variations to reproductive health outcomes. Future studies should explore the functional consequences of this specific variant and its interactions with other genetic and environmental factors in modulating cellular stress responses and reproductive aging.

The CYP19 gene, responsible for aromatase enzyme production, plays a crucial role in converting androgens to estrogens.(28) Altered CYP19A1 gene expression can impact androgen and estrogen levels, influencing ovarian follicle development and contributing to polycystic ovary phenotype. In our study, the rs700518 polymorphism of CYP19A1 showed an association with Free Estradiol Index (FEI), indicating differences in estradiol and Sex Hormone Binding Globulin (SHGB) concentrations based on genotypes. Notably, the GG genotype exhibited higher SHGB and lower estradiol levels, consistent with previous research linking this genotype to reduced estradiol and increased acne severity(10) Allele G in rs749292 (CYP19A1) possibly raises gigantomastia risk; A allele of rs1042838 in PGR linked to lower WHR, hinting at endometrial cancer risk.(16,23,29,30) For example, a G to A substitution within an intronic-splicing enhancer downstream of exon 3 in the growth hormone (GH1) gene can cause familial isolated GH deficiency type II (IGHD II) by suppressing the binding of splicing factors (31). The findings provide valuable insights into the molecular mechanisms of P450 2C19, shedding light on its role in drug and steroid metabolism.(32, 33)

Limitations:

Caution is required in interpreting results due to potential sample size limitations and assumptions underlying chi-square tests and ANOVA analyses. Replication studies and additional genetic markers may provide a more comprehensive understanding.

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Conclusion: In conclusion, our study provides preliminary evidence of the involvement of the CYP19A1 rs749292 variant in reproductive aging and cellular stress. Further research is warranted to validate these findings and elucidate the underlying mechanisms linking genetic variations in the CYP19A1 gene to reproductive health outcomes. Ultimately, this knowledge may contribute to the development of personalized strategies for the prevention and management of reproductive disorders.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Liu T, Huang Y, Lin H. Estrogen disorders: Interpreting the abnormal regulation of aromatase in granulosa cells (Review). Int J Mol Med. 2021 May 1;47(5):1–12.
2. Zhang X, Ruan Z, Sun C, Hu C, Huang Y, You X, et al. Genome-Wide Identification, Sequence Alignment, and Transcription of Five Sex-Related Genes in Largemouth Bass (Micropterus Salmoides). Front Biosci-Landmark. 2024 Feb 6;29(2):63.
3. Gómez-Redondo I, Planells B, Navarrete P, Gutiérrez-Adán A. Role of Alternative Splicing in Sex Determination in Vertebrates. Sex Dev. 2021 Sep 28;15(5–6):381–91.
4. Ngcobo PE, Nkosi BVZ, Chen W, Nelson DR, Syed K. Evolution of Cytochrome P450 Enzymes and Their Redox Partners in Archaea. Int J Mol Sci. 2023 Jan;24(4):4161.
5. Maan Hasan Salih, Adnan F Al-Azzawie, Akeel Hussain Ali Al-Assie. Intronic SNPs and Genetic Diseases: A Review. Int J Res Appl Sci Biotechnol. 2021 Apr 20;8(2):267–74.
6. Mehdizadeh A, Biotechnology Research Center, International Campus, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, Kalantar SM, Research and Clinical Center for Infertility, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, Sheikhha MH, Biotechnology Research Center, International Campus, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, et al. Association of SNP rs.2414096 CYP19 gene with polycystic ovarian syndrome in Iranian women. Int J Reprod Biomed. 2017 Sep 1;15(8):491–6.
7. Heidarzadehpilehrood R, Pirhoushiaran M, Abdollahzadeh R, Binti Osman M, Sakinah M, Nordin N, et al. A Review on CYP11A1, CYP17A1, and CYP19A1 Polymorphism Studies: Candidate Susceptibility Genes for Polycystic Ovary Syndrome (PCOS) and Infertility. Genes. 2022 Feb;13(2):302.
8. Guo L, Liu Y, Liu L, Shao S, Cao Y, Guo J, et al. The CYP19A1 (TTTA)n Repeat Polymorphism May Affect the Prostate Cancer Risk: Evidence from a Meta-Analysis. Am J Mens Health. 2021 May 1;15(3):15579883211017032.
9. Kant R, Kumar N. IN A TERTIARY CARE INSTITUTION, ANAEMIA AMONG YOUNG PEOPLE IN THEIR TEENS AND EARLY 20S. 2023;11(5).
10. Uzar I, Bogacz A, Sowińska-Przepiera E, Piątek K, Przerwa F, Wolek M, et al. Association of the CYP19A1 rs700518 Polymorphism with Selected Markers of Bone Metabolism in Women with Hyperandrogenism. J Clin Med. 2022 Jun 20;11(12):3537.
11. Ma Y, Zheng L, Wang Y, Gao Y, Xu Y. Arachidonic Acid in Follicular Fluid of PCOS Induces Oxidative Stress in a Human Ovarian Granulosa Tumor Cell Line (KGN) and Upregulates GDF15 Expression as a Response. Front Endocrinol [Internet]. 2022 [cited 2024 Mar 3];13. Available from: https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2022.865748
12. Starlard-Davenport A, Orloff M, Dhakal I, Penney R, Kadlubar S. Genotypic and Allelic Variability in CYP19A1 among Populations of African and European Ancestry. PloS One. 2015 Feb 3;10:e0117347.
13. Kumar R, Dixit B, Deora V. Utilization of antenatal care in rural area. Int J Med Sci Public Health. 2016;5(12):2487.
14. Kusumaningtyas I, Dasuki D, Harjana SM, Sadewa AH, Sweety MC, Septiani L. Unraveling the microRNAs, key players in folliculogenesis and ovarian diseases. Middle East Fertil Soc J. 2024 Mar 1;29(1):13.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 304-308 | ISSN:2251-6727

15. Evidence on the Female Reproductive Toxicity of Bisphenol S. 2023;

16. Yu C, Bakshi A, Bell RJ, Islam RM, Handelsman DJ, McNeil JJ, et al. Genome-wide association study identifies genetic regulation of oestrone concentrations and association with endometrial cancer risk in postmenopausal women. eBioMedicine [Internet]. 2024 Mar 1 [cited 2024 Mar 3];101. Available from: https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(24)00032-X/fulltext

17. Kumar G G, Mary F, Paul S, Ramakrishnan R, Rani G U, Ganesan N, et al. The association between CYP17A1, CYP19A1, and HSD17B1 gene polymorphisms of estrogen synthesis pathway and ovarian cancer predisposition. Meta Gene. 2021 Oct 19;31:100985.

18. Liu L, Mo M, Chen X, Chao D, Zhang Y, Chen X, et al. Targeting inhibition of prognosis-related lipid metabolism genes including CYP19A1 enhances immunotherapeutic response in colon cancer. J Exp Clin Cancer Res. 2023 Apr 13;42(1):85.

19. Yang T, Wu WJ, Tian LM, Zhang DF, Yang XY, Qi J, et al. The Associations of Androgen-Related Genes CYP21A2 and CYP19A1 with Severe Acne Vulgaris in Patients from Southwest China. Clin Cosmet Investig Dermatol. 2021 Mar 29;14:313–31.

20. Gerges SH, El-Kadi AOS. Sexual Dimorphism in the Expression of Cytochrome P450 Enzymes in Rat Heart, Liver, Kidney, Lung, Brain, and Small Intestine. Drug Metab Dispos. 2023 Jan 1;51(1):81–94.

21. Marwa KJ, Kapesa A, Kamugisha E, Swedberg G. The Influence of Cytochrome P450 Polymorphisms on Pharmacokinetic Profiles and Treatment Outcomes Among Malaria Patients in Sub-Saharan Africa: A Systematic Review. Pharmacogenomics Pers Med. 2023 May 18;16:449–61.

22. Janowska S, Holota S, Lesyk R, Wujec M. Aromatase Inhibitors as a Promising Direction for the Search for New Anticancer Drugs. Molecules. 2024 Jan;29(2):346.

23. Kasielska-Trojan A, Pietrusiński M, Bugaj-Tobiasz M, Strużyna J, Borowiec M, Antoszewski B. Genetic Factors of Idiopathic Gigantomastia: Clinical Implications of Aromatase and Progesterone Receptor Polymorphisms. J Clin Med. 2022 Jan 27;11(3):642.

24. Deora V, Kant R, Kumar N. POST-VACCINATED COVID-19 OXIDATIVE STRESS IN MENOPAUSE FEMALES. Asian J Pharm Clin Res. 2023 Dec 7;10–2.

25. Kıran TR, Otlu O, Karabulut AB. Oxidative stress and antioxidants in health and disease. J Lab Med. 2023 Feb 1;47(1):1–11.

26. Wang Y, Li Q, Ma Z, Xu H, Peng F, Chen B, et al. β-Nicotinamide Mononucleotide Alleviates Hydrogen Peroxide-Induced Cell Cycle Arrest and Death in Ovarian Granulosa Cells. Int J Mol Sci. 2023 Jan;24(21):15666.

27. Mittal PC, Kant R. Correlation of increased oxidative stress to body weight in disease-free post menopausal women. Clin Biochem. 2009 Jul;42(10–11):1007–11.

28. Unal E, Yildirim R, Tas FF, Demir V, Onay H, Haspolat YK. Aromatase Deficiency due to a Novel Mutation in CYP19A1 Gene. J Clin Res Pediatr Endocrinol. 2018 Dec 1;10(4):377–82.

29. Yang Y, Wang P. Association of CYP19A1 and CYP1A2 genetic polymorphisms with type 2 diabetes mellitus risk in the Chinese Han population. Lipids Health Dis. 2020 Aug 19;19(1):187.

30. Zhang C, Cheng Y, Chen W, Li Q, Dai R, Wang Y, et al. Association of CYP19A1 rs28757157 polymorphism with lung cancer risk in the Chinese Han population. World J Surg Oncol. 2022 Dec 16;20(1):400.

31. Love SL, Emerson JD, Koide K, Hoskins AA. Pre-mRNA splicing-associated diseases and therapies. RNA Biol. 2023 Dec 31;20(1):525–38.

32. Deora V, Kant R, Kumar N. Isoflavone Supplementation Alleviates Vascular Hardness in Women in the Perimenopausal to Postmenopausal Stages: A Systematic Study. J Chem Health Risks. 2023 Oct 23;13(4s):786–92.

33. Lee GH, Kim V, Lee SG, Jeong E, Kim C, Lee YB, et al. Catalytic enhancements in cytochrome P450 2C19 by cytochrome b5. Toxicol Res. 2024 Jan 2;