

Research Article



The Effects of two TP53 Polymorphisms on Its Expression and Folding and Association with the Pathogenesis of Polycystic Ovary Syndrome: in-silico analysis

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ABSTRACT

Objectives: Polycystic ovary syndrome (PCOS) is a multifactorial endocrinopathy characterized by various reproductive and metabolic abnormalities. The tumor suppressor p53 (*TP53*) plays a crucial role in cellular stress responses. Alterations in its structure or expression can influence *PCOS* pathogenesis. We aim to use in-silico analyses to predict the effects of the rs2287499 and rs1042522 genetic variants on the expression and structural stability of the *TP53* protein.

Methods: This study investigated the association of two genetic variants, rs2287499 and rs1042522, with the expression levels and folding stability of *TP53* protein through in-silico analyses. Utilizing bioinformatics tools (*VMD*, *WebLogo* and *PROMO*), we examined the potential impacts of these variants on *TP53* transcriptional activity, protein structure, and functional integrity.

Results: Our findings indicate that the rs2287499 variant significantly influences *TP53* expression level, while rs1042522 is associated with altered protein folding dynamics. These changes may disrupt *TP53* normal regulatory functions, contributing to *PCOS* etiology. Furthermore, our study establishes a framework for integrating genetic variants into the understanding of *TP53*-mediated mechanisms in *PCOS*, which could pave the way for developing targeted therapeutic strategies.

Conclusion: These results underscore the importance of genetic variants in *PCOS* hormonal and metabolic dysregulation.

Keywords: TP53, PCOS, Bioinformatics, rs1042522, rs2287499.

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Introduction

Polycystic ovarian syndrome (PCOS) is a hormonal disorder characterized by multiple symptoms, including irregular menstrual cycles, hirsutism, acne, and polycystic ovaries. PCOS mechanisms are not fully understood (1, 2). Its pathophysiology involves genetic, environmental, and hormonal factors (3). It has been shown that variations in certain genes may be associated with the development of this syndrome.

Tumor suppressor p53 (TP53), also known as tumor protein 53 or p53, is a gene that encodes a protein involved in cell cycle regulation, apoptosis, DNA repair, and other essential cellular processes (4, 5). While TP53 is recognized for its role in cancer biology, emerging research suggests it may also be involved in PCOS pathophysiology. TP53 may be involved in PCOS through cell cycle regulation, apoptosis and follicle development, insulin resistance, oxidative stress and inflammation. TP53 is a critical cell cycle regulator (6). Dysregulation of the cell cycle has been implicated in various reproductive disorders, including PCOS (7). In abnormal ovarian follicles, TP53 may influence ovarian follicle growth and maturation and affect oocyte quality (6). TP53 plays a critical role in apoptosis, especially in cellular stress and DNA damage (8). In the ovaries, dysfunction in apoptosis may contribute to follicle accumulation and the characteristic polycystic appearance. Apoptosis regulation could lead to non-functional follicles instead of normal ovulation (3). TP53 has also been linked to metabolic processes. Insulin resistance is a common feature of PCOS and associated with metabolic syndrome. TP53 may influence adipose tissue function and insulin signaling, impacting metabolic health in PCOS women (1). TP53 is also involved in oxidative stress response. Increased oxidative stress has been suggested as a factor in PCOS pathogenesis, particularly in relation to oocyte quality and follicular health (9). Chronic low-grade inflammation is often seen in PCOS, and some studies suggest that TP53 may play a role in inflammatory pathways (10) (11).

The TP53 gene is polymorphic. In DNA, single nucleotide polymorphisms (SNPs) occur when one nucleotide is replaced with another. Cancer risk, progression, or response to treatment have been reported to be associated with these changes of the TP53 protein (12). In this regard, prior studies have suggested an association between the rs2287499 and rs1042522 SNPs and various diseases (13, 14). Importantly, the association between these two variants of the P53 gene with PCOS has been previously reported (1, 15).

The in-silico approach provides a powerful tool for predicting how SNPs may influence the expression of genes and folding of proteins. In this study, we aim to study the impact of the variants of TP53 gene on its expression and folding. In particular, we in this study

investigated the effects of the rs2287499 and rs1042522 variants of the TP53 gene on the expression and folding. By analyzing these variants' potential impacts using computational modeling, we can gain insights into their functional consequences, which would be challenging to assess experimentally in a clinical setting.

Methods

Analysis of protein dynamics

We predicted whether allele substitution in the TP53 rs1042522 would change its visual molecular dynamics (VMD). PDB information for the TP53 protein with 393 amino acids (ID: P04637) was retrieved from UniProt (<https://www.uniprot.org>) and displayed in VMD software (16) to analyze the TP53 protein structure under the influence of the rs1042522 variant.

Analysis of Conservation

WebLogo v.2.8.2 was used to identify preserved regions of polymorphisms. Sequence logos are generated by WebLogo to represent the patterns in multiple sequence alignments. Sequence logos provide a richer and more precise characterization of the sequence identity than consensus sequences. By using them, alignment features that would otherwise be difficult to detect can be discovered. Each letter in an individual logo is represented by a stack of letters. Stack heights (as measured by bits) indicate sequence conservation at each position, and nucleic acid abundance is determined by symbol heights (17). Schneider and Stephens describe sequence conservation as the symbol distribution's observed entropy minus its maximum potential entropy. Multiple sequence alignments are available at <https://weblogo.threeplusone.com/create.cgi>. Based on their frequency, SNPs were scaled.

Variations' effect on the transcription factor binding sites

The current study used PROMO v.3.0.2 to identify transcription factor binding sites (TFBS) in DNA sequences (18). With the TRANSFAC v.8.3 database, we made unique binding site weight matrices to find the transcription factor binding site in the TP53-rs2287499 C>G promoter polymorphism. We selected homo sapiens factors and their corresponding sites of recognition accordingly. We observed a 5% discrepancy between the actual binding site of the transcription factor and the anticipated site, based on predictions made under a dissimilarity threshold of less than 5%. We then included the gene sequence from the NCBI database associated with the promoter location.

Results

Functional Impact of the rs1042522 Missense Variant

Our analysis of the TP53 gene revealed (Table 1) that the rs1042522 polymorphism (a G-to-C substitution)

Table 1. Specifications of studied variants

GENOMIC ^a							PROTEIN ^b			
Chr. ^c	Cytoband	Coordinate ^d	SNP ID ^e	Ref. ^f	Alt. ^g	Gene ^h	Codon (strand) ⁱ	AA pos. ^j	AA change ^k	Consequence(s) ^l
17	p13.1	7676154	rs1042522	C	G	TP53	cCc/cGc	72	Pro/Arg	Missense
17	p13.1	7688850	rs2287499	C	G	TP53	-	-	-	2KB Upstream Variant

^a Gene and nucleotide level annotations; ^b Amino acid/protein level annotations; ^c Chromosome; ^d Genomic coordinate; ^e User entered variant identifier; ^f Reference allele; ^g Alternative allele; ^h HGNC short gene name; ⁱ Change of the codon containing the variant nucleotide the position of which is capitalized; ^j Position of the amino acid containing the variant in the displayed isoform; ^k Three letter amino acid code for the reference and alternative alleles; ^l A description of the consequence of the variant.

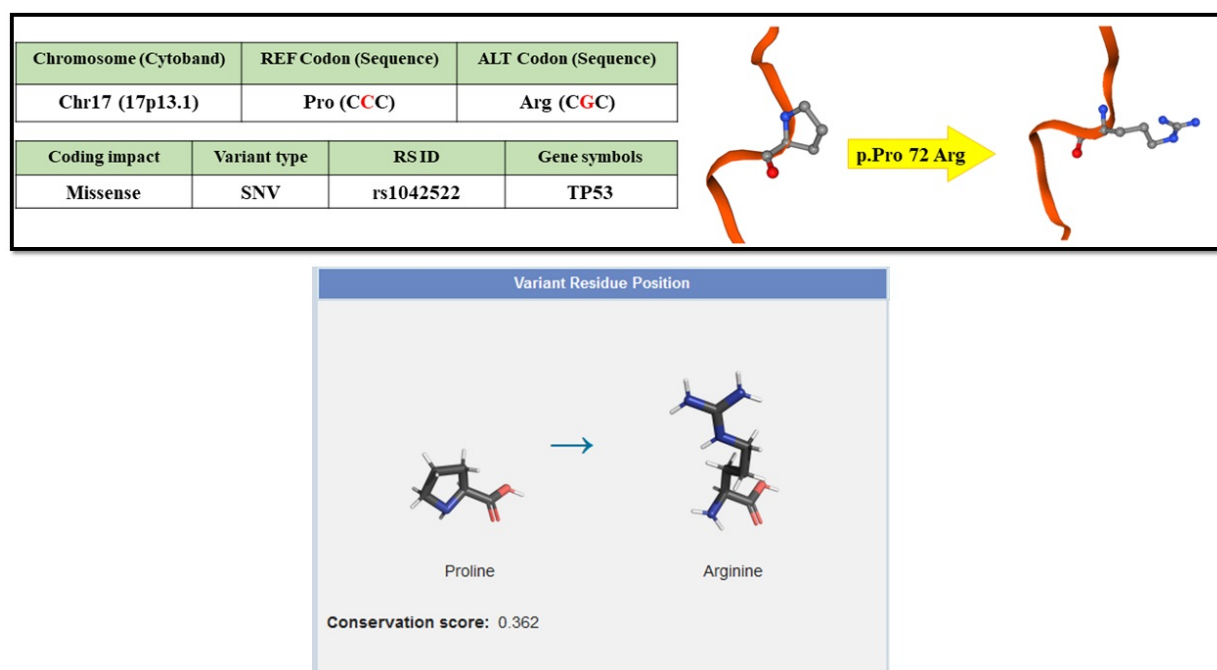


Figure 1. The TP53 visual molecular dynamics (VMD) images, shown by a new cartoon, the model presents the effect of Arginine residue on Turn structure of the protein in position 72.

results in a non-synonymous change at the protein level, changing the amino acid from proline (Pro) to arginine (Arg) in the DNA-binding domain of *TP53* (Figure 1). Given that proline is a rigid, structure-disrupting residue while arginine is positively charged and often involved in protein-DNA interactions, this substitution could significantly alter p53's DNA-binding affinity or protein stability. Previous studies have reported the association of this variant (commonly known as the *P72R* polymorphism) with differences in cancer susceptibility and apoptosis efficiency, supporting the notion that this variant has functional consequence (15, 19).

Evolutionary Conservation Analysis Using WebLogo

To evaluate whether the identified variants reside in evolutionarily constrained regions, we performed a sequence conservation analysis using the *WebLogo* server. The results indicated that none of the variant positions were located within highly conserved regions

across mammalian species (Figure 2). This suggests that these loci may be under relaxed selective pressure, allowing for genetic variation without severely disrupting essential protein functions. However, the lack of conservation does not necessarily rule out functional significance, as some regulatory or structural variants may still influence phenotype in a species-specific manner.

Transcriptional Regulation Alteration at rs2287499

A particularly intriguing finding emerged from the analysis of the rs2287499 variant, located in the promoter region of *TP53*. Using the *PROMO* transcription factor binding prediction tool, we discovered that the alternative allele (G) creates a stronger binding site for the glucocorticoid receptor- α (GR- α , T00337), a key regulator of stress response and cell proliferation (Figure 3). Since GR- α is known to modulate gene expression in response to hormonal signals, this allelic variation

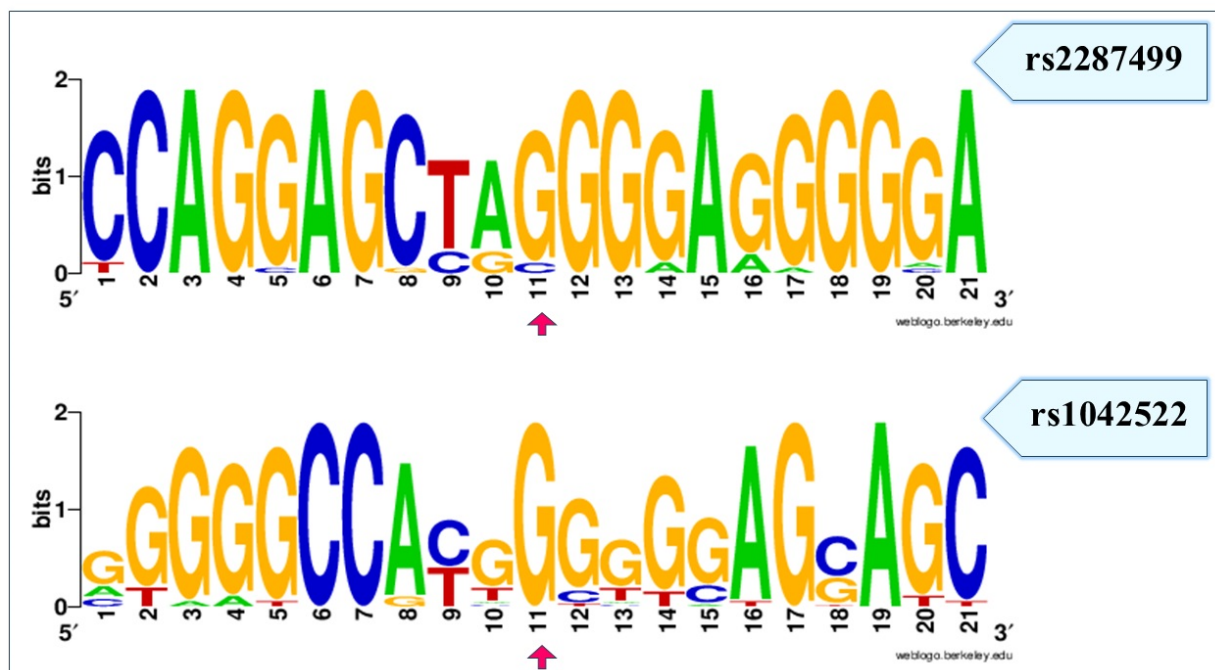


Figure 2. Schematic representation of DNA sequence conservation using the WebLogo tool around rs1042522 and rs2287499 TP53 SNPs locus. Pink arrow shows the position of locus variations in humans and wild allele conservation among mammalian species. Smaller and more varied nucleotides have less conservation.

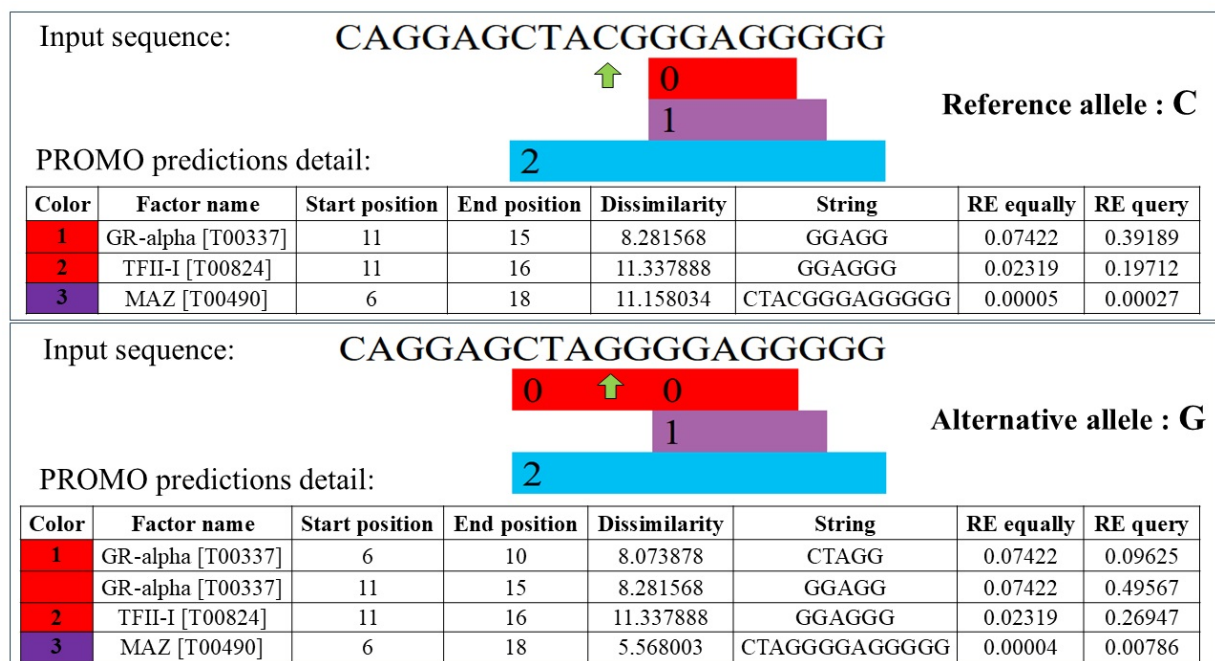


Figure 3. TFBS prediction at rs2287499 in the *TP53* gene promoter. The Random Expectation (RE) gives the number of expected occurrences of the match in a random sequence of the same length as the query sequence based on the dissimilarity index. Data is achievable through http://factor.genexplain.com/cgi-bin/transfac_factor/search.cgi via inserting the transcription factor ID. TFBS, transcription factor binding site; GR- α , glucocorticoid receptor α ; TFII-I, Transcription factor II-I; MAZ, MYC associated zinc finger protein.

suggests that individuals carrying the G allele may exhibit enhanced *TP53* transcriptional activity under conditions where GR- α is activated (e.g., glucocorticoid

exposure). Given that *p53* is a critical tumor suppressor, this regulatory change could influence cancer risk, therapy response, or stress-induced apoptosis.

Discussion

The rs1042522, also known as *TP53* codon 72 polymorphism, is a SNP found within the *TP53* gene. It plays a critical role in tumor suppression (19). This polymorphism occurs where a guanine (G) or cytosine (C) is present at codon 72, leading to amino acid substitutions: arginine (Arg) for G and proline (Pro) for C. This SNP has been extensively studied for its associations with various cancers and other diseases (20, 21). The different amino acids produced by rs1042522 (Arg vs. Pro) may influence the protein's interaction with other cellular proteins, its stability, and its ability to induce apoptosis. Studies indicate that the Arg variant might enhance the apoptotic response and DNA damage repair, suggesting a more effective tumor suppression role than the Pro variant (22). In this study, we found that the substitution from proline to arginine at position 72 in the *TP53* protein resulted in a relatively noticeable structural change. This missense mutation occurs in rare cases but alters protein interactions when it occurs. The polypeptide backbone is not affected, but the side chains of the two amino acids are distinct. Hydrophobicity and charge are unique to each amino acid. Mutated and wild-type proteins exhibit differences in these characteristics. The wild amino acid is smaller than the altered residue, influencing its interaction with other molecules. It is found in the turn structure that the amino acid number 72 appears (Figure 1). The study found that it can naturally engage with proteins that regulate the expression of protein arginine methyltransferase 1 (*PRMT1*) (23) and cell cycle and apoptosis regulator 2 (*CCAR2*) (24) genes. The *VMD* study showed that the 17p13.1 missense change could change the secondary structure and characteristics of the *TP53* protein. This change affects *PRMT1* and *CCAR2*, which regulate cell proliferation (25). Restelli et al. claim that knocking out *CCAR2* directly affects the activation of serine/threonine kinase Akt (26); however, normal human cells do not support these findings. Recent research found that negative Akt signaling pathway modulation enhances *PCOS* granulosa cell death risk (27). Another investigation by Song et al. revealed that reduced Akt-mTOR signaling may cause *PCOS* (28). Asymmetric dimethylarginine (ADMA) affects *PCOS* women's metabolic and endocrine systems. Oxidative stress can increase ADMA levels by decreasing dimethylaminohydrolase (DDAH) activity and raising *PRMT1* activity, which play a role in ADMA synthesis. The same methyltransferase that operates on meiotic recombination 11 (*MRE11*) is *PRMT1*, which methylates arginine at the glycine arginine-rich (GAR) motif of TP53BP1. Due to 53BP1 recruitment to double-strand DNA breaks and the creation of unique nuclear foci, oxidative stress-exposed cells identify and repair these damages early (29). In vitro studies of the DDAH and *PRMT1* enzymes have shown that redox-sensitive mechanisms regulate ADMA levels (30). Changing ADMA levels in ovarian cells is a notion that needs

more research.

Our *in-silico* analysis showed that the promoter allele polymorphism (in alternative allele G) enhances the gene's factor site for GR- α . Thus, the *TP53* gene is likely more regulated. This means that the presence of the G allele could provide the basis for GR- α effect. We believe that this variant of the *TP53* gene can potentially change *PCOS* symptoms. *TP53* is involved in the regulation of ovarian follicular development and atresia (the process of degeneration of ovarian follicles) (31). Overexpression of *TP53* could lead to increased apoptosis of ovarian follicles, potentially contributing to the formation of cysts and affecting ovulatory function (32). Corticosteroid resistance is heavily influenced by the glucocorticoid receptor α isoform. Through modifying corticosteroid signaling pathway protein expression and activity, inflammatory cytokines reduce steroid sensitivity. Steroid-mediated anti-inflammatory effect depends on GR expression and activation. GR requires HSP90 to prevent protein degradation. HSP90 is released when GR binds to the corticosteroid to mature and bind to the glucocorticoid response element (GRE) (33). GR- α is prevalent in the cytoplasm and up-regulates IKB- α and directly binds to NF-kappaB to prevent its activation. The upregulation of histone acetyltransferase (HAT) and creation of NF-kB/HAT complexes cause inflammation. After activation by ligand hormones, GR- α increases HDAC2 recruitment to the protein complex to decrease NF-kB/HAT complex formation and deacetylate histones in the promoter area of important pro-inflammatory cytokines (33). The relationship between GR- α and *PCOS* involves several complex biological mechanisms, as both hormones and transcription factors play significant roles in the regulation of ovarian function and metabolic pathways (34). Glucocorticoids influence ovarian function, affecting steroidogenesis and ovarian follicle development (35). Disruption of normal glucocorticoid signaling may contribute to *PCOS*'s abnormal hormonal profiles, such as elevated androgens. Many women with *PCOS* exhibit insulin resistance, which is associated with dysregulation of GR- α . Insulin can influence glucocorticoid signaling, leading to altered GR activity and further contributing to the hormonal imbalance's characteristic of the syndrome (36).

PCOS women often experience inflammation and stress (9). The GR- α pathway modulates inflammatory responses, and aberrations in this signaling may contribute to *PCOS* pathology. Understanding the role of GR- α in *PCOS* might open new avenues for targeted therapies. Modulating glucocorticoid activity or improving insulin sensitivity could alleviate some *PCOS* symptoms. Some studies suggest that alterations in GR- α expression or function may be associated with *PCOS* symptoms severity (36). Further research is ongoing to delineate the exact molecular mechanisms linking GR- α to *PCOS* pathophysiology. In summary,

GR- α likely plays a role in the etiology and symptoms of PCOS through its influence on ovarian steroidogenesis, insulin action, and inflammatory processes.

Although research is ongoing to better understand the precise role of *TP53* in PCOS, it's critical to note that it is likely just one piece of the larger puzzle. The interplay between various genes, hormones, environmental factors, and lifestyle issues complicates PCOS understanding, and further studies are needed to clarify how *TP53* and other molecular pathways contribute to this condition. Considering the high importance of *TP53*'s role in many diseases, it especially requires a comprehensive investigation from molecular and bioinformatics angles. This investigation should also include its effect on signaling processes and cell cycle.

In summary, the *in-silico* analysis of the association effects of the rs2287499 and rs1042522 variants on the expression and folding of the *TP53* protein enhances our understanding of the molecular mechanisms underlying PCOS. The findings suggest that these genetic variants may significantly influence the stability and functionality of *TP53* protein. This protein is a key regulator of cellular stress responses and reproductive functions. By elucidating the relationship between these variants and *TP53* dysregulation, this study provides valuable insights into how genetic predispositions can contribute to the pathogenic mechanisms of PCOS. Future research, integrating *in vitro* and clinical studies, will be essential to validate these *in-silico* observations and to further explore the therapeutic implications of modulating *TP53* activity in the context of PCOS.

Authors Contribution

MS-A, HS and MM designed the study; MS-A, HS, MM, RA, RS, MZ and KS wrote the manuscript; MM, HS and RS revised the manuscript; HS and MM supervised the project. All authors read and consented to the last version of the article.

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Conflict of Interest

The authors declared that they have no conflict of interest.

Ethical Approval

The ethics committee of Zahedan University of Medical Sciences authorized the study protocol (ethical code: IR.ZAUMS.REC.1402.434).

References

- Biglari-Zadeh G, Sargazi S, Mohammadi M, Ghasemi M, Majidpour M, Saravani R, Mirinejad S. Relationship Between Genetic Polymorphisms in Cell Cycle Regulatory Gene *TP53* and Polycystic Ovarian Syndrome: A Case-Control Study and In Silico Analyses. *Biochem Genet.* 2023;1-23. <https://doi.org/10.1007/s10528-023-10349-1>
- Sabeti Akbar-Abad M, Majidpour M, Sargazi S, Ghasemi M, Saravani R. Unraveling the Role of Cathepsin B Variants in Polycystic Ovary Syndrome: Insights from a Case-Control Study and Computational Analyses. *Reprod Sci.* 2025;32(4):1166-79. <https://doi.org/10.1007/s43032-025-01806-w>.
- Govahi Kakhki F, Sargazi S, Montazerifar F, Majidpour M, Karajibani A, Karajibani M, Ghasemi M. IGF2BP2 and IGFBP3 Genotypes, Haplotypes, and Genetic Models Studies in Polycystic Ovary Syndrome. *J Clin Lab Anal.* 2024;38(5):e25021. <https://doi.org/10.1002/jcla.25021>.
- Majidpour M, Sargazi S, Ghasemi M, Sabeti Akbar-Abad M, Sarhadi M, Saravani R. LncRNA MEG3, GAS5, and HOTTIP polymorphisms association with risk of polycystic ovary syndrome: a case-control study and computational analyses. *Biochem Genet.* 2024;1-23. <https://doi.org/10.1007/s10528-024-10977-1>.
- Bathaie SZ, Ashraf M, Azizian M, Khademian N, Abroun S. Crocetin regulates cell cycle progression in N-nitroso-Nmethylurea (NMU)-induced breast cancer in rat: cyclin D1 suppression, p21Cip1 and p53 induction. *Acta Biochim Iran.* 2024. <https://doi.org/10.18502/abi.v2i1.16244>.
- Zanjirband M, Hodayi R, Safaiejad Z, Nasr-Esfahani M, Ghaedi-Heydari R. Evaluation of the p53 pathway in polycystic ovarian syndrome pathogenesis and apoptosis enhancement in human granulosa cells through transcriptome data analysis. *Sci Rep.* 2023;13(1):11648. <https://doi.org/10.1038/s41598-023-38340-1>.
- Rakhshanizade N, Sargazi S, Karajibani M, Majidpour M, Karajibani A, Montazerifar F, Ghasemi M. Influence of Suppressor of Cytokine Signaling 1 (SOCS1) Gene Variations on Polycystic Ovary Syndrome. *Indian J Clin Biochem.* 2024;1-10. <https://doi.org/10.1007/s12291-024-01248-2>.
- Wang C, Tan JYM, Chitkara N, Bhatt S. TP53 Mutation-Mediated Immune Evasion in Cancer: Mechanisms and Therapeutic Implications. *Cancers (Basel).* 2024;16(17):3069. <https://doi.org/10.3390/cancers16173069>.
- Taghizadeh N, Mohammadi S, Saeedi V, Haghighi L, Nourbakhsh M, Nourbakhsh M, Azar MR. Association between steroid hormones and insulin resistance in patients with polycystic ovary syndrome. *Acta Biochim Iran.* 2023. <https://doi.org/10.18502/abi.v1i1.14062>.
- Saito A, Omura I, Imaizumi K. CREB3L1/OASIS: cell cycle regulator and tumor suppressor. *FEBS J.* 2024;291(22):4853-66. <https://doi.org/10.1111/febs.17052>.
- Asma K, Akram Vatannejad V, Sara B, Maryam T, Molood B, Farzad A, et al. Association of Homocysteine with body mass index in women with polycystic ovary Syndrome. *Acta Biochim Iran.* 2025;3(1). <https://doi.org/10.18502/abi.v3i1.19346>.
- Huszno J, Grzybowska E. TP53 mutations and SNPs as prognostic and predictive factors in patients with breast cancer. *Oncology letters.* 2018;16(1):34-40. <https://doi.org/10.3892/ol.2018.8627>.
- Biglari-Zadeh G, Sargazi S, Mohammadi M, Ghasemi M, Majidpour M, Saravani R, Mirinejad S. Relationship between genetic polymorphisms in Cell Cycle Regulatory Gene *TP53* and polycystic ovarian syndrome: a case-control study and in Silico Analyses. *Biochemical Genetics.* 2023;61(5):1827-49. <https://doi.org/10.1007/s10528-023-10349-1>.
- Naidoo P, Maharaj AB, Ghazi T, Chuturgoon AA. MTHFR C677T rs1801133 and TP53 Pro72Arg rs1042522 gene variants in South African Indian and Caucasian psoriatic arthritis patients. *Genet Mol Biol.* 2025;48(1):e20230325. <https://doi.org/10.1590/1678-4685-GMB-2023-0325>.

15. Siddamalla S, Reddy TV, Govatati S, Gurusaiiah P, Deenadayal M, Shivaji S, Bhanoori M. Influence of tumour suppressor gene (TP53, BRCA1 and BRCA2) polymorphisms on polycystic ovary syndrome in South Indian women. *Eur J Obstet Gynecol Reprod Biol.* 2018;227:13-8. <https://doi.org/10.1016/j.ejogrb.2018.05.027>
16. Humphrey W, Dalke A, Schulten K. VMD: visual molecular dynamics. *Journal of molecular graphics.* 1996;14(1):33-8, 27-8. [https://doi.org/10.1016/0263-7855\(96\)00018-5](https://doi.org/10.1016/0263-7855(96)00018-5).
17. Crooks GE, Hon G, Chandonia JM, Brenner SE. WebLogo: a sequence logo generator. *Genome research.* 2004;14(6):1188-90. <https://doi.org/10.1101/gr.849004>.
18. Farré D, Roset R, Huerta M, Adsua JE, Roselló L, Albà MM, Messeguer X. Identification of patterns in biological sequences at the ALGGEN server: PROMO and MALGEN. *Nucleic Acids Res.* 2003;31(13):3651-3. <https://doi.org/10.1093/nar/gkg605>.
19. Huang X, Wu F, Zhang Z, Shao Z. Association between TP53 rs1042522 gene polymorphism and the risk of malignant bone tumors: a meta-analysis. *Bioscience Reports.* 2019;39(3):BSR20181832. <https://doi.org/10.1042/BSR20181832>.
20. Babu G, Bin Islam S, Khan MA. A review on the genetic polymorphisms and susceptibility of cancer patients in Bangladesh. *Mol Biol Rep.* 2022;49(7):6725-39. <https://doi.org/10.1007/s11033-022-07282-8>.
21. Rahman MA. Study of p53 gene polymorphism and risk of hepatocellular carcinoma: in a Bangladeshi cohort: © University of Dhaka; 2023.
22. Ahmed S, Safwat G, Moneer MM, El Ghareeb A, El Sherif AA, Loutfy SA. Prevalence of TP53 gene Pro72Arg (rs1042522) single nucleotide polymorphism among Egyptian breast cancer patients. *Egypt J Med Hum Genet.* 2023;24(1):24. <https://doi.org/10.1186/s43042-023-00405-1>.
23. An W, Kim J, Roeder RG. Ordered cooperative functions of PRMT1, p300, and CARM1 in transcriptional activation by p53. *Cell.* 2004;117(6):735-48. <https://doi.org/10.1016/j.cell.2004.05.009>.
24. Qin B, Minter-Dykhouse K, Yu J, Zhang J, Liu T, Zhang H, et al. DBC1 functions as a tumor suppressor by regulating p53 stability. *Cell Rep.* 2015;10(8):1324-34. <https://doi.org/10.1016/j.celrep.2015.01.066>
25. Repenning A, Happel D, Bouchard C, Meixner M, Verel-Yilmaz Y, Raifer H, et al. PRMT1 promotes the tumor suppressor function of p14(ARF) and is indicative for pancreatic cancer prognosis. *The EMBO journal.* 2021;40(13):e106777. <https://doi.org/10.15252/embj.2020106777>.
26. Restelli M, Magni M, Ruscica V, Pinciroli P, De Cecco L, Buscemi G, et al. A novel crosstalk between CCAR2 and AKT pathway in the regulation of cancer cell proliferation. *Cell Death Dis.* 2016;7(11):e2453-e. <https://doi.org/10.1038/cddis.2016.359>
27. Tan M, Cheng Y, Zhong X, Yang D, Jiang S, Ye Y, et al. LNK promotes granulosa cell apoptosis in PCOS via negatively regulating insulin-stimulated AKT-FOXO3 pathway. *Aging (Albany NY).* 2021;13(3):4617-33. <https://doi.org/10.18632/aging.202421>.
28. Song WJ, Shi X, Zhang J, Chen L, Fu SX, Ding YL. Akt-mTOR Signaling Mediates Abnormalities in the Proliferation and Apoptosis of Ovarian Granulosa Cells in Patients with Polycystic Ovary Syndrome. *Gynecol Obstet Invest.* 2018;83(2):124-32. <https://doi.org/10.1159/000464351>.
29. Boisvert F-M, Rhie A, Richard S, Doherty AJ. The GAR motif of 53BP1 is arginine methylated by PRMT1 and is necessary for 53BP1 DNA binding activity. *Cell Cycle.* 2005;4(12):1834-41. <https://doi.org/10.4161/cc.4.12.2250>.
30. Rashidi BH, Mohammad Hosseinzadeh F, Alipoor E, Asghari S, Yekaninejad MS, Hosseinzadeh-Attar MJ. Effects of Selenium Supplementation on Asymmetric Dimethylarginine and Cardiometabolic Risk Factors in Patients with Polycystic Ovary Syndrome. *Biol Trace Elem Res.* 2020;196(2):430-7. <https://doi.org/10.1007/s12011-019-01954-6>.
31. Celestino J, Chaves R, Matos M, Silva MSJ, Bruno J, Maia-Júnior J, Figueiredo J. Mechanisms of atresia in ovarian follicles. *Anim Reprod.* 2018;6(4):495-508.
32. Otsuka I. Mechanisms of High-Grade Serous Carcinogenesis in the Fallopian Tube and Ovary: Current Hypotheses, Etiologic Factors, and Molecular Alterations. *Int J Mol Sci.* 2021;22(9):4409. <https://doi.org/10.3390/ijms22094409>.
33. Jiang Z, Zhu L. Update on molecular mechanisms of corticosteroid resistance in chronic obstructive pulmonary disease. *Pulm Pharmacol Ther.* 2016;37:1-8. <https://doi.org/10.1016/j.pupt.2016.01.002>.
34. Anderson G. Polycystic Ovary Syndrome Pathophysiology: Integrating Systemic, CNS and Circadian Processes. *Frontiers in bioscience (Landmark edition).* 2024;29(1):24. <https://doi.org/10.31083/j.fbl2901024>.
35. Narani MS, Vatannejad A, Kheirollahi A, Teimouri M, Bayat S, Jadidzadeh F. Changes of biochemical parameters in normal weight and overweight/obese women with polycystic ovary Syndrome. *Acta Biochim Iran.* 2023. <https://doi.org/10.18502/abi.v1i3.14547>
36. Hu M, Zhang Y, Guo X, Jia W, Liu G, Zhang J, et al. Perturbed ovarian and uterine glucocorticoid receptor signaling accompanies the balanced regulation of mitochondrial function and NFκB-mediated inflammation under conditions of hyperandrogenism and insulin resistance. *Life sciences.* 2019;232:116681. <https://doi.org/10.1016/j.lfs.2019.116681>.