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Identification of Two Novel Mutations in Exon 2 of the Bmp15 Gene in Infertile Pakistani Females

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Abstract

Female reproductive lifespan, marked by the timing of natural menopause, has significant implications for fertility, healthspan, and susceptibility. It has been critically evaluated the evidence for previously reported monogenic causes of premature ovarian insufficiency, demonstrating that many variants originally classified as pathogenic show substantially reduced penetrance in population-based cohorts. We have highlighted the emerging discoveries from exome-wide association studies, including novel genes such as ZNF518A, ETAA1, and SAMHD1 that harbor rare variants with large effects on menopause timing. We explore the pleiotropic effects of reproductive ageing genes on cancer susceptibility, particularly the trade-off between later menopause and increased malignancy risk mediated by SAMHD1 and CHEK2. Finally, we discussed clinical implications, including the reclassification of genetic variants, the potential for polygenic risk scoring, and the need for population-specific studies to address global diversity in reproductive ageing genetics.

Introduction

Infertility is a growing global health concern, affecting approximately 8–15% of couples worldwide, with female factors contributing significantly to this burden. One of the key biological determinants of female fertility is proper ovarian function, which involves folliculogenesis, oocyte maturation, and ovulation. Disruptions in these processes often arise due to genetic abnormalities decreased fertility is mainly due to ovarian ageing, oxidative stress and genetic mutations that affect oocyte quality and quantity. These results highlight the need to characterise the genetic factors involved in ovarian function, particularly in populations with limited genomic data such as Pakistani females.[1]

The BMP15 (Bone Morphogenetic Protein 15) gene is one of the genes involved in female reproduction, which plays a vital role in follicular development and oocyte competence. BMP15 is an oocyte-derived growth factor of the TGF-β superfamily and is required for granulosa cell proliferation, follicle maturation and ovulation. Recent studies in 2025 have shown that BMP15 interacts with other oocyte-secreted factors, including GDF9, to regulate granulosa cell development and enhance oocyte quality. Furthermore, altered BMP15 expression levels have been strongly linked to oocyte maturity and embryo developmental potential in assisted reproductive technologies. These results confirm that BMP15 is a major molecular regulator of female fertility.

Mutations in the BMP15 gene have been widely linked to reproductive diseases such as premature ovarian insufficiency (POI) and infertility. Novel BMP15 mutations that directly affect protein function and cause ovarian dysfunction and reduced fertility have been identified in recent studies. For instance, the pathogenic role of a homozygous mutation (C320Y) in BMP15 was directly reported as a cause of ovarian disease in a 2024 study. Similarly, a 2025 review characterised BMP15 as a promising candidate gene for infertility and recommended further population-specific mutation analysis. These studies suggest that even small changes in BMP15 can have a large impact on reproductive outcomes.[2]

Also, population-based genetic studies have suggested that rare and novel mutations may have stronger effects as compared to common variants especially in under-represented populations. Reproductive genetics found that polymorphisms in genes like BMP15 and GDF9 can affect ovarian reserve and fertility differently across ethnic groups. This emphasises the importance of regional genetic studies, especially in countries such as Pakistan where genetic diversity and consanguinity may increase the prevalence of rare mutations.

Therefore, identification of novel mutations in exon 2 of BMP15 gene is of high significance to understand the genetic basis of infertility in Pakistani females. These studies not only contribute to the enlargement of the global mutation spectrum of BMP15, but also provide insights for early diagnosis, genetic counselling, and personalised treatment strategies. Recent advances in molecular genetics and sequencing technologies support the exploration of rare variants, better suited to identify pathogenic mutations associated with female infertility.[3]

Ovarian Ageing from Fetal Development to Menopause:

Dynamics of Ovarian Follicle Reserve:

The human fetal ovary at mid-gestation contains ~6-7 million primordial follicles, the highest germ cell pool. This reserve is only created at birth. Attrition at birth reduces this figure to 1-2 million follicles and it further decreases to approximately 300,000 at menarche.[4]

Two primary mechanisms account for follicle loss: ovulation and atresia. While ovulation accounts for approximately 400-500 oocytes released during reproductive life, the vast majority of follicle loss occurs through atresia programmed follicular degeneration mediated by apoptotic pathways.[3] Follicle depletion accelerates after age 35 years, and menopause ensues when the follicle count falls below approximately 1,000 follicles.[5]

Recent research has elucidated cellular mechanisms underlying age-related follicle depletion. Oxidative stress accumulation in granulosa cells leads to mitochondrial DNA mutations, with mutation rates increasing tenfold with advancing age.[6] The NRF2-KEAP1 antioxidant pathway becomes dysregulated in aged granulosa cells, resulting in increased pro-inflammatory cytokine secretion.[7]

Phenotypes and Clinical Criteria:

Natural age at menopause (ANM) is defined as the age at final menstrual period, excluding women who have undergone oophorectomy, hysterectomy, or hormone replacement therapy.[7] Premature ovarian insufficiency (POI) is diagnosed when menopause occurs before age 40 years, accompanied by hypoestrogenism and FSH levels exceeding 25 IU/L Primary amenorrhea, the most severe phenotype, is defined as absence of menarche by age 15 years.[8]

The UK Biobank includes a very large dataset that facilitates genetic analyses of phenotypes from 104,733 white women living in Europe.[9] Recently, additional analyses of women with phenotypes from 132,370 women have allowed robust identification of rare variant associations through the use of more advanced analytic methods than were

originally used.[10]

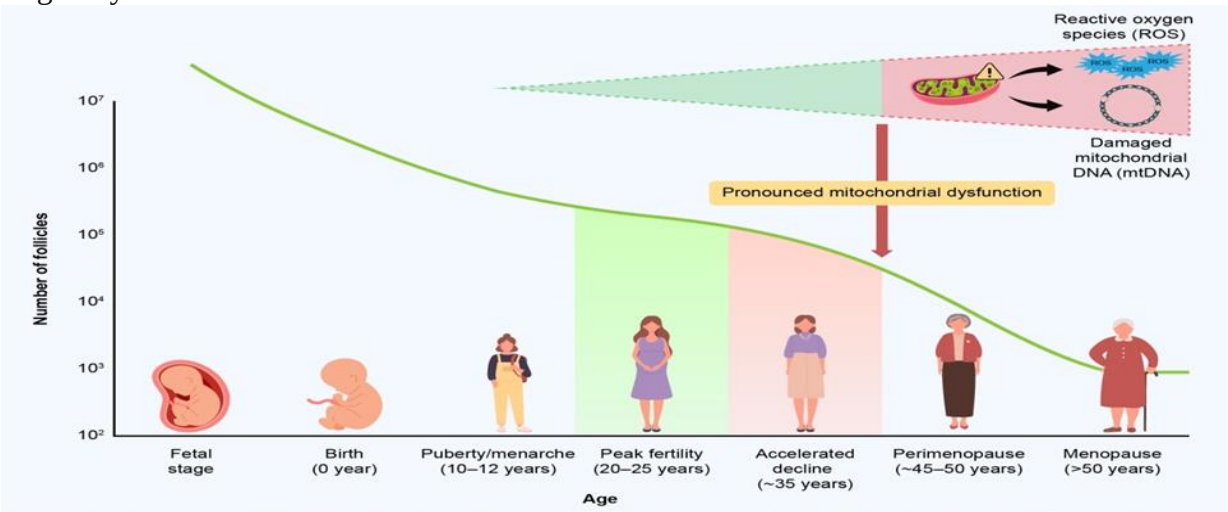

Figure 1: Aging-related decrease in primordial follicles and mitochondrial dysfunction in ovarian aging.[44]

GDF9 and BMP15: Crucial Female Factors:

Gene Function and Structure:

Growth Differentiation Factor 9 (GDF9) and Bone Morphogenetic Protein 15 (BMP15) are part of the transforming growth factor beta (TGF-β) family, acting as oocyte-derived factors controlling follicular developmen.[11] GDF9 maps to chromosome 5q31.1, whereas BMP15 maps to the X chromosome (Xp11.2).[12] These genes are only expressed in oocytes and act by influencing adjacent granulosa cells in a paracrine manner. Some downstream consequences are the proliferation of granulosa cells, inhibition of apoptosis, modulation of follicle-stimulating hormone (FSH) sensitivity, and oocyte competence.[13]

Animal Studies:

For sheep populations, some particular Fec genes that cause the increase in number of ovulation have been described. Three main genes are BMPR1B (FecB), BMP15 (FecX), and GDF9 (FecG).[14] The level of expression of both BMPR1B and GDF9 was significantly higher in polytocous breeds than monotocous breeds ($P < 0.01$). As for Egyptian goat populations, the presence of SNP (760 G>C) causing glutamic acid to be substituted by glutamine at codon 254 has been shown for all females with large litters of four goat breeds.[15,16]

Human Premature Ovarian Insufficiency:

Genetic factors are responsible for about 20-25% of the total POI patients.[17] BMP15 presents dosage sensitivity where wild type results in normal fertility, heterozygous mutations present variable penetrance in POI, while homozygous mutations result in infertility.[18] A new missense mutation in BMP15 gene (c.226C>T/p.Arg76Cys) was observed in a 33-year-old Iranian patient with POI, where analysis indicated a decrease in BMP15 binding to BMPR1B.[19] However, population-scale research disapproves the assumption that heterozygous BMP15 mutations are a common cause of POI. Genomic research in 104,733 female individuals demonstrated that rare missense mutations did not correlate with ANM, and there were no heterozygous loss-of-function carriers.[20]

BMP15 MicroRNA Regulation:

MicroRNAs control the level of gene expression by complementarily binding sequences. As per Kamel and Kandala (2024), BMP15 gene expression was reduced by

0.220 times in infertile patients having hyperprolactinemia. On the other hand, miR-3. Other fertility-associated microRNAs include miR-21, miR-224, and miR-320.[20,21]

Penetrance of Variants:

The penetrance of variants for 105 POI-related genes was investigated based on data from the UK Biobank. In 37 out of 40 heterozygous genes, protein truncating variants failed to lead to premature menopause. 99.9% of protein truncating variants were found in non-menopausal women with ANM ranging from 45-56 years.[22]

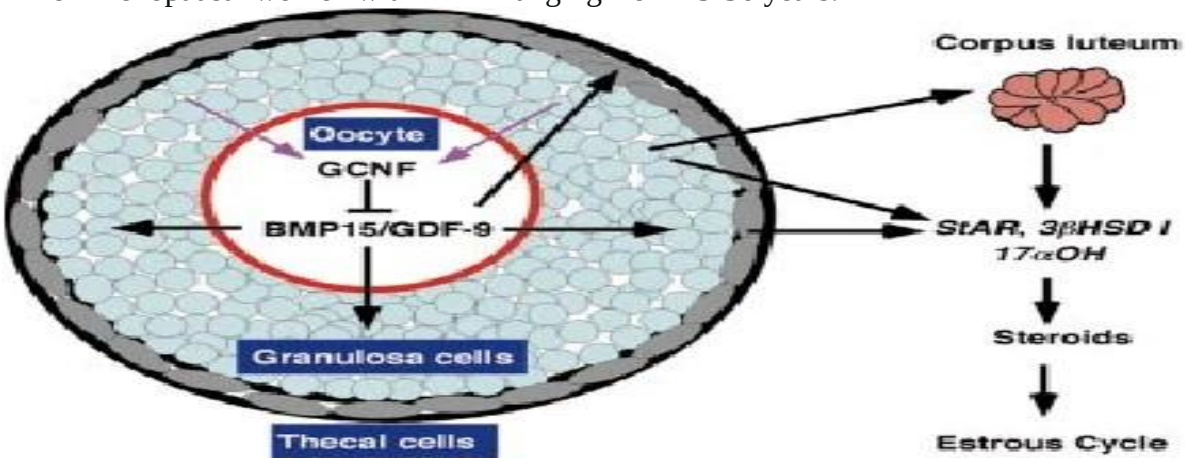

Figure 2: A model for GCNF regulation of BMP-15/GDF-9 signaling during female reproduction. GCNF represses BMP-15/GDF-9 expression, which in turn affects steroidogenesis and female fertility.[48]

Exome-Wide Discovery of Novel Genes:

Genes Associated with Earlier Menopause:

Analysis of 106,973 postmenopausal women identified nine genes with exome-wide significance.[23] ETAA1 truncating variants shorten ANM by 2.28 years ($p = 5.30 \times 10^{-10}$). ETAA1 activates the ATR kinase pathway during replication fork stalling (Bass et al., 2023). HROB truncations reduce ANM by 2.89 years ($p = 1.90 \times 10^{-9}$). HROB recruits the MCM8-MCM9 helicase complex for homologous recombination repair.[24] BRCA2 truncating variants decrease ANM by 1.18 years ($p = 2.60 \times 10^{-9}$), and PALB2 truncations reduce ANM by 1.78 years ($p = 4.8 \times 10^{-9}$).[25] PNPLA8 truncations, affecting mitochondrial lipid metabolism, are associated with reduced ANM ($p = 1.9 \times 10^{-9}$).[26]

Genes Associated with Later Menopause:

CHEK2 damaging mutations delay menopause by 1.57 years ($p = 1.60 \times 10^{-21}$). CHEK2 is involved in p53-mediated cell death, and the lack of CHEK2 leads to decreased cell death and increased ovarian reservoir.[26] Mutations in HELB lead to delayed onset of menopause by 1.84 years ($p = 4.20 \times 10^{-9}$).[27] Damage to the gene SAMHD1 causes delayed onset of menopause by 1.

DNA Damage Repair: The Central Pathway in Ovarian Ageing:

The most important discovery is that DNA damage repair (DDR) is essential for ovarian aging. [28] Of 290 genetic variants linked with ANM, many occur within DDR genes such as BRCA1, BRCA2, CHEK2, HELB, and RAD51.[29] The reason for this convergence is because of the unique biology of oocytes. Being formed during fetal life and undergoing arrest in prophase I for decades, the oocyte has accumulated much DNA damage and relies only on DDR ability to survive.[30] Mutations in DDR genes cause atresia and premature menopause, but those which block apoptosis cause delayed menopause. while mutations that inhibit apoptosis delay menopause. Examples of mechanistic hypotheses are: ETAA1 inhibition leads to replication stress resistance

failure; HROB deletion influences double-strand breaks repair; SAMHD1 inhibition changes dNTP concentrations; CHEK2 depletion allows the survival of damaged oocytes.[31]

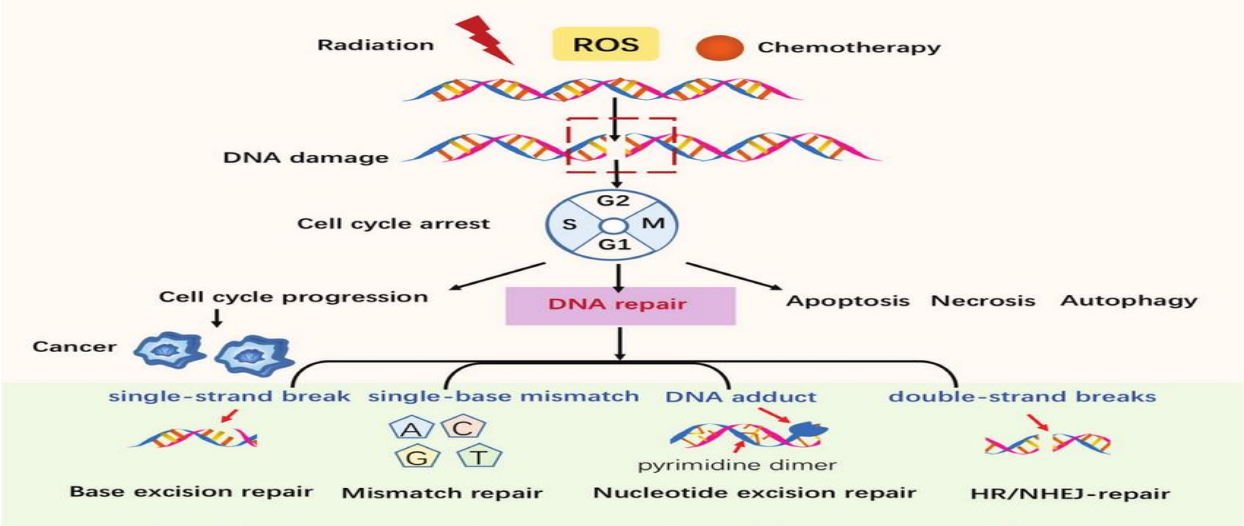

Figure 3: DNA Damage Repair Defects in Cancer: From Mechanisms to Therapeutic Strategies.[47]

Reproductive Aging and Cancer: The Two Edges of a Sword:

According to epidemiological evidence, premature ovarian aging decreases the chances of developing breast cancer, whereas delayed ovarian aging raises the probability (Collaborative Group on Hormonal Factors in Breast Cancer). Mutations that damage the SAMHD1 gene lead to the postponement of ovarian aging, raising the chances of cancer development (all cancers, OR = 2.12 in males, $p = 4.7 \times 10^{-13}$; 1.61 in female.[31] BRCA2 and PALB2 mutations accelerate reproductive aging while predisposing to breast cancer.[32] These findings have clinical implications: mutation carriers require counseling about both cancer risk and fertility implications, and enhanced cancer surveillance for SAMHD1 and CHEK2 variant carriers.[4]

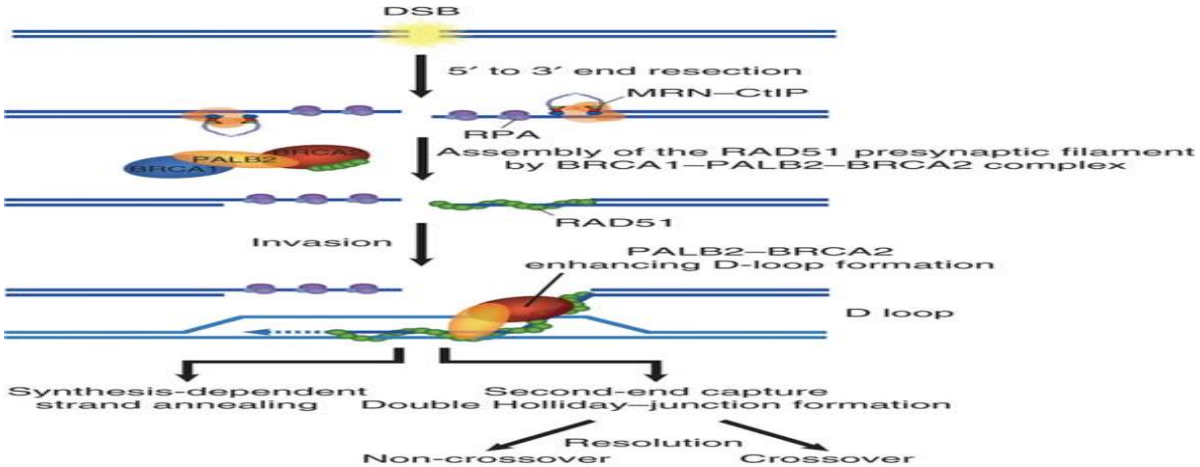

Figure 4: Cooperation of breast cancer proteins PALB2 and piccolo BRCA2 in stimulating homologous recombination.[46]

Cystic Fibrosis: CFTR Gene Mutations:

Cystic fibrosis (CF) is caused by mutations in the CFTR gene (chromosome 7q31.2), encoding a chloride channel.[31] F508del is the most common mutation worldwide, with ~70% prevalence among Caucasians.[33]

Studies in Pakistan demonstrate substantially lower F508del frequency. A 2025 study of 95 Pakistani CF patients found F508del absent in 73.74% of cases.[34] Whole- exome sequencing identified three novel variants, most non-responsive to CFTR modulators like Trikafta. High consanguinity (73.40%) was observed.

Optimized a Sanger sequencing protocol using capillary electrophoresis, achieving ~80% cost reduction through reaction volume reduction (20µl to 10µl), primer concentration reduction (3.2 to 1.6 pmol), and Ready Reaction Premix reduction (4 to 0.7µl).[35]

SCAPER Gene and Syndromic Intellectual Disability:

Intellectual Developmental Disorder and Retinitis Pigmentosa (IDDRP, OMIM#618195) is a rare autosomal recessive syndrome characterized by intellectual disability and retinitis pigmentosa.[35] The SCAPER gene (chromosome 15q24.3) regulates cell cycle progression through cyclin A/Cdk2 complex formation.[35]

Identified a novel homozygous mutation c.2605A>T (p.Lys869Ter) in six affected individuals from a consanguineous Pakistani pedigree.[33] Clinical features included mild-moderate intellectual disability (100%), decreased visual acuity (100%), decreased visual fields (100%), strabismus (17%), and broad-based gait (33%). In silico analysis predicted extensive structural distortion with only 3.34% sequence identity with wild-type.

Previous SCAPER mutations have been identified in Bedouin, European, and other populations.[34,36]

Consanguinity and Population Genetics:

Consanguineous marriages in Pakistan range from 50-60% of all marriages. A 2025 study of 867 individuals with congenital anomalies found parental consanguinity in 62% of cases Population-specific mutation profiles include.[37]

CFTR: F508del frequency lower in Pakistanis (27-33%) vs. Caucasians (70%).[1]

SCAPER: Different variants across Bedouin, European, Pakistani, and Iranian populations.[8]

BMP15: Novel mutations in Bulgarian and Iranian populations.[10,11]

These observations necessitate population-specific genetic testing panels.

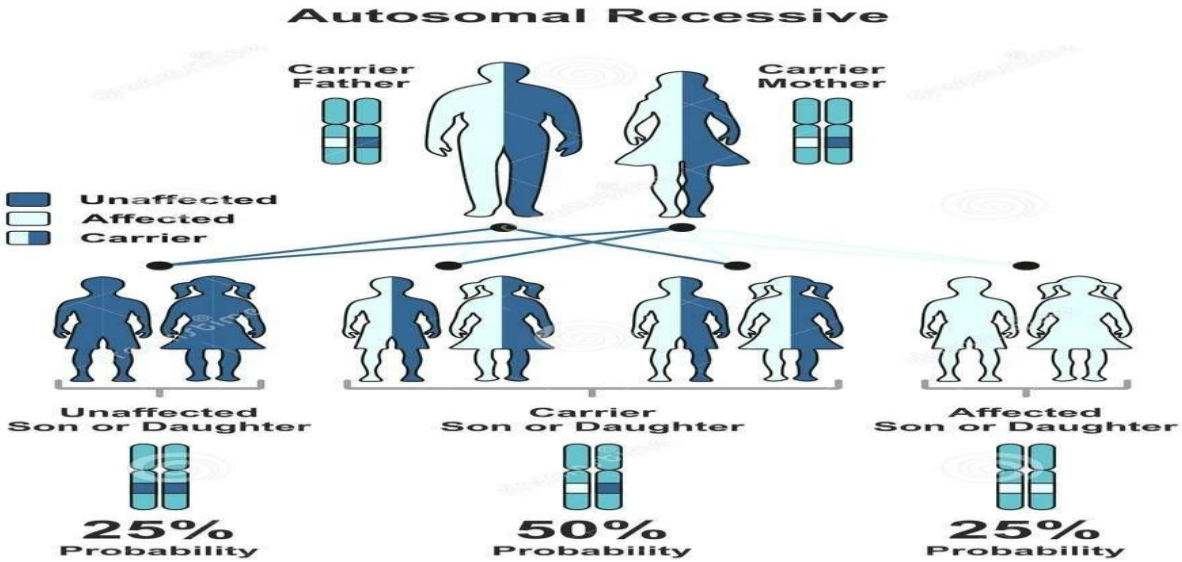

Figure 5: **A Consanguinity and Population Genetics of Autosomal recessive. [45]**

Cost-Effectiveness and Diagnostic Approaches:

Available testing technologies include Sanger sequencing (gold standard, accurate but lengthy), capillary electrophoresis (affordable, lower throughput), whole exome sequencing (comprehensive, costly), and whole genome sequencing (most expensive).[4,35]

The optimized Sanger sequencing protocol achieves ~80% cost reduction. The recommended stepwise diagnostic approach for consanguineous populations is:[38]
Clinical evaluation with condition-specific testing.
Population-specific mutation screening.
Exon-targeted Sanger sequencing.
Whole exome sequencing for unresolved cases.
Genetic counseling.

Implications of Research Findings:

Female POI/Infertility:

Current applications include microRNA profiling (miR-378) as a biomarker candidate, marker-assisted selection in livestock, and genetic screening for BMP15/GDF9 mutations.[39] Future applications may include CRISPR gene editing and RNA-based therapies.[40]

Cystic Fibrosis:

Challenges in Pakistan include lack of population-specific panels, high drug costs, limited genetics laboratories, and most Pakistani mutations being non-responsive to existing modulators.[41]

SCAPER-IDDRP:

Applications include early detection, genetic counseling (25% recurrence risk), and monitoring for retinitis pigmentosa.[42]

Polygenic Risk Scores:

Generated a PRS for 290 common variants associated with ANM. Women in the top 1% have fivefold higher POI risk. Rare variants with large effects (e.g., ZNF518A truncations reducing ANM by 5.6 years) have low carrier frequency (<0.1%), limiting population impact.[43]

Conclusion:

This paper reviews current advancements in genetics of ovarian aging and associated pathologies. Firstly, BMP15 and GDF9 act as dose-sensitive regulators, but large-scale analyses suggest that BMP15 mutations do not occur in POI patients as frequently as expected. Secondly, whole-exome sequencing identified nine genes involved in ANM, with DNA damage repair being the core mechanism responsible for ovarian aging. Thirdly, population-related mutation spectrums require personalized testing methods, as illustrated by low F508del mutation rate among Pakistani CF patients. Fourthly, cost-effective methods of diagnosis may help decrease expenses on genetic tests by as much as 80%. Fifthly, DDR genes are subject to a trade-off between prolonged oocyte survival and increased cancer risk, as evidenced by the correlation between late menopause and cancer predisposition caused by mutations in SAMHD1 and CHEK2 genes. Sixthly, a combination of different strategies can enhance the results of the analysis. Population diversity is not accounted for in current research.

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