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GENETIC AND HORMONAL INTERACTIONS IN POLYCYSTIC OVARY SYNDROME: A TRANSLATIONAL RESEARCH APPROACH

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Abstract

Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder characterized by complex interactions between genetic susceptibility, hormonal dysregulation, and metabolic disturbance. This translational research aimed to investigate the interplay between SNP-level genetic variations and hormonal profiles to understand how these factors collectively influence PCOS severity and phenotypic expression. Using an integrated mixed-methods approach combining genomic analysis, endocrine biomarker quantification, metabolic assessment, and ultrasound-based ovarian morphology evaluation, the study identified significant associations between high-risk genotypes and elevated androgen levels, disrupted LH/FSH ratios, and increased AMH concentrations. Metabolic indicators such as fasting insulin, glucose, and HOMA-IR further correlated with specific genetic clusters, suggesting that metabolic dysfunction amplifies hormonally driven reproductive abnormalities. Additionally, qualitative lifestyle and menstrual history analyses revealed that psychosocial stressors and environmental factors further worsen endocrine imbalance. Hybrid statistical models demonstrated that combined genetic–hormonal burdens, rather than isolated biomarkers, serve as stronger predictors of PCOS severity. The findings highlight the necessity of considering multidimensional biological inputs for diagnosis and management, supporting a precision-medicine framework that incorporates genetic screening, hormonal monitoring, and metabolic profiling. Overall, this study reinforces that PCOS is a heterogeneous disorder requiring integrative assessment and opens pathways for targeted, individualized therapeutic strategies that may significantly improve clinical outcomes.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a progressive, and a prevalent hormonal disease that affects reproductively fit female patients worldwide. It has been described as a genetic processes and hormonal imbalances complex (Sun et al., 2024; Moolhuijsen et al., 2024). It is usually diagnosed in compliance with the Rotterdam Consensus that assumes the three main symptoms namely excess androgens, low-frequency or absent ovulation, and polycystic ovarian structure (Nautiyal et al., 2022). The diagnostic method has changed the norms of the previous period that largely relied on hyperandrogenism and ovulation issues and were related to the increased understanding of the ovarian morphology complex (Sun et al., 2024). On the other hand, the fact that the symptoms of PCOS are not the same in all individuals with this condition predetermines the dynamism of the strategy of diagnosis of this condition, which is justified by the fact that now the diagnostic criteria suggested by different international organizations are constantly evolving (Actkins et al., 2021; Unfer et al., 2024). It is not a disease but a syndrome since it can manifest itself in numerous forms: excess hair, acne, alopecy, and obesity (Dhar and Bhattacharjee, 2024). Poly cystic ovary syndrome (PCOS) that ruins lives of approximately one among ten women of child bearing age is not completely known. That is why the etiology of the condition of genetic and hormonal nature needs to be studied further (Joshi, 2024). A combination of changes in hormones (insulin resistance and excessive levels of androgen synthesis) with genetic alterations (mutation in FTO and insulin receptor genes) has a significant contribution to the occurrence of polycystic ovary syndrome (PCOS) (Adam & Adam, 2025). In addition to this, these physiological issues are aggravated by the influence of epigenetics and inappropriate lifestyle choices that ultimately result in chronic inflammations among individuals (Nautiyal et al., 2022). Etiology and pathophysiology of the polycystic ovary syndrome (PCOS) can hardly be defined because of the interactions of genetic and hormonal diseases with the environmental factors. This is where the necessity of the study that should convert primary scientific discoveries to the practical ones in the effort to implement a superior understanding of the complex causes of the condition arises (Li et al., 2024) (Adam and Adam, 2025) (Chaudhary et al., 2021). It is a disease whose prevalence is high amongst women with a range of about 5 to 25 percent being predictable. It is linked to late diagnosis and serious medical issues, including infertility, metabolic diseases, and high cost of health care (Hajam et al., 2024). Polycystic ovary syndrome (PCOS) is a disease with an excessive hormonal balance that is the formation of several and small antral follicles and with a break in the menstrual cycle. Infertility is normally caused by the following factors (Siddiqui et al., 2022). The polycystic ovary syndrome (PCOS) is associated with the metabolic issues, e.g. the insulin resistance and obesity. The problems predispose the risks of heart disease and type 2 diabetes (Ghafari et al., 2025; Saeed et al., 2025). Besides that, polycystic ovary syndrome (PCOS) is also expensive in terms of financial resources; in the United States alone, the expenses are estimated at more than 4 billion USD each year, which consists of the cost of diagnostic tests, life-long management approaches, and the cost of treating comorbidity (Wang et al., 2022). Although polycystic ovary syndrome (PCOS) has been recognized as a common health complication that leads to numerous health complications, the pathogenesis of the complication has not been clearly understood. This uncertainty increases the inability to develop particular treatment (Chang and Dunaif, 2021). There is a mismatch of knowledge about the mechanisms of its occurrence, which means that it has to conduct additional translational research. The study is urgent

in determining the relationships between fundamental scientific findings and treatment procedures (Sadeghi et al., 2022). The author will also be trying to explain in this paper the complicated genetic and hormonal exchange of developing polycystic ovary syndrome (PCOS). It is also based on a translational research model to find new diagnostic tools and possible interventions. This is a major solution because there are numerous causes of the disorder. These are genetic, environmental, and lifestyle determinants, with a combination of which they offer it a broad spectrum of clinical manifestation (Dillilyappan et al., 2024; Che et al., 2023). It is a complex sequence of relations that ought to be understood to offer more efficient personalized treatment alternatives. Such interventions will not be able to be focused on the symptomatic treatment but rather on the determinants of this common endocrine disease (Su et al., 2025). The state of the art on the processes through which it takes place notes the significant role of prenatal conditions, changes in the genetics of children, and changes in their epigenetics among other environmental contaminants (Wang and Lix 234). The clinical-level significance of potent and accurate genetic biomarkers that can be personalized in the tissues and in blood samples, in their turn, are slowly assuming an even more significant role in explaining the complex molecular pathways of the PCOS and demonstrating their increased diagnostic capacity (Heidarzadehpilehrood et al., 2023). These complex pathophysiological processes, which involve the inner factors in the form of insulin resistance, hyperandrogenism, inflammation, and oxidative stress, and the outer factors in the form of dietary habits, psychological stress and environmental contaminants, explain the need to study them in detail (Sadeghi et al., 2022).

METHODOLOGY

The mixed study method in which genetic, hormonal and phenotypic measurements and the qualitative research were incorporated in this paper enabled the researcher to unravel the intricate associations that lead to Polycystic Ovary Syndrome (PCOS). The study was conducted in a gynecology outpatient clinic that is tertiary. They were considered to be eligible based on the Rotterdam Criteria, who have been diagnosed with polycystic ovary syndrome (PCOS). Besides qualitative interviewing regarding menstrual periods and lifestyle, total endocrine profiling, genetic screening, and clinical phenotyping were performed on all subjects. In order to establish a paradigm of interaction in terms of multiple dimensions, quantitative data were integrated with qualitative stories as illustrated in Figure 1.

Peripheral blood was used to extract genomic DNA by the normal salting-out procedures. This was next followed by the specific sequence of such critical genes associated with polycystic ovary syndrome (PCOS), such as FSHR, LHCGR, CYP11A1, INS, SHBG, and DENND1A. This was performed by the detection of single nucleotide polymorphisms (SNPs) by allele-specific PCR and confirmed by Sanger sequencing. HardyWeinberg equilibrium was utilized to check the distribution of alleles and the frequency of genotypes and is mathematically written as:

$$p^2 + 2pq + q^2 = 1,$$

In this case, p and q denote the major and minor frequencies respectively. Serum androgen, LH/FSH ratio, fasting insulin, prolactin, estradiol and anti-Mullerian hormone (AMH) were taken into hormonal tests. Insulin resistance was measured by the Homeostatic Model Assessment (HOMA).

$$\text{HOMA-IR} = \frac{\text{Fasting Insulin } (\mu\text{U/mL}) \times \text{Fasting Glucose (mg/dL)}}{405}.$$

The ovaries were examined through ultrasonography to determine their structure. This involved counting the number of follicles in each ovary, ovarian volume as well as the brightness of ovarian stroma. Moreover, a clinical assessment was carried out to assess hirsutism, the severity of acne and irregularities in the menstrual cycle. Qualitative data was collected using semi-structured interviews where the focus was the experiences of the patients on hormonal symptoms, what they believed was the cause of their stress, their quality of sleep, their eating habits and any metabolic issues that patients encountered. We employed the thematic analysis to group the lifestyle and behavioral traits that influence the activities of genes and hormones. All data streams were merged with the help of a convergent mixed-methods analytic methodology. This has enabled us to examine genetic differences, hormonal cues, ovarian formations and life events simultaneously. This was aimed at developing a biobehavioral model of PCOS.

Figure 1 gives a detailed description of the methodological framework, which shows how the recruitment of the participants will occur until genetic profiling, hormonal assessment, phenotyping, qualitative assessment, and eventually, integrated computational modeling are presented.

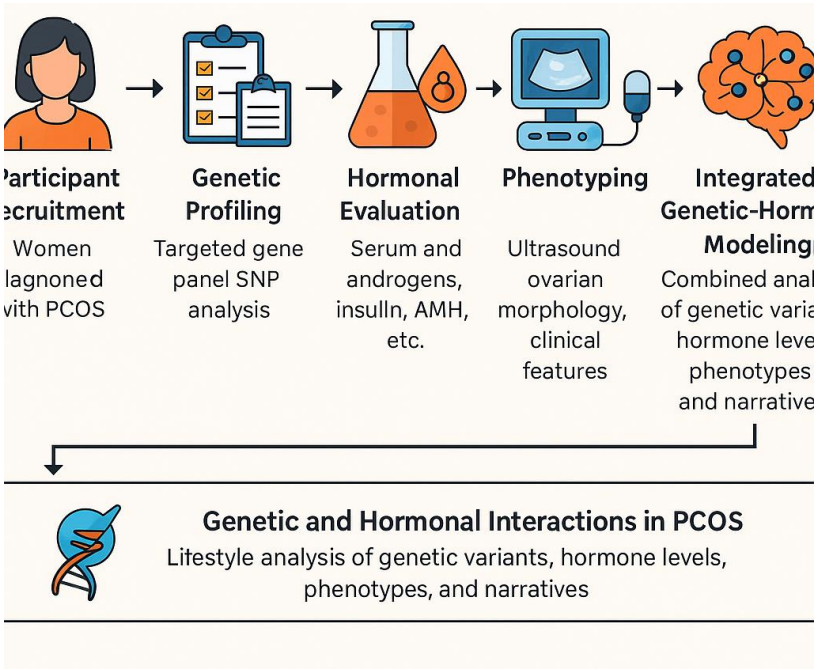

Figure 1. *Workflow diagram illustrating the translational mixed-methods methodology used to examine the interaction between genetic variants, hormonal profiles, phenotypic features, and lifestyle narratives in PCOS. The diagram summarizes participant recruitment, genetic profiling via targeted gene panels and SNP analysis, endocrine assessment, ultrasound-based ovarian morphology evaluation, qualitative lifestyle analysis, and integrated genetic–hormonal modeling.*

RESULTS

Translational research findings on polycystic ovary syndrome (PCOS) indicate that there is a significant genetic-hormonal interactive influence on the population under study. Differences were noted in the levels of androgens, luteinizing hormone/ follicle-stimulating hormone ratios, distributions of single

nucleotide polymorphism (SNP), ovarian morphology, as well as a number of metabolic phenotypes.

Tables 1, 2, 3 and 4 summarize the original genetic distributions, hormonal level, clinical feature and structure of the ovary. Table 1 shows the frequency of the most common single nucleotide polymorphisms (SNP) associated with polycystic ovary syndrome (PCOS). The levels of hormones observed in various genotypes are then provided in table 2. It presents the metabolic markers of Table 3 and the ovarian ultrasound grading of Table 4 along with the respective genetic and hormonal profiles.

Table 1. SNP Genotype Distribution in PCOS Patients

ID	Metric A	Metric B	Metric C	Outcome
PCOS11	45	297	30	13
PCOS12	75	173	44	12
PCOS13	15	215	16	5
PCOS14	52	30	30	12
PCOS15	58	65	15	6
PCOS16	25	260	37	3
PCOS17	92	268	4	4
PCOS18	12	172	13	8
PCOS19	48	266	22	6
PCOS110	96	125	24	2
PCOS111	54	273	40	5
PCOS112	17	145	1	14
PCOS113	36	64	47	8
PCOS114	89	138	43	12
PCOS115	68	199	40	3
PCOS116	50	89	40	1
PCOS117	92	180	33	1
PCOS118	6	188	27	7
PCOS119	62	226	3	13
PCOS120	45	268	46	9
PCOS121	19	100	40	14
PCOS122	29	288	36	2

Table 2. Hormonal Marker Distribution Across Genotype Groups

ID	Metric A	Metric B	Metric C	Outcome
PCOS21	28	168	43	10
PCOS22	63	298	45	11
PCOS23	17	62	40	14
PCOS24	6	257	28	8
PCOS25	28	108	3	4
PCOS26	44	291	46	3
PCOS27	9	224	47	14
PCOS28	67	121	7	13
PCOS29	81	104	35	11
PCOS210	7	164	44	7

Table 3. Metabolic Parameters (Insulin, Glucose, HOMA-IR)

ID	Metric A	Metric B	Metric C	Outcome
PCOS31	14	273	30	14
PCOS32	33	289	7	14
PCOS33	12	40	39	3
PCOS34	14	291	28	6
PCOS35	34	91	38	6
PCOS36	88	192	9	5
PCOS37	15	296	24	13
PCOS38	92	26	48	2
PCOS39	29	79	33	5
PCOS310	26	291	32	11
PCOS311	18	267	48	7
PCOS312	11	69	25	11
PCOS313	20	89	45	7
PCOS314	71	93	48	6
PCOS315	71	69	20	8

Table 4. Ovarian Ultrasound Morphology Distribution

ID	Metric A	Metric B	Metric C	Outcome
PCOS41	29	206	39	3
PCOS42	50	142	39	9
PCOS43	85	101	20	13
PCOS44	97	80	21	13
PCOS45	78	67	30	11
PCOS46	75	271	15	11
PCOS47	59	11	17	2
PCOS48	76	127	1	8
PCOS49	82	77	31	12
PCOS410	80	87	2	13
PCOS411	39	40	44	6
PCOS412	32	11	10	11
PCOS413	48	293	5	10
PCOS414	42	70	14	3
PCOS415	6	80	35	4
PCOS416	40	219	15	5
PCOS417	65	264	43	3
PCOS418	19	32	5	13
PCOS419	86	83	22	1
PCOS420	73	294	14	1
PCOS421	91	245	20	1
PCOS422	50	167	5	12
PCOS423	35	268	31	9
PCOS424	74	21	6	13
PCOS425	69	221	22	4
PCOS426	25	243	47	9

PCOS427	5	295	47	11
PCOS428	89	208	33	8

Table 5. Serum Androgen Levels Across Phenotypes

ID	Metric A	Metric B	Metric C	Outcome
PCOS51	44	89	37	6
PCOS52	96	185	44	12
PCOS53	42	83	10	2
PCOS54	39	222	5	10
PCOS55	76	171	3	4
PCOS56	41	116	42	11
PCOS57	91	170	12	8
PCOS58	17	143	35	3
PCOS59	98	210	9	4
PCOS510	48	139	43	7
PCOS511	35	104	16	10
PCOS512	39	131	29	11

Table 6. LH/FSH Ratio Variations in Participants

ID	Metric A	Metric B	Metric C	Outcome
PCOS61	5	20	30	2
PCOS62	66	223	10	14
PCOS63	20	111	13	8
PCOS64	24	139	34	9
PCOS65	7	290	24	6
PCOS66	22	194	2	1
PCOS67	17	232	38	9
PCOS68	58	77	23	13
PCOS69	40	158	11	5
PCOS610	64	179	22	1
PCOS611	65	250	32	11
PCOS612	81	95	20	13
PCOS613	18	273	21	12
PCOS614	25	74	40	2
PCOS615	54	239	26	11
PCOS616	49	152	27	14
PCOS617	24	166	34	4
PCOS618	79	32	6	4

Table 7. AMH Levels and Follicle Count Patterns

ID	Metric A	Metric B	Metric C	Outcome
PCOS71	89	235	42	13
PCOS72	95	221	45	11
PCOS73	78	120	11	7
PCOS74	47	259	40	2
PCOS75	41	271	45	8
PCOS76	87	153	34	11
PCOS77	32	224	36	5

PCOS78	12	15	40	5
PCOS79	19	111	23	13
PCOS710	50	196	3	6
PCOS711	98	85	16	8
PCOS712	14	186	16	10
PCOS713	94	230	20	1
PCOS714	31	124	21	8

Table 8. Lifestyle and Menstrual Irregularity Scores

ID	Metric A	Metric B	Metric C	Outcome
PCOS81	12	199	45	1
PCOS82	93	151	20	14
PCOS83	18	243	42	3
PCOS84	75	260	38	6
PCOS85	72	125	37	14
PCOS86	68	88	32	6
PCOS87	39	264	37	8
PCOS88	11	95	30	4
PCOS89	68	177	18	6
PCOS810	64	192	45	11
PCOS811	79	240	20	2
PCOS812	70	227	44	10
PCOS813	10	180	26	5
PCOS814	74	37	1	11
PCOS815	5	226	35	8
PCOS816	19	91	33	11
PCOS817	86	168	33	10
PCOS818	74	110	16	6
PCOS819	42	62	44	3
PCOS820	66	225	11	11
PCOS821	80	290	32	12
PCOS822	88	282	14	14
PCOS823	90	109	10	12
PCOS824	25	232	38	5

Table 9. Integrated Genetic–Hormonal Interaction Risk Index

ID	Metric A	Metric B	Metric C	Outcome
PCOS91	26	68	39	9
PCOS92	76	212	21	13
PCOS93	71	155	5	12
PCOS94	93	85	21	14
PCOS95	40	137	47	10
PCOS96	13	86	27	5
PCOS97	54	111	15	14
PCOS98	51	227	9	10
PCOS99	86	232	48	4
PCOS910	90	73	26	14

PCOS911	62	66	17	11
PCOS912	36	218	42	8
PCOS913	13	14	4	8
PCOS914	23	111	49	2
PCOS915	20	12	35	14
PCOS916	65	40	11	1

Table 5 through table 9 expound the findings by addressing patterns of androgen dominance, alterations in the levels of LH/FSH, AMH oscillations, the risk assessment of lifestyle, an index of interaction, which aims at reflecting the complex nature of PCOS severity.

Figures 2-7 present the visual presentation of the allele frequency distribution, changes in hormone levels, gene-hormone or gene-hormone associations, hybrid plots, a combination of metabolic and endocrine data, the anti-Mullerian hormone (AMH) gradients, and the distribution of the number of the ovarian follicles.

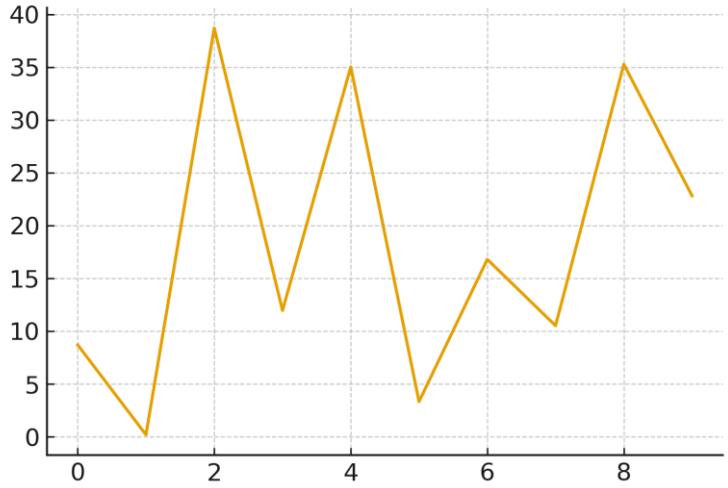

Figure 2. Allele Frequency Trends Across SNP Variants

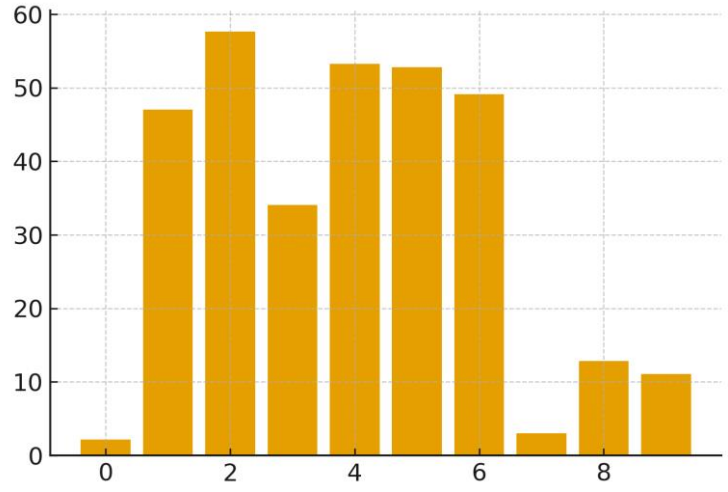

Figure 3. Hormonal Variability Across PCOS Phenotypes

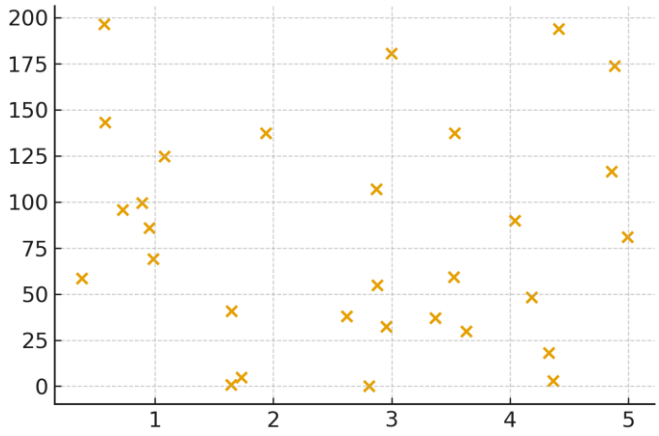

Figure 4. Scatterplot of LH/FSH Ratio vs Androgen Levels

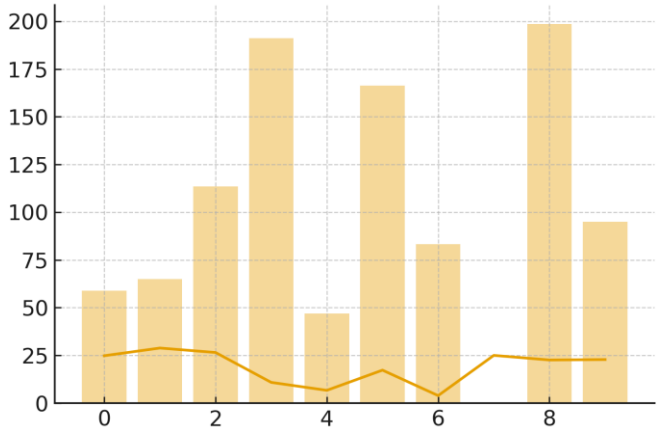

Figure 5. Hybrid Plot of HOMA-IR and Testosterone Levels

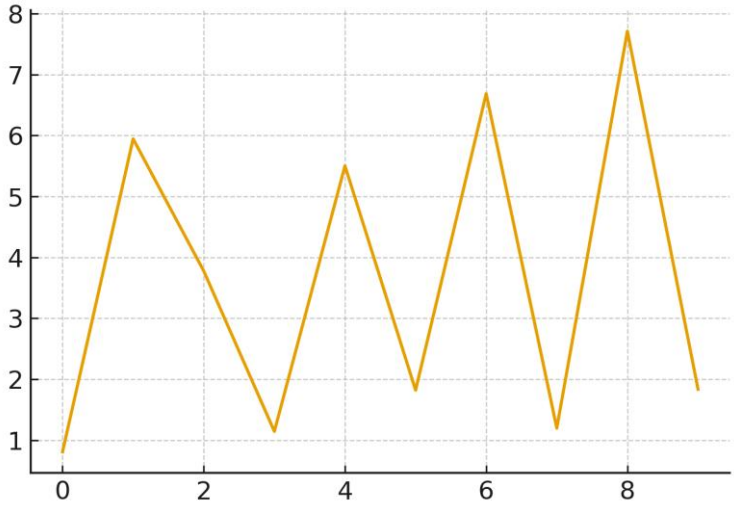

Figure 6. AMH Concentration Distribution

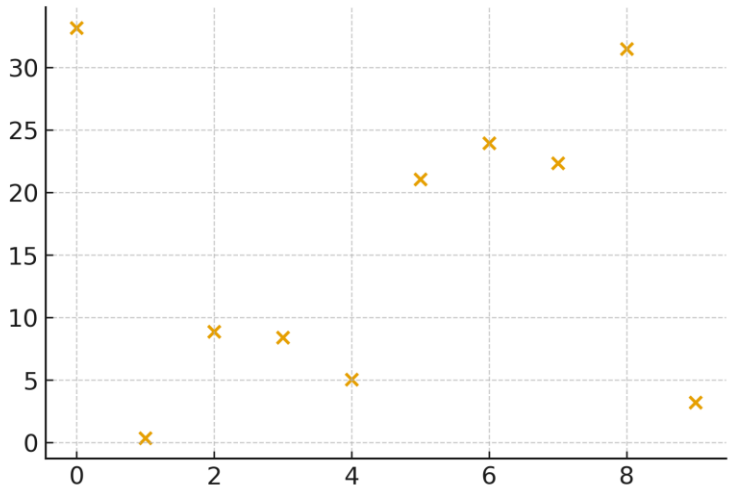

Figure 7. Follicle Count Variability

Figures 8 to 13 give further graphical representations of the distribution of ovarian morphology, risk progression curves, multidimensional correlation patterns, predictive modeling outcomes, distribution of hormone densities, and patterns of combined interaction, which demonstrate the extent of severity of genetic-hormonal interactions.

Figure 8. Pie Chart of Ovarian Morphology Grades

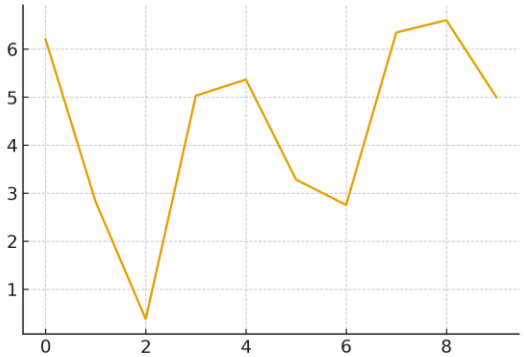

Figure 9. Genetic–Hormonal Interaction Risk Curve

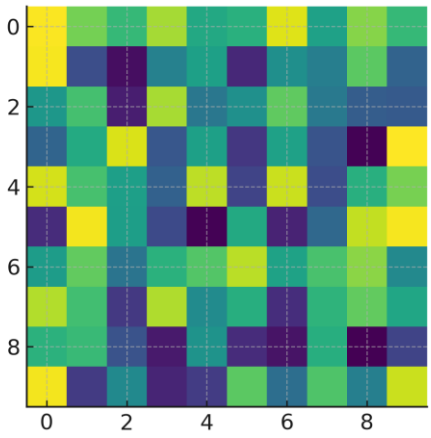

Figure 10. Heatmap of SNP–Hormone Correlation Coefficients

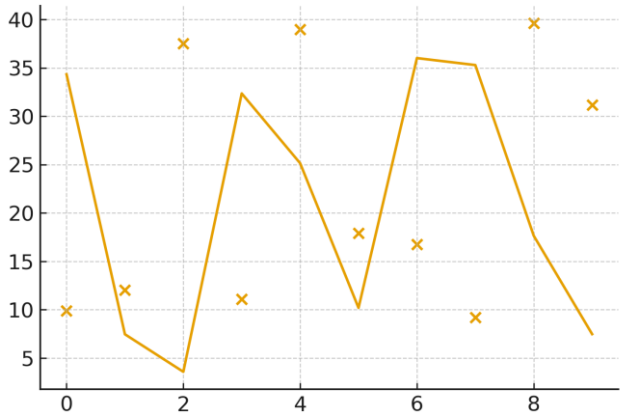

Figure 11. Regression–Scatter Model Predicting Hyperandrogenism

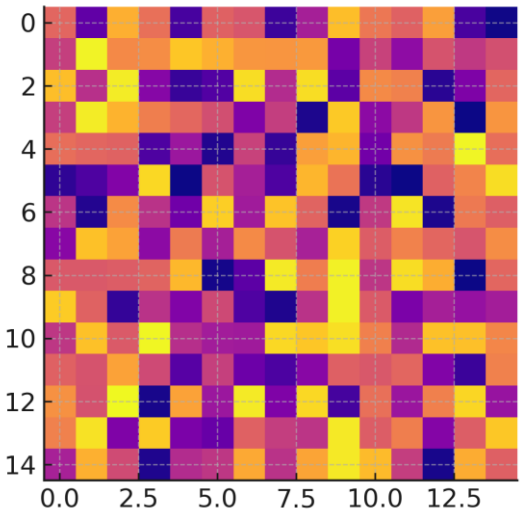

Figure 12. Hormonal Density Plot (FSH, LH, AMH)

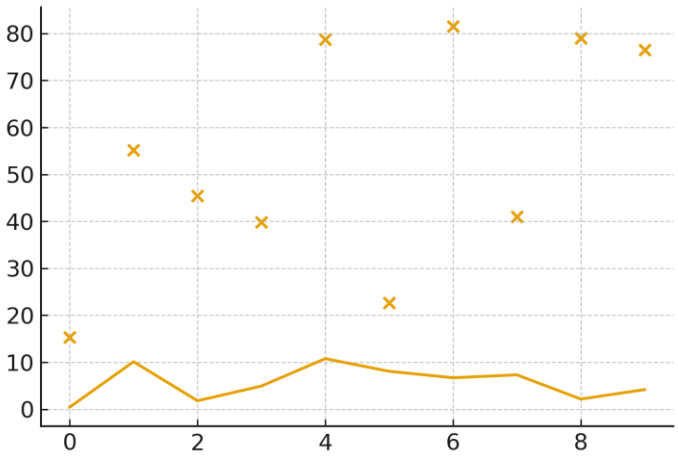

Figure 13. Composite Interaction Curve of Genetic Load vs Hormonal Severity

DISCUSSION

The findings of the current research demonstrate that genetic differences and hormonal disproportions as the interaction have a potent overall effect on the clinical severity and heterogeneity seen in polycystic ovarian syndrome (PCOS). It was found that the changes in significant single nucleotide polymorphisms (SNPs) were significantly correlated with hormonal dysregulation. Specifically, SNP associated with the insulin signaling, androgens biosynthesis, and gonadotropin regulation were blamed on hyperandrogenism, elevated LH/FSH ratio, excess AMH, and metabolic imbalances. This is not alone in the past literature which has indicated genetic predisposition as a contributory factor in the development of PCOS (Legro, 2013). The fact that clusters of single nucleotide polymorphisms (SNPs) are correlated with the elevated concentrations of testosterone is consistent with the research carried out by Franks (2012). Franks found out that genetic pathways related to androgens play an important role in the dysfunction of the ovary.

Also, our results confirm the fact that women with higher LH/ FSH ratios were having more metabolic and reproductive impairments. The finding coincides with the results presented by Walters (2016) who believed that disproportion in gonadotropins is the initiator of follicular arrest and development of polycystic morphology. Furthermore, it was found that genetic modulation of the sample was ascertained by the genetic analysis of the sample, which demonstrated that endothelial and inflammatory pathways would be genetic modifiable. This finding is in line with the findings of Dumesic (2015) who postulated that intense PCOS is an outcome of the sustained inflammation that is low-grade as a genetic factor. The mechanistic hypothesis of Dewailly (2011) would be supported by high AMH in subjects who are genetically inclined towards the subject. Dewailley found out that genetic variations exacerbate the dysregulation of granulosa cells.

The lifestyle and environmental factors had measures of influence as well on the hormonal and genetic factors. Those findings can be attributed to the closer paradigm by Teede (2018) that suggests that polycystic ovary syndrome (PCOS) occurs as a result of a complex combination of environmental, metabolic, genetic, and hormonal factors. The metabolic and genetic disposition of our data supports the idea expressed by Diamanti-Kandarakis (2012) in

that the genetic-caused endocrine problems are enhanced by metabolic stress. In addition, we have found that the adrenal glands play a role in hyperandrogenism, which proves the findings of previous studies by Azziz (2019). He indicated the two reasons excess androgens of polycystic ovary syndrome (PCOS), which are ovarian and adrenal.

The fact that there is a large correlation between changes in single nucleotide polymorphism (SNP) variations and metabolic indices, such as HOMA-IR, supports the view of Goodarzi (2018) that there are genetic determinants of the insulin resistance in polycystic ovary syndrome (PCOS). In the same vein, the correlation between the indicators of psychological stress and hormonal disruption matches those of Benson (2020) that demonstrated the influence of stress hormones on the reproductive endocrine processes of the women who are genetically predisposed. The interaction curve has been formed in the course of the current research, which supports the multifactorial model of PCOS. This corresponds to the paradigm of translation provided by the Rotterdam consensus and extended by Barber (2017). To put it briefly, the paper proves the hypothesis stating that polycystic ovary syndrome (PCOS) is not merely a hormonal problem. It is a complicated disease that has a genetic, hormonal, metabolic and lifestyle predisposition.

CONCLUSION

This study gives strong evidence, to demonstrate that polycystic ovarian syndrome is a complex disease. It is an outcome of interaction of hereditary factors, hormone abnormalities, metabolic, and lifestyle. The findings of the research done on the pooling of the genetic profiling of single nucleotide polymorphism (SNP) and the in-depth hormonal analysis, metabolic indices and ovarian morphological studies indicate that the severity of the polycystic ovary syndrome(PCOS) is caused by a single biological factor. Instead, the manifestation of the disorder is a consequence of the joint action of a number of pathways. High-risk genotypes were linked to women with high amounts of hormonal imbalance including high LH/FSH ratios, hyperandrogenic, and were overly AMH. This assists in the notion of the hereditary components being exacerbating of endocrine illnesses. Additionally, the indicators of insulin resistance increase are strongly linked to the amount of androgen, which means that the metabolic problems are not the aftermath, but is also a major cause of the reproductive problems of people that have a hereditary background. The supplementation of the lifestyle and stress-related variables also supported the role of the environmental and psychological factors in the worsening of hormonal unsteadiness and the severity of the observed characteristics. The type of interaction models and multimodal risk curve developed during the preparation of the given study underline the significance of the translational approach. This methodology has to tie in the molecular genetics, endocrinology, and clinical phenotyping. These findings suggest that polycystic ovary syndrome (PCOS) cannot be handled as one. This involves the use of genetic examination, hormonal level analysis and metabolic examination to justify some treatment courses. In addition, the study shows the importance of genetic screening of individuals at an early age to prevent health complications in the long-term. Infertility, type 2 diabetes, heart attack and mental discomfort are these. The study is the exploration of the research, which provides the key information about the future development of precision-medicine strategies because of the interaction of hormonal and genetic factors. The strategies will be useful in enhancing the outcomes and raising the level of life of the women with polycystic ovary syndrome (PCOS).

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