ASSOCIATION OF THE AR RS6624304 POLYMORPHISM WITH THE RISK OF POLYCYSTIC OVARY SYNDROME IN WOMEN OF REPRODUCTIVE AGE

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Ovarian hyperandrogenism in women of reproductive age represents one of the key pathogenetic components of polycystic ovary syndrome (PCOS), a multifactorial endocrine disorder characterized by ovulatory dysfunction, androgen excess, and metabolic disturbances. This phenotype is associated with dysregulated steroidogenesis in ovarian theca cells and reduced peripheral tissue sensitivity to insulin and steroid hormones (Franks et al., 2008; Goodarzi et al., 2011). Marked phenotypic heterogeneity of PCOS, including variability in obesity patterns, the severity of hyperandrogenic manifestations, and the risk of metabolic and cardiovascular complications, substantiates the search for molecular genetic determinants of the disorder, including immunogenetic mechanisms affecting regulation of the hypothalamic pituitary ovarian axis (Dunaif, 2006; Rosenfield and Ehrmann, 2016). Among the most promising candidates are polymorphisms in genes involved in androgen signaling and steroidogenesis.

The androgen receptor gene (*AR*) encodes a ligand dependent nuclear transcription factor located at Xq11–Xq12 and comprising eight exons. The AR protein contains an N terminal transactivation domain, a DNA binding domain, a ligand binding domain, and a nuclear localization region. Binding of testosterone or dihydrotestosterone triggers receptor translocation to the nucleus, dimerization, and interaction with androgen response elements in DNA, thereby regulating transcription of genes involved in reproductive function, androgen dependent dermatologic traits, and lipid and carbohydrate metabolism (Gelmann, 2002; Walters et al., 2012; Roy et al., 2017). AR expression is detected in the ovaries, hypothalamus and pituitary, endometrium, and adipocytes, and within the ovary the receptor contributes to folliculogenesis, steroidogenesis, and ovulation. In PCOS, clinical hyperandrogenism may reflect not only circulating androgen concentrations but also

increased tissue androgen sensitivity, which is related to AR expression levels and genetically determined regulatory features of the receptor (Franks et al., 2008; Palomba et al., 2015).

According to RegulomeDB and Ensembl, *rs6624304* is potentially located within transcription factor binding regions and may overlap epigenetically active loci, supporting its putative functional relevance.

Objective. To evaluate the association of the *AR rs6624304* polymorphism with the presence of PCOS in women of reproductive age in a case control study.

Materials and methods. Women of reproductive age were examined and assigned to a PCOS group (n=114) and a control group (n=80). PCOS was verified using clinical laboratory and ultrasound criteria. Genotyping of the *AR rs6624304 C/T* polymorphism was performed, followed by calculation of allele and genotype frequencies. Group differences in distributions were assessed using the chi square test, and odds ratios with 95% confidence intervals were calculated. Statistical significance was set at $p<0.05$.

Results. The distribution of *AR rs6624304* (*C>T*) alleles and genotypes differed significantly between women with PCOS and controls. The *T* allele was markedly more frequent in the PCOS group (40.35%, 92/228) than in controls (6.87%, 11/160) ($\chi^2=52.33$, $p<0.0001$) and was associated with increased odds of PCOS (OR=9.16, 95% CI 4.70–17.86). In contrast, the *C* allele predominated in controls (93.13% vs 59.65% in PCOS) and showed a protective association (OR=0.11, 95% CI 0.056–0.213).

Genotype analysis supported a T allele carriage model. The *C/C* genotype was substantially more common in controls than in the PCOS group (86.25% vs 42.98%) ($\chi^2=35.14$, $p<0.0001$; OR=0.12, 95% CI 0.058–0.251), consistent with a protective effect. The *C/T* genotype was significantly enriched in women with PCOS compared with controls (42.10% vs 13.75%) ($\chi^2=16.55$, $p<0.0001$; OR=4.56, 95% CI 2.18–9.63). The *T/T* genotype was observed in 14.92% of women with PCOS (17/114) and was absent in controls, indicating the strongest association with the disorder ($\chi^2=11.28$, $p=0.00078$).

Overall, rs6624304 showed a robust genetic association with PCOS in the studied cohort, with the T allele acting as a risk allele and the *C* allele demonstrating a protective

effect. Differences in allele and genotype frequencies support the potential relevance of this intronic AR variant as a molecular marker of PCOS susceptibility.

Conclusion. The *AR rs6624304* polymorphism was associated with the risk of PCOS. The *T* allele and the *C/T* and *T/T* genotypes were linked to increased likelihood of hyperandrogenic phenotypes, whereas the *C/C* genotype displayed a protective pattern and was associated with more favorable hormonal and metabolic characteristics. These findings support consideration of *AR rs6624304* as a functionally relevant marker that may influence regulation of AR expression and contribute to individual susceptibility to PCOS.