GENETIC VALIDATION OF THE NCCAHSCREENF SCREENING SCALE THROUGH MOLECULAR ANALYSIS OF STEROL 21-HYDROXYLASE GENE VARIANTS IN WOMEN OF FERTILE AGE

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Annotation: *This study evaluates the genetic validity of the NCCAHSCREENF screening scale through next-generation sequencing of the sterol 21-hydroxylase encoding gene in 215 fertile-age women, establishing robust genotype-phenotype correlations and confirming the scale's molecular-biological and population-level diagnostic relevance.*

Keywords: *sterol 21-hydroxylase gene, CYP21A2 variants, genetic validation, congenital adrenal cortex hyperplasia, genotype-phenotype correlation, next-generation sequencing, allele frequency, compound heterozygosity, fertile age, molecular diagnostics.*

Today, definitive confirmation of nonclassical congenital adrenal cortex hyperplasia requires identification of pathogenic variants in the sterol 21-hydroxylase encoding gene, designated CYP21A2, located at chromosomal locus 6p21.3 within the human leukocyte antigen genomic region. Population-based studies demonstrate that compound heterozygosity for mild and severe CYP21A2 variants accounts for 75 to 85 percent of nonclassical cases, yet such variants are identified in routine clinical practice in fewer than 30 percent of

phenotypically affected women, a discrepancy that reflects the absence of systematic genotype-guided screening tools adapted to fertile-age populations.

Genetic validation of the NCCAHSCREENF scale was conducted by enrolling 215 women stratified by screening score into two analytical groups. Genomic deoxyribonucleic acid was extracted from peripheral blood leukocytes using a salting-out protocol. Targeted next-generation sequencing of the complete CYP21A2 coding region and flanking intronic sequences was performed on an Illumina MiSeq platform with a minimum read coverage of 100 times. All identified variants were classified according to American College of Medical Genetics and Genomics 2015 criteria as pathogenic, likely pathogenic, variant of uncertain significance, likely benign, or benign.

Among 112 women with NCCAHSCREENF scores of 6 or above, pathogenic or likely pathogenic CYP21A2 variants were identified in 89 individuals, representing 79.5%. The most prevalent variant was the missense substitution p.Val281Leu (c.841G>T), detected in 54.5% of genetically confirmed cases, followed by the intronic variant c.293-13C>G in 18.0% and the p.Pro30Leu substitution in 11.2%. Compound heterozygosity constituted the predominant genetic architecture, observed in 67.4% of variant carriers - a pattern consistent with the mild enzymatic impairment characteristic of the nonclassical phenotype. Among 103 women with NCCAHSCREENF scores below 6, pathogenic variants were detected in only 7 individuals (6.8%), confirming strong genotype-phenotype concordance with the screening instrument. Receiver operating characteristic analysis using genetic diagnosis as the reference standard yielded an area under the curve of 0.93 (95% confidence interval: 0.89-0.97), with optimal sensitivity of 89.1% and specificity of 85.2% at the threshold score of 6. The p.Val281Leu allele

frequency of 0.31 in the study population aligned closely with published Central Asian and Eastern European population data, supporting external generalizability.

Genetic validation of NCCAHSCREENF confirms its biologically grounded diagnostic architecture, endorsing its application as a primary triage instrument to identify fertile-age women requiring targeted molecular genetic investigation for sterol 21-hydroxylase deficiency.

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