Allelic frequencies of CYP21A2 variants and genotype-phenotype correlations in a cohort of 660 CAH patients from Germany and Austria

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Context and Objective
Congenital adrenal hyperplasia (CAH) due to a CYP21A2 defect leads to salt wasting (SW), simple virilizing (SV), or non-classical (NC) phenotypes depending on residual 21-hydroxylase (21-OH) function. Phenotype correlates with genotype in 80-90%. We set out to test prediction of CAH phenotype based on genotype classification.

Patients and Methods
Patient data from 37 centres were retrieved from a central data base as part of a German quality assurance program (AQUAPE*) within the German Association for Pediatric Endocrinology and Diabetes (DGKD). Allelic frequency and distribution of deletions/conversions (del/con) and the 11 most common CYP21A2 mutations were analysed in 660 homoygous or compound heterozygous CAH patients (Figure 1). Associated clinical phenotypes (n=515) as classified by the treating physician were compared with predicted phenotypes from genotype classification according to magnitude of residual 21-OH function (group Null=0%; group A=2-2%; group B=2-5%; group C=20-60%). Moreover, patients were stratified according to time at diagnosis (pre-screening versus screening), including analysis of genital virilization (Prader stages) in girls.

Results
Allelic frequency of mutations was comparable to previous studies, with del/con (29.6%) and I2G (29.2%) being the most common, followed by 1I27N (13.1%) (Table 1). Severe genotypes (Null and A) correlated well with expected phenotypes (SW in 97% and 91%, respectively), whereas weaker genotypes (B and C) showed poorer correlation (SV in 45% and NC in 57%, respectively) with higher clinical severity than expected, specifically associated with 1I27N and P30L. In C genotypes, this was underlined by the degree of virilization (Prader Stage >1 in 28%; Figure 2). SW was ascertainment in 90% of screened patients with classical CAH as compared to 74% of pre-screening patients, whereas Prader stages did not differ between these two groups (Table 3).

Figure 1. Breakdown of eligible patients according to genotype/phenotype availability and timepoint at diagnosis

Phenotypes SW, SV, NC

515 patients with genotype Null, A, B, or C (D excluded)

Pre-screening/Screening

327 patients Pre-screening (212f)
188 patients with Screening (89f)

Table 1. Frequency (%) of CYP21A2 variants in our population as compared to published data. Common mutations were present in 1285/1320 alleles (96.8%)

Table 2. CAH phenotype distribution according to genotype in pre-screening and screening patient groups

Discussion

- In this largest European CAH series reported to date, allelic frequencies of CYP21A2 mutations were comparable to former studies.
- Prediction was accurate, i.e. in line with expected phenotype, in del/con and severe mutations (genotypes Null and A), but unreliable in weaker genotypes (genotypes B and C).
- By treating all screening-positive babies as SW-CAH from the start, current management strategies might result in overrating of clinical phenotype.
- CAH severity should be regarded as a continuum requiring ongoing reevaluation of phenotype and flexibility in clinical management.

References

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Figure 2. Genital virilization (Prader stages) in CAH girls according to genotypes

Table 3. Prader stages in pre-screening and screening female CAH patients

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AQUAPE is supported by NOVO Nordisk Germany