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Genotype–phenotype correlation in 1,507 families with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency

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Over the last two decades, we have extensively studied the genetics of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency (CAH) and have performed 8,290 DNA analyses of the *CYP21A2* gene on members of 4,857 families at risk for CAH—the largest cohort of CAH patients reported to date. Of the families studied, 1,507 had at least one member affected with one of three known forms of CAH, namely salt wasting, simple virilizing, or nonclassical CAH. Here, we report the genotype and phenotype of each affected patient, as well as the ethnic group and country of origin for each patient. We showed that 21 of 45 genotypes yielded a phenotypic correlation in our patient cohort. In particular, contrary to what is generally reported in the literature, we found that certain mutations, for example, the P30L, I2G, and I172N mutations, yielded different CAH phenotypes. In salt wasting and nonclassical CAH, a phenotype can be attributed to a genotype; however, in simple virilizing CAH, we observe wide phenotypic variability, particularly with the exon 4 I172N mutation. Finally, there was a high frequency of homozygous I2G and V281L mutations in Middle Eastern and Ashkenazi Jewish populations, respectively. By identifying the predominant phenotype for a given genotype, these findings should assist physicians in prenatal diagnosis and genetic counseling of parents who are at risk for having a child with CAH.