High Incidence of Heterozygous ABCC8 and HNF1A Mutations in Czech Patients With Congenital Hyperinsulinism.

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Abstract

CONTEXT: Congenital hyperinsulinism of infancy (CHI) represents a group of heterogeneous disorders characterized by oversecretion of insulin from pancreatic β-cells causing severe hypoglycemia.

OBJECTIVE: We studied the distribution of genetic causes of CHI in a Czech population.

METHODS: Countrywide collection of patients with CHI included 40 subjects (12 females, median age of diagnosis, 1 wk [interquartile range, 1–612 wk]). We sequenced the ABCC8, KCNJ11, GLUD1, GCK, HADH, UCP2, SLC16A1, HNF4A, and HNF1A genes and investigated structural changes in the ABCC8 gene. We functionally tested novel variants in the ABCC8 gene by Rb(86+) efflux assay and novel variants in the HNF1A gene by transcriptional activation and DNA-binding tests.

RESULTS: We found causal mutations in 20 subjects (50%): 19 carried a heterozygous mutation while one patient was homozygous for mutation in the ABCC8 gene. Specifically, we detected 11 mutations (seven novel) in ABCC8, one
novel mutation in KCNJ11, five mutations (two novel) in HNF1A, two novel mutations in HNF4A, and one in GCK. We showed a decrease of activation by diazoxide in mutant KATP channels with novel ABCC8 variants by 41–91% (median, 82%) compared with wild-type (WT) channels and reduced transcriptional activity of mutant HNF1A proteins (2.9% for p.Asn62Lysfs93* and 22% for p.Leu254Gln) accompanied by no DNA-binding ability compared with WT HNF1A.

CONCLUSION: We detected a higher proportion of heterozygous mutations causing CHI compared with other cohorts probably due to lack of consanguinity and inclusion of milder CHI forms. Interestingly, HNF1A gene mutations represented the second most frequent genetic cause of CHI in the Czech Republic. Based on our results we present a genetic testing strategy specific for similar populations.


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