112.00

CONGENITAL HYPOTHYROIDISM IN CZECH POPULATION: SCREENING FOR MUTATIONS IN CANDIDATE GENES WITH FOCUS ON PARTICULAR PHENOTYPES

E. Al Taji[1, 2], H. Biebermann[2], P. Ambrugger[2], N. Haufs[2], Z. Limanova[3], O Hnikova[1], J. Lebl[1], A. Grueters[2], H. Krude[2]

[1]Department of Paediatrics, 3rd Faculty of Medicine, Charles University, Prague, Czech Republic
[2]Paediatric Endocrinology, Department of Paediatrics, Otto-Heubner Centre, Charite, Humboldt University,
Berlin, Germany [3]rd Medical Department - Clinical Department of Endocrinology and Metabolism, 1st Faculty of Medicine, Charles University, Prague, Czech Republic
evataji@hotmail.com

Background: The aim of this study was to get a first insight into molecular mechanisms that underlie congenital hypothyroidism in Czech population by providing a systematic screening for mutations in coding regions of candidate genes involved in thyroid development and function, with a focus on particular phenotypes.
Objectives and methods: 193 children were included to the study. Mutation screening techniques DHPLC (TPO), SSCP (TPO, PAX-8) and restriction enzyme analysis (TPO) were used. Coding regions of NKX2.5, NKX2.1/TTF-1, TTF-2 and HEX gene were directly sequenced in patients with associated congenital anomalies.
Results: Screening for mutations in PAX-8 gene revealed a new mutation in exon 3 (G155C) leading to a substitution in a highly conserved residue of the DNA-binding domain (R52P). The heterozygous index case was not detected in the neonatal screening and was diagnosed due to his family history of a non-autoimmune hypothyroid mother and grandmother in the first year of life when he was asymptomatic. The same R52P mutation was detected in his mother and grandmother. Compound heterozygous mutations in TPO gene were detected in 2 patients with eutopic normal or goitrous thyroid glands.
Conclusions: In a population based cohort the mutation detection rate in known candidate genes for congenital hypothyroidism is very low even in a phenotype-focused screening study. The identification of a new PAX8 mutation in a three-generation pedigree confirms the dominant inheritance of mild hypothyroidism due to PAX8 haploinsufficiency.