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The incidence and genetic analysis of congenital hypothyroidism in Guangxi, China and the predictors for differentiating permanent and transient congenital hypothyroidism

Chunyun Fu[1], Haiyang Zheng[1], Shiyu Luo[1], Shujie Zhang[1], Jiasun Su[1], Qi Yang[1], Xuyun Hu[1], Jin Wang[1], Yun Chen[1], Rongyu Chen[1], Xin Fan[1], Jingsi Luo[1], Chuan Li[1], Bobo Xie[1], Jiale Qian[1], Shang Yi[1], Yunli Lai[1], Shaoke Chen[1], Xuefan Gu[2] and **Yiping Shen[1,3]**

[1]Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region, PR China

[2]Xinhua Hospital-Shanghai Jiaotong University School of Medicine, China

[3]Boston Children's Hospital-Harvard Medical School, USA

Objectives: To investigate the incidence of congenital hypothyroidism (CH) based on the newborn screening program in Guangxi Zhuang Autonomous Region, China, to analyze the genetic factors of CH and to analyze the predictors that might allow for an early differentiation between permanent (P) and transient (T) congenital hypothyroidism (CH).

Methods: Data from newborn screening program over a six year period (January 2009 to January 2015) at Guangxi Maternal and Child Health Hospital are analyzed. Blood samples were collected on filter paper between 72 h and 7 days after birth, TSH level was measured by time-resolved fluorescence assay. Individuals with increased TSH (TSH≥8 mIU/l) levels detected by newborn screening were recalled for further evaluation. Serum TSH, FT3 and FT4 were determined by electrochemiluminescence assay. Diagnosis of CH is based on elevated TSH levels (TSH≥10 mIU/l) and decreased FT4 levels (FT4<12 pmol/l). Patients with elevated TSH levels and normal FT4 levels (normal range12-22 pmol/L) were diagnosed as subclinical congenital hypothyroidism (SCH). Permanent or transient CH was determined using results of thyroid function tests after temporary withdrawal of L-T4 therapy at approximately 2-3 years of age. All exons and their exon-intron boundary sequences of the 12 known CH associated genes in 66 CH patients were screened by next-generation sequencing (NGS).

Results: Among 1,238,340 infants in the newborn screening program, 14443 individuals were recalled for reevaluation (re-call rate1.18%), 1039 and 668 individuals were subsequently determined to have SCH and CH respectively, thus a prevalence of 1:1192 and 1:1854 for SCH and CH. Of the 668 patients with CH, 131 patients were diagnosed with permanent CH (PCH), and 132 patients were diagnosed with transient CH (TCH), the other 405 patients are too young to determine their subtypes. NGS analysis of 12 known CH associated genes revealed that 33 patients (33/66, 50%) were detected to have at least one potentially functional variant. 21, 9, 2, 1, 1, 1 and 1 patients were found to have potential pathogenic variants in DUOX2, TG, PAX8, SLC26A4, TSHR, GLIS3 and TPO genes, respectively. Patients with PCH during the first few years required an increasing dose of L-T4, whereas patients with TCH required decreased doses of L-T4. The TSH levels at diagnosis and the dose of L-T4 used were significantly higher in permanent CH cases than in transient cases. The FT4 levels at diagnosis were significantly lower in permanent CH cases than in transient cases. The TSH levels at diagnosis, FT4 levels at diagnosis and L-T4 doses at 90 days were evaluated as predictors and their accuracy at their respective optimal cutoffs were determined to be 60.6%, 66.7% and 93.9%, respectively.

Conclusion: The CH incidence in Guangxi Zhuang Autonomous Region is slightly higher (1:1854) compared to the worldwide levels (1/2000-1/4000). The permanent CH and transient CH ratio is close to 1, thus the estimated PCH incidence is 1/3708, which is similar to reported worldwide average incidence (1/3000). 50% CH patients had at least one potential pathogenic variant. We found relatively high frequency of DUOX2 (31.8%) and TG (13.6%) mutations in our cohort. The L-T4 dose required at 90 days (>30μg/day) has the highest predictive value for PCH. Earlier differentiation of PCH and TCH helps to determine appropriate treatment course.

fuchunyun2008@sina.com