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Mutation screening of the *GLIS3* gene in a cohort of 592 Chinese patients with congenital hypothyroidism

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ABSTRACT

Objectives: Defects in the human GLI-similar 3 (*GLIS3*) gene are reported to be a rare cause of congenital hypothyroidism (CH) and neonatal diabetes. The aim of this study was to examine the prevalence of *GLIS3* mutation among CH patients in the Guangxi Zhuang Autonomous Region of China and to define the relationships between *GLIS3* genotypes and clinical phenotypes.
Methods: Blood samples were collected from 592 patients with CH in Guangxi Zhuang Autonomous Region, China, and genomic DNA was extracted from peripheral blood leukocytes. All exons of the *GLIS3* gene with their exon-intron boundaries were screened by next-generation sequencing (NGS) and CNVplex®. Chromosomal microarray analysis (CMA) was performed to detect the existence of the adjacent gene deletion.
Results: NGS and CNVplex® analysis of *GLIS3* in 592 CH patients revealed two different variations in two individuals (2/592, 0.3%). Patient 1 was the paternal allele of 9p24.3p23 heterozygous deletion including the whole *GLIS3* gene, and patient 2 was heterozygous for c.2159G > A (p.R720Q) *GLIS3* variant combined with compound heterozygous *DUOX2* mutations (p.R683L/p.L1343F).
Conclusions: Our study indicated that the prevalence of *GLIS3* variations was 0.3% among studied Chinese CH patients. Multiple variations in one or more CH associated genes can be found in one patient. We found a novel *GLIS3* variation c.2159G > A (p.R720Q), thereby expanding the variation spectrum of the gene.

1. Introduction

Defects in the human GLI-similar 3 (GLIS3) gene (NM_001042413) are reported to be one of the rare cause of congenital hypothyroidism (CH) and neonatal diabetes [1–4]. GLIS3, a member of the GLI-similar zinc finger protein family encoding for a nuclear protein with 5 C2H2-type zinc finger domains, maps to chromosome 9p24.3-p23. The protein is expressed early in embryogenesis and plays a critical role as both a repressor and activator of transcription. It is specifically involved in the development of pancreatic β-cells, the thyroid, eye, liver, and kidney although tissue expression occurs to a lesser extent in the heart, skeletal muscle, stomach, brain, adrenal gland, and bone [2,5]. *GLIS3* gene was also reported to be a candidate imprinted gene, which is paternally expressed in human placenta [6].

Patients with *GLIS3* mutations presented with a wider phenotype consisting mainly of neonatal diabetes and CH, in addition to multiple features involving different organs [7]. Up to now, 19 CH patients caused by *GLIS3* mutations were reported with an autosomal recessive inheritance pattern, and partial gene deletions as the most common type of *GLIS3* mutations [7–11]. Given the rarity of this condition, the genotype-phenotype relationships has not yet been fully established, and little is known about its mutational spectrum and prevalence among Chinese CH patients. Here we performed the *GLIS3* gene screening in a cohort of 592 patients with CH in Guangxi Zhuang Autonomous Region, China.

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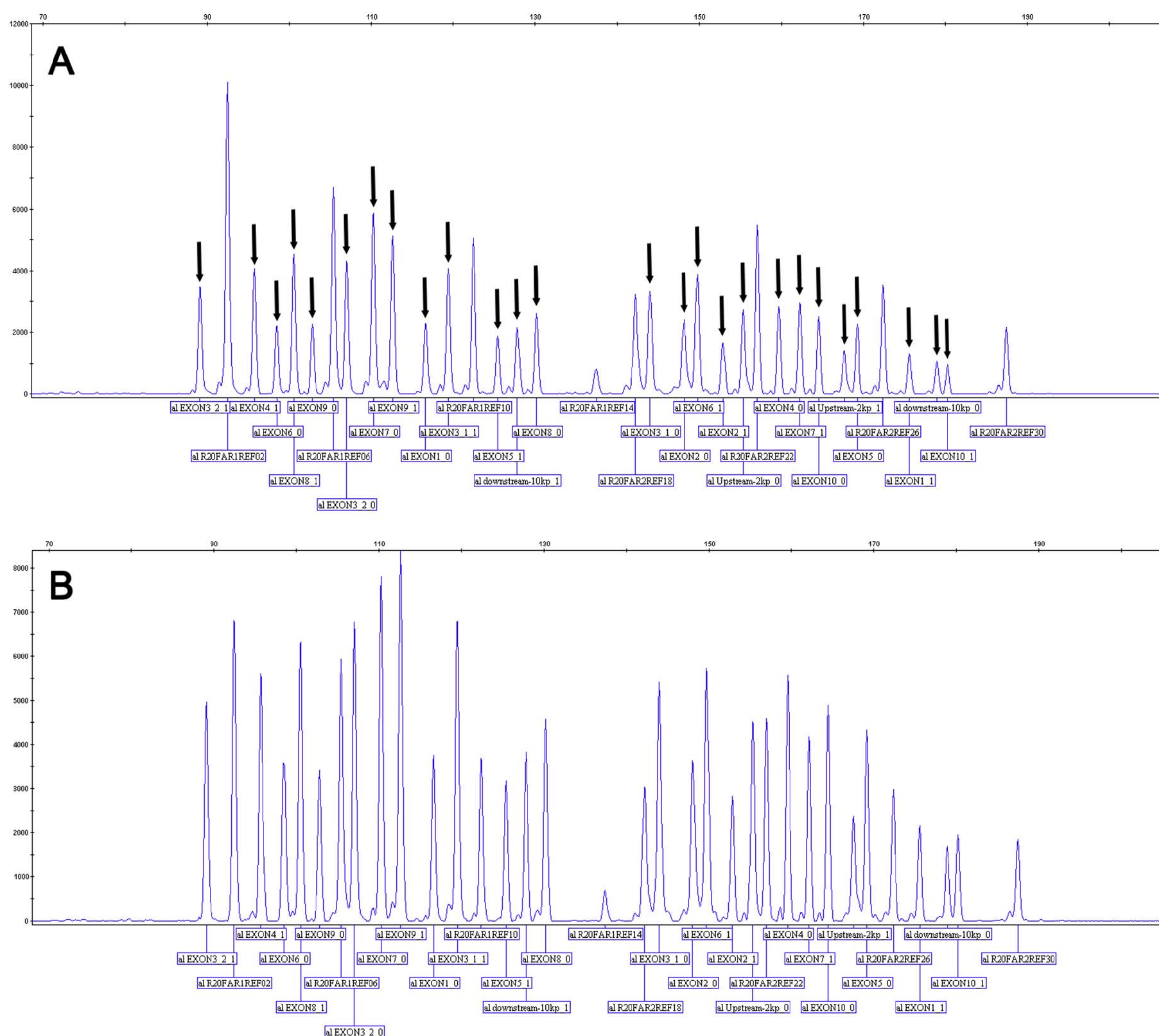

Fig. 1. CNVplex® analysis of GLIS3 gene. A) patient 1 was detected to be heterozygous for Exons 1-11 del/- *GLIS3* mutation; B) normal control.

2. Materials and methods

2.1. Patients

A total of 592 patients were enrolled in this study, who were identified through newborn screening among 1,143,000 newborns in the Guangxi Zhuang Autonomous Region of China from June 2009 to June 2016. The methods of newborn screening of CH have been described in detail previously [12,13]. This study was approved by the local Medical Ethics Committee of the Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region. Written informed consent was obtained from the parents of the patients.

2.2. Mutation detection and interpretation

Peripheral venous blood samples were collected from the patients. Genomic DNA was extracted from peripheral blood leukocytes using QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's protocol. All exons of the *GLIS3* gene with their exon-intron boundaries were screened by NGS and CNVplex®. CNVplex® is based on the MLPA method, it can be used for the detection of chromosomal alterations [14]. When the whole *GLIS3* gene deletions were found, chromosomal microarray analysis (CMA) was later performed in order to detect the presence of the adjacent gene deletion. The methods and workflows of NGS [15], CMA [16] and CNVplex® [14] have been described in detail previously.

In addition, a cohort of 600 ethnicity-matched healthy participants was used to assess the variant frequencies in normal control. All control participants had normal FT4 and TSH levels.

2.3. Sanger sequencing

Sanger sequencing was used to validate the variants identified from next-generation sequencing.

3. Results

3.1. Next generation sequencing and CNVplex® analysis of GLIS3 and other CH associated genes

In this study, we identified two different *GLIS3* variants in two individuals. Sequencing of other CH candidate genes in the 2 patients with the *GLIS3* variations showed that patient 1 was heterozygous for Exons 1-11 del/- *GLIS3* mutation (Fig. 1), and patient 2 was heterozygous for c.2159G > A (p.R720Q) *GLIS3* variation combined with compound heterozygous *DUOX2* mutations [c.2048G > T (p.R683L)/ c.4027G > T (p.L1343F)]. All missense variants were confirmed by Sanger sequencing (Fig. 2). The present study identified a novel *GLIS3* variation c.2159G > A (p.R720Q) that was not detected in our normal control population and classified as variant of uncertain significance (VUS) according to the ACMG/AMP guideline (Table 1).

CMA analysis was performed using the Illumina HumanSNPcyto-12

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