

AB022. *Genetic analysis of 11 Sudanese families with congenital hypothyroidism

Reham Shareef¹, Yui Watanabe², Matthew K. Creech¹, Dana M. Bis³, Stephan Züchner², Mohamed A. Abdullah¹, Alexandra M. Dumitrescu⁴, Samuel Refetoff⁴, Roy E. Weiss²

¹Department of Paediatrics and Child Health, Faculty of Medicine, University of Khartoum, Al Khurtum, Sudan; ²Department of Medicine, ³Department of Human Genetics and Genomics, University of Miami Miller School of Medicine, FL, USA; ⁴Departments of Medicine, Pediatrics and Committee on Genetics, The University of Chicago, IL, USA

Abstract: The aim of this study was to investigate the genetic cause of CH in Sudanese families. We obtained DNA of 51 individuals, including 27 affected children, from 11 unrelated Sudanese families with CH. Proband was identified by the presence of low IQ, goiter or short stature. The geographic Sudanese origin were 5 from the North, 1 from the East, 3 from the West and 1 from the South and 1 was unknown. Five families had consanguineous marriages. Whole exome sequencing (WES) was carried out on each affected child and unaffected mother. We analyzed the results with published data of single nucleotide polymorphism (SNP) array in Sudanese. Principal component analysis (PCA) was performed on the 260 Sudanese data and we compared mutation frequencies in the candidate genes for CH between the Sudanese and all populations from the genome aggregation database (gnomAD). WES identified 4 novel mutations in the *TG* gene, 2 missense, 1 splicing and 1 nonsense variants, including c.7021G > A, c.4816+1G > T, c.6989T > A and c.7655C > G; 1 novel frameshift mutation in the *DUOX2* gene, c.1395_1396delCC; 1 novel missense mutation in the *SLC5A5* gene, c.1042T > G; 1 novel missense mutation in the *TSHB* gene, c.141T > G and 1 rare mutation in the

TPO gene, c.2578G > A. Each affected child harboring the mutation was homozygous for the variant. Functional in silico prediction algorithms (SIFT or PolyPhen2) suggested that the 5 missense mutations were deleterious. Seven of the 11 probands had low IQ and 8 had goiter. Of the 4 probands with normal IQ, 3 had the following homozygous mutations: *TG* (missense), *TG* (splicing) and *TSHB* (missense). PCA revealed a clear distinction between NE and SW Sudanese. The CH mutation carriers appear to fall in-between the two major population groups. However, given the observed allelic heterogeneity of CH a founder effect was not present, rather the increased frequency might point out better access to clinical services associated with the group with CH. Still, the studied Sudanese samples had significantly higher mutation frequency in the *TG* gene with 645 SNPs compared to the populations of mixed ethnic origin (mutant allele frequency; 0.1512 vs. 0.1406, P<0.01). In conclusion, 7 novel mutations in the *TG*, *DUOX2*, *SLC5A5* and *TSHB* genes and 1 rare mutation in the *TPO* gene were identified in 11 Sudanese families with CH. The group with CH represented different sub-population from NE or SW Sudanese. *TG* gene mutations occurred at higher frequencies in the Sudanese than other populations represented in widely used genetic databases.

Keywords: XXXXXXXX

Footnote

*, mutations in multiple genes cause congenital hypothyroidism (CH). The most common cause of CH worldwide is thyroid dysgenesis (85%) followed by dyshormonogenesis (10–15%). CH commonly causes mental retardation in Sudan because of lack of neonatal screening. It was reported that the predominant etiology of CH in the Sudan was dyshormonogenesis (62%), however the genetic cause is unreported.

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