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Homozygous deletion of the *TSH beta subunit* gene causes congenital secondary hypothyroidism in a consanguineous family of Turkish descent

Pia Hermanns[1], Cherise Klotz[2], Robert Couch[3], Norma Leonard[2], Joachim Pohlenz[1]

[1)]*Department of Pediatrics, Johannes Gutenberg University Medical School, Mainz, Germany,*

[(2)]*University of Alberta Hospital, Edmonton, Canada,* [(3)]*Walter Mackenzie Health Sciences Centre, Edmonton, Canada*

Background: A 6-week-old male was admitted for investigation of prolonged jaundice. The pregnancy was unremarkable with a normal at term delivery. The neonatal screening was unremarkable. The boy was born to consanguineous parents of Turkish descent. At presentation serum levels of thyrotropin, T4 and T3 were low and prolactin slightly elevated. Venous TSH was undetectable low. Central hypothyroidism was diagnosed and a *TSH beta* gene mutation was hypothesized.

Methods: Using different PCR protocols, we were unable to amplify both coding exons of the boy's *TSHbeta* gene, which suggested a deletion of the coding sequence. An *array comparative genomic hybridization (aCGH)* was performed using specific probes around the *TSHbeta* gene locus on chromosome 1.

Results: The propositus was homozygous for a 6 kb deletion spanning all exons, as well as parts of the 5' untranslated region of the *TSHbeta* gene. Both parents were heterozygous for this deletion.

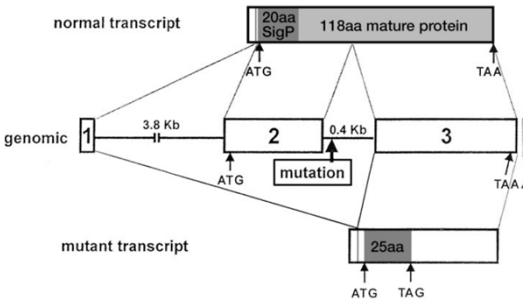

Fig. 1: Cartoon of *TSHbeta* gene locus. 9 different mutations have been described so far. Most frequently identified mutation is C105VfsX9. In patients of Turkish descent mostly the splice site mutation IVS1_2SD+5G>A has been found.

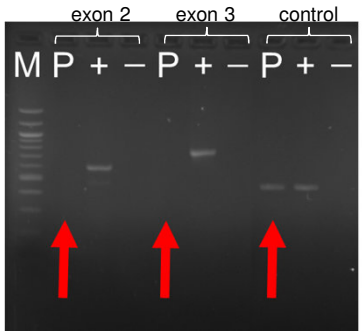

Fig. 2: Agarose gel analysis of PCR roducts. No amplification of the coding exons of the *TSHbeta* gene in the patient, but PCR of healthy control worked well. A control region was amplified successfully in the patient as well as the control. P: patient, +: positive control; -: negative control, control: control region

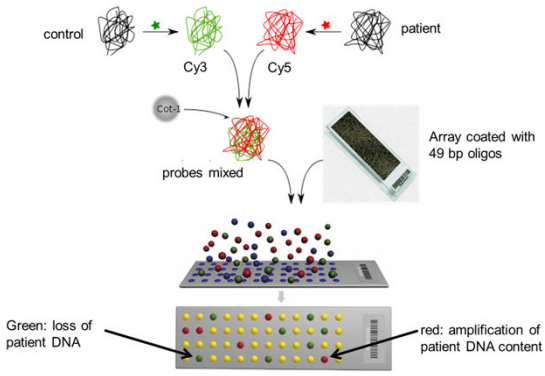

Fig. 3: Cartoon of aCGH analysis. Custom made chromosome 1 specific array from Agilent with 59 878 probes in duplicate has been designed. A genomic region of 10.5 kbp of the *TSHbeta* gene locus was covered. The genomic DNA was enzymatically labelled with Cy3- and Cy5-dUTPs, respectively.

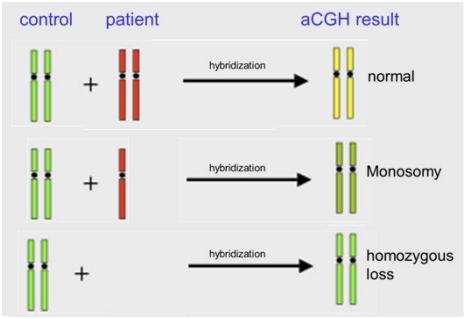

Fig. 4: Schematic of possible aCGH results. If there is an equal amount of patient and control DNA then a yellow signal will be detected. If there is one chromosome missing in the patient DNA then a greenish signal will be seen. If there is a total loss of patient DNA then a green signal will be visible.

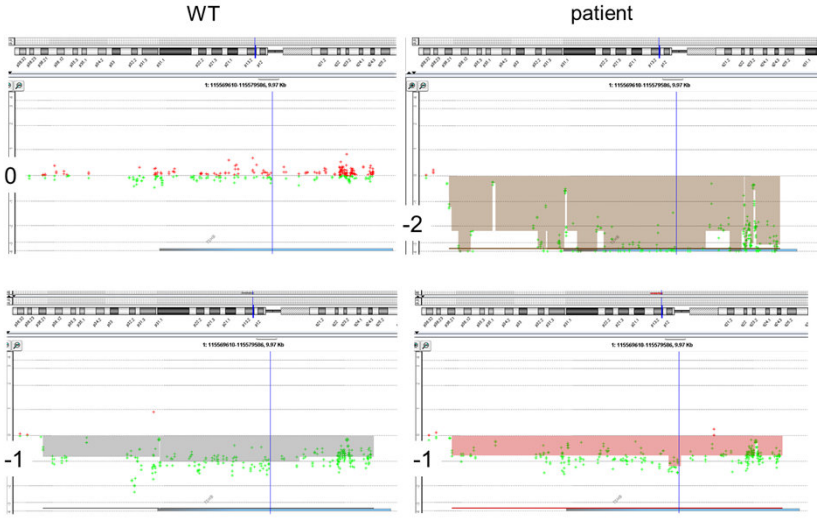

Fig. 5: aCGH result of the analysis of the *TSHbeta* gene locus of the patient and his parents. Upper pannel: On the left the WT control shows an equal distribution of red and green signals (0). On the right site the analysis of the patient is shown. A total loss of the *TSHbeta* gene region can be seen (-2). Lower pannel: The aCGH results of the patient's parents is shown. Both parents show a heterozygous (-1) loss of DNA in the *TSHbeta* gene locus.

Summary:

An aCGH analysis identified a deletion of 6.3 kbp of the *TSH beta* gene locus in our patient. All exons including 5' promoter regions of the *TSH beta* gene are deleted. The patient carries a homozygous deletion, whereas both parents are heterozyous for this deletion.

Conclusion:

This is the first report of a large deletion in the *TSH beta* gene. The deletion was confirmed by aCGH analysis. The aCGH is a very valuable tool to detect deletions or duplications. It can be applied to identify the molecular cause of other diseases as well. Isolated congenital secondary hypothyroidism (ICSH) is rare but important, since most patients with ICSH are diagnosed later in life, which results in severe growth failure and intellectual disability. Our study shows again that neonatal screening for both, fT4 and TSH is desirable. It would help to prevent symptoms of hypothyroidism in affected individuals.

Dr. Pia Hermanns, Children's Hospital, University of Mainz, Molecular Pediatric Endocrinology, AG J. Prof. Pohlenz, Langenbeckstr. 1, 55101 Mainz, Germany, pia.hermanns@unimedizin-mainz.de