DUOX2 Deficiency in Quebec : From Life-threathening Compressive Goiter in Infancy to Lifelong Euthyroidism

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TOPIC: Thyroid

CONTEXT

Congenital hypothyroidism caused by DUOX2 deficiency has a wide range of clinical presentations and phenotype-genotype correlations are not always straightforward[1].

OBJECTIVES

To describe four children from Quebec with bi-allelic DUOX2 variants and widely variable phenotypes.

METHODS

Case series of four children seen at the endocrinology service of the Ste-Justine Hospital or the Centre Hospitalier de l'Université Laval for evaluation of thyroid function. Clinical and biochemical data were analyzed and molecular genetic studies were performed to document the etiology of thyroid dysfunction. In an attempt to explain the variability of their clinical presentation, exome sequencing targeting 12 other genes implicated in thyroid function was performed in all index cases.

RESULTS

Patient 1 is a 13 week-old boy who presented with a rapidly developing goiter resulting in severe tracheal compression and overt hypothyroidism of recent onset. Respiratory distress was successfully managed with levothyroxine replacement

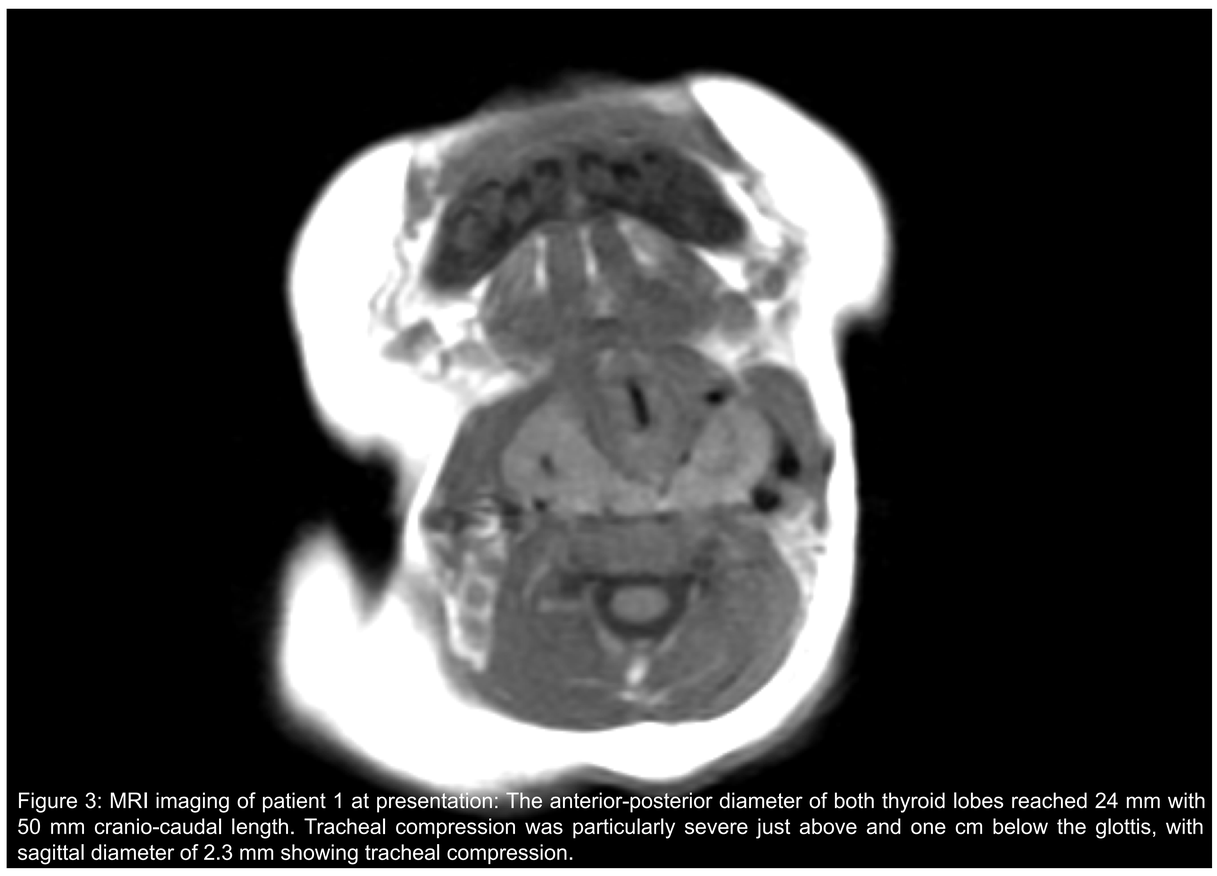

Figure 3: MRI imaging of patient 1 at presentation: The anterior-posterior diameter of both thyroid lobes reached 24 mm with 50 mm cranio-caudal length. Tracheal compression was particularly severe just above and one cm below the glottis, with sagittal diameter of 2.3 mm showing tracheal compression.

Patient 4 was the only one with a positive neonatal congenital hypothyroidism screening result. He presented with mild persistent CH (TSH 22 mU/L, N< 15), as typically associated with bi-allelic DUOX2 variants. His sister was found to harbor homozygous mutations and, apart from a TSH level in the normal high range at neonatal screening (TSH 14 mU/L), is euthyroid. His mother bears the same DUOX2 variants as her son yet is lifelong euthyroid.
All other parents were heterozygous and euthyroid.

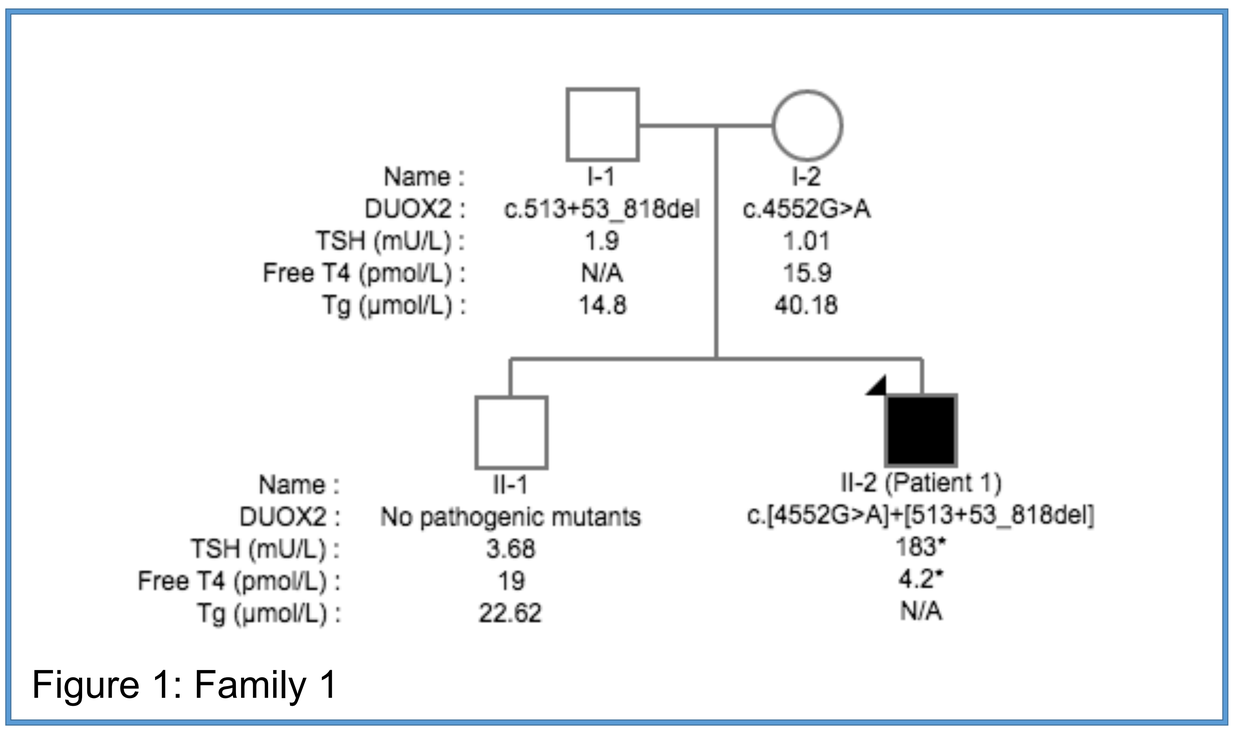

Figure 1: Family 1

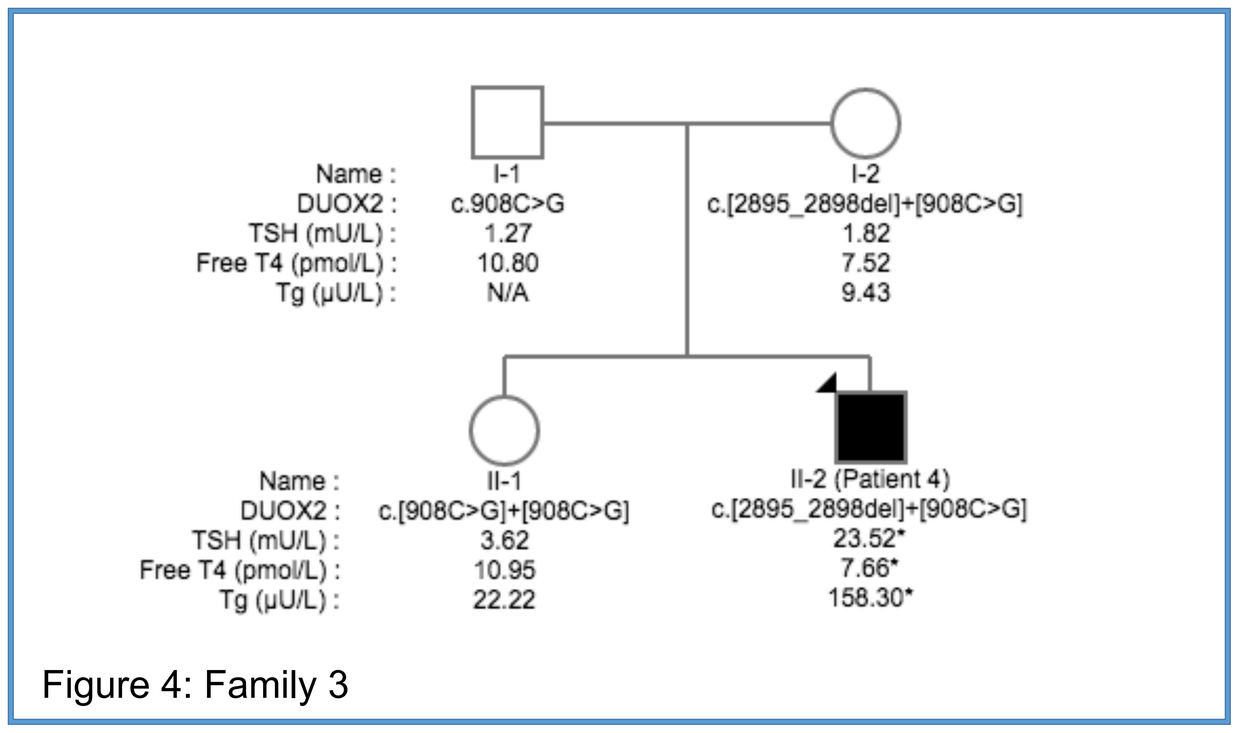

Figure 4: Family 3

Patients 2 and 3 are siblings who harbor the same compound heterozygous mutations of DUOX2, yet presented with greatly discordant phenotypes: the sister had overt hypothyroidism at 14 months (TSH 93 mU/L, fT_4 3.96 pmol/L) which evolved to mild hyperthyrotropinemia at 15 years (TSH 7.22 mU/L, fT_4 8.12 pmol/L), while the brother has lifelong euthyroidism

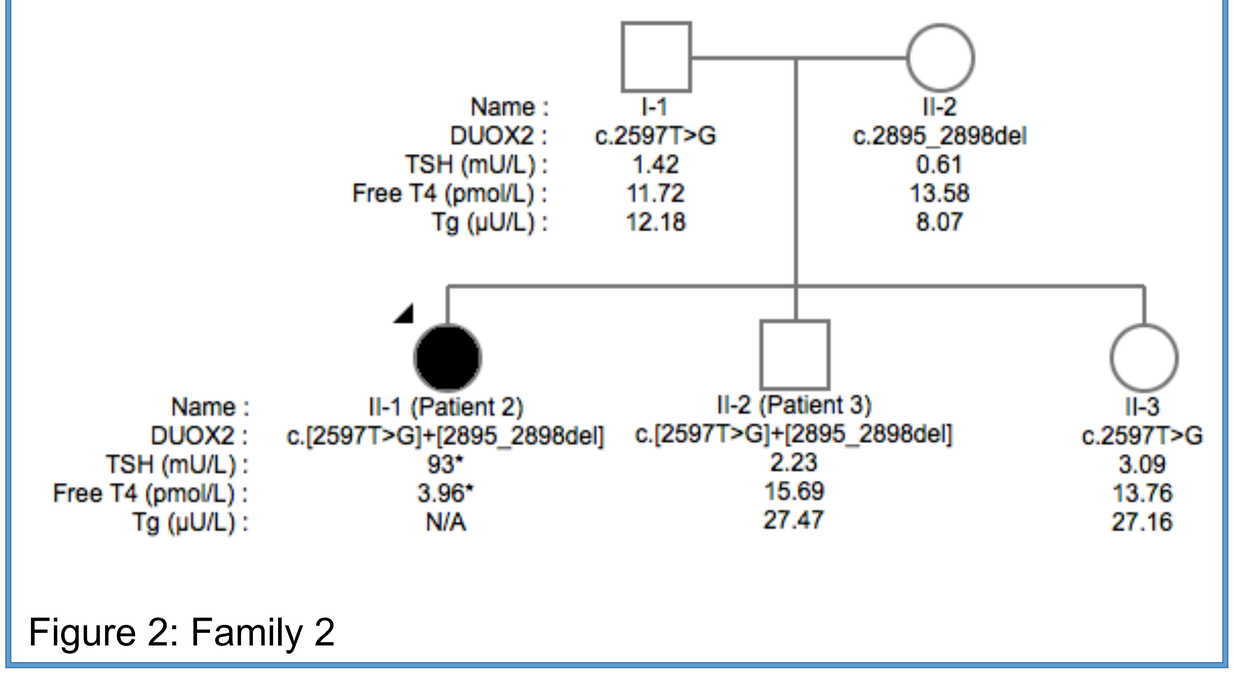

Figure 2: Family 2

CONCLUSIONS

Clinical expression of bi-allelic variants of DUOX2 is widely heterogeneous. Patient 1 is the first reported case of an infant with DUOX2 deficiency presenting with a compressive goiter with secondary respiratory distress, rapid diagnosis and medical treatment of which alleviated the need for surgery. Targeted exome study was not able to identify genetic modifiers of DUOX2 activity explaining the important inter and intra-pedigree phenotypic variability.

REFERENCES

Muzza M, Fugazzola L. Disorders of H2O2 generation. *Best practice & research Clinical endocrinology & metabolism.* 2017;31(2):225-240.

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