Germline mutation c.4031C>T (S1344L) in the RNase Illa domain of DICER1 causes GLOW syndrome

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Fig 1. Patient characteristics. a. Ear pits of left helix. b. Frontal portrait of patient showing a broad, furrowed, forehead, mild hypertelorism and large mouth c. Profile portrait of patient showing macrocephaly and ear pits of the right helix. d. CT scan of patient showing pulmonary cysts. e. Chest X-ray of patient showing scoliosis.

Background

DICER1 is an endoribonuclease central to the generation of microRNA (miRNA) important for embryogenesis and early somatic development. DICER1 syndrome - a pleiotropic cancer predisposition syndrome, includes benign and malignant tumors with reduced penetrance e.g. pleuropulmonary blastomas, cystic nephromas, Sertoli-Leydig cell tumors and multinodular goiter. The most common mechanisms underlying DICER1 syndrome are germline loss of function mutations combined with somatic in trans mutations in hotspot residues of the RNase IIIb domain, impairing maturation of essential tumor suppressor miRNAs.¹ GLOW (Global developmental delay, Lung cysts, Overgrowth, Wilms tumor) is a novel DICER1 related syndrome previously described in two patients with mosaic germline mutations affecting the catalytic cleft of the RNase IIIb domain.² Recently, in vitro cell experiments have shown that RNase Illa-Ser1344 site mutations cause miRNA-5p depletion analogous to RNase IIIb hotspot mutations³ and that the RNase IIIb mutations described in GLOW syndrome result in the activation of PI3K/AKT/mTOR signaling via modulation of specific miRNA populations.⁴ Here, we present a boy with a de novo heterozygous c.4031C>T (S1344L) variant diagnosed with macrocephaly, lung and renal cysts, polydactyly, autism, intellectual disability, scoliosis, multiple nevi, ear pits and Wilms tumor in early childhood. He is the first child from healthy, non-consanguineous parents with no family history of malignant or benign tumors, intellectual disability, cysts or other anomalies.

Methods

Genomic DNA was extracted from peripheral blood leucocytes, oral mucosa and skin biopsy using standard protocols. Standard 30x whole genome sequencing (WGS) and bioinformatic analysis were performed at Clinical Genomics, SciLifeLab, Stockholm, using the Illumina HiSeq X Ten platform. Frequency of the mutant allele was quantified using QuantStudio 3D Digital PCR and commercially available TagMan® assay for DICER1 c.4031C>T mutation (Applied Biosystems, CA, USA).

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³Vedanayagam J et al. (2019) Nat Com ⁴Klein SD et al. (2020) Microrna, 9(1):70-80.

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Conclusions

We show that heterozygous germline mutation c.4031C>T (S1344L) in the RNase IIIa domain of DICER1 is compatible with life, causing a phenotype that strongly resembles two previously reported children with GLOW syndrome. Our findings expand the GLOW syndrome spectrum and support recent results from integrated genetic analysis and in vitro cell experiments that RNase Illa-Ser1344 site mutations induce a similar pattern of miRNA dysregulation as cancer hotspot mutations of RNase IIIb, suggesting a novel mechanism behind Wilms tumor development. Further studies are warranted to explain the overgrowth phenotype, intellectual disability and high risk of Wilms tumor in these patients.



Fig 2. Digital PCR results from skin biopsy. Detected level of c.4031C>T was found to be approximately 50% in all samples analyzed i.e. blood, buccal cells, saliva, skin. Blue cluster represents mutant allele, red signals represent reference allele and green signals display both mutant and reference alleles. Yellow cluster represents the wells where no plification signal was detected

Results

WGS identified a de novo heterozygous c.4031C>T variant in the RNase IIIa domain of DICER1. The mutation was confirmed and quantified with digital PCR, revealing a mutant allelic frequency of 50% in the analyzed blood as well as the buccal cell sample and skin biopsy, thus confirming the heterozygous, non-mosaic state of the mutation.

