Title: Homozygous loss-of-function mutations in *SLC26A7* cause goitrous congenital hypothyroidism.

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ABSTRACT

Objective Congenital hypothyroidism (CH), the commonest neonatal endocrine disorder, is caused by either maldevelopment of the gland (dysgenesis) or failure of hormone biosynthesis in a structurally intact gland (dyshormonogenesis). Recent studies suggest that dyshormonogenic causes may be more important than previously recognised. We hypothesized that genetic analyses of cases lacking pathogenic mutations in known dyshormonogenesis genes might identify novel causes of defective thyroid hormone biosynthesis.

Methods 13 cases with CH from Pakistani, Turkish and Finnish families were investigated, of whom eight exhibited goitre. Four cases underwent perchlorate discharge tests, exhibiting preserved iodide uptake and partially defective iodide organification (14.5-47% discharge). Thyroid biochemistry demonstrated a greater reduction in circulating Free T4 concentrations than Free T3. All cases harboured homozygous truncating mutations in the anion transporter *SLC26A7* (c.679C>T, p.R227* families A, B and C, c.1893delT, p.F631Lfs*8 families D E and F). We characterized the mutant SLC26A7 proteins and investigated the thyroidal role of SLC26A7.

Results *SLC26A7* mRNA is most highly expressed in human and murine thyroid. *SLC26A7* c.679C>T was predicted to undergo nonsense mediated decay whereas SLC26A7 p.F631Lfs*8 would destabilise the carboxyterminal STAS domain required for membrane localization. Consequently, whereas wild-type, GFP-tagged SLC26A7 localized to the membrane in transfected cells, p.F631Lfs*8-SLC26A7 remained intracellular. Although homologous to the iodide transporter pendrin, SLC26A7 did not mediate iodide transport in vitro.

Slc26a7 null mice exhibited goitrous hypothyroidism, with decreased intrathyroidal TG-bound and free thyroid hormones suggesting defective hormone biosynthesis, partially reversed by iodide supplementation. Unlike in humans, radioiodine uptake was reduced with normal perchlorate discharge. Additionally, only *Slc26a7* null mice exhibited distal renal tubular acidosis.

Conclusion Despite differences in effects (thyroidal uptake, perchlorate discharge, renal acidosis) of SLC26A7 deficiency in humans versus mice, both species exhibit profound goitrous CH, likely due to impaired intrathyroidal iodide availability. We therefore delineate a critical role for SLC26A7 in human and murine thyroid hormone biosynthesis.