MedicalXpress

New cause of thyroid hormone deficiency discovered

November 12 2012

International researchers, including a team at McGill University, have discovered a new cause for thyroid hormone deficiency, or hypothyroidism. This common endocrine disorder is typically caused by problems of the thyroid gland, and more rarely, by defects in the brain or the pituitary gland (hypophysis). However, a new cause of the disease has been discovered from an unsuspected source and is reported in the journal *Nature Genetics*. The scientists, led by McGill Professor Daniel Bernard, Department of Pharmacology and Therapeutics in the Faculty of Medicine, identified a new hereditary form of hypothyroidism that is more prevalent in males than in females. This sex bias shone a light on where to look for the underlying cause.

"Our collaborators in the Netherlands had been following a family in which two cousins had an unusual syndrome of hypothyroidisim and enlarged testicles," said Prof. Bernard. "Using state-of-the-art DNA sequencing technologies, we identified a mutation in a gene called immunoglobulin superfamily, member 1 (IGSF1), in both boys and their maternal grandfather. As one of few labs in the world studying this gene, we initiated a collaboration to determine whether the observed mutation might cause the disorder. At the time, the IGSF1 gene was known to be active in the pituitary gland, but its function was a mystery".

"Shortly after, we were contacted independently by a second group of researchers, studying a second family, in which two young brothers suffered from hypothyroidism and also harbored a mutation in the IGSF1 gene, though it was a different mutation than that observed in the

Dutch family," said Prof. Bernard, "The fact that there were two unrelated families with the same male-biased clinical syndrome and mutations in the same gene strongly suggested that the mutations played a causal role in hypothyroidism".

The groups reached out to researchers in the Netherlands, the UK, Italy and Australia who were following similar families and found that affected males all had mutations in their IGSF1 gene. Overall, the team identified 11 families with 10 different mutations in IGSF1.

"We went on to show that mutations in IGSF1 block the protein it encodes from moving to the cell surface, where it normally functions", explained Beata Bak, McGill Ph.D. student and the paper's co-first author. "We also observed that the pituitary glands of mice lacking IGSF1 had reduced levels of the receptor for a brain-derived hormone known as thyrotropin-releasing hormone (TRH). If we think of TRH as a key, then its receptor is the lock into which the key fits to produce its effects. Our results suggest that in the absence of IGSF1, the pituitary gland becomes less sensitive to the brain's instructions to secrete thyroid-stimulating hormone (TSH). As a result, the thyroid gland receives a reduced impetus to produce thyroid hormones".

The group's findings are significant as IGSF1 mutations cause a variable, though principally mild, form of hypothyroidism that would likely escape detection by most perinatal thyroid function screening methodologies. In addition, since the IGSF1 gene is highly polymorphic, there may be many individuals (boys and men, in particular) in the general population with presently undetected, but clinically significant hypothyroidism.

Symptoms of the disease include fatigue, weight gain, cold sensitivity, and muscle weakness. If left untreated, hypothyroidism increases the risk of developing heart disease. In infants, hypothyroidism can cause

neurodevelopmental delay and, in extreme circumstances, cretinism.

"A simple test could identify carriers of IGSF1 gene mutations or variants who might benefit from thyroid hormone replacement therapy. Our results highlight a fundamental role for this protein in how the brain and pituitary gland control thyroid function and therefore the whole body metabolism. We hope our work will inspire new research on IGSF1's function in the pituitary gland under various physiological and pathophysiological conditions", said Prof. Bernard.

Provided by McGill University