

## Searching for Genetic Causes of Congenital Hypothyroidism

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Donald Zimmerman, MD, and other Children's Memorial investigators are helping to unravel the molecular genetics in the etiology of congenital hypothyroidism, as part of an ongoing world-wide research collaboration led by Peter Kopp, MD, at Northwestern University's Feinberg School of Medicine. Characterizing the numerous genetic factors involved in congenital hypothyroidism may help future genetic counseling and offer insights into various postnatal thyroid diseases, such as thyroid cancer.

"Currently, we can account for a miniscule percentage of what is really causing congenital hypothyroidism. Defects in thyroid development are responsible for most cases of congenital hypothyroidism and we know very little about this process," says Zimmerman, Head of the Endocrinology Division at Children's Memorial and Professor of Pediatrics at Feinberg School of Medicine. To date, mutations implicated in congenital hypothyroidism have been found in the proteins encoded by 3 genes involved in thyroid development, including the paired box transcription factor PAX8 and the thyroid transcription factors TTF1 and TTF2.

PAX8 is expressed in the thyroid diverticulum, as well as in the developing kidney, midbrain and hindbrain. Defects in PAX8 have been associated with an abnormally positioned and incompletely developed thyroid gland.

TTF1 is involved in the thyroid gland development and in transcriptional control of receptor genes for thyroglobulin, thyroperoxidase, and thyrotropin. It is also expressed in the development of the pituitary gland, the forebrain, and the lung. Congenital thyroid dysfunction and impaired lung maturation have been linked to chromosomal deletions of the TTF1 locus.

TTF2 is expressed during development of the thyroid and the anterior pituitary. Mutations in TTF2 have been found in infants born without a thyroid gland and with a cleft palate, choanal atresia, bifid epiglottis, and spiky hair.

"Due to parsimony of nature, certain classes of proteins, such as PAX8 and the other thyroid transcription factors, are used for development of different tissues," explains Zimmerman. "We are using an observation that there is an increased frequency of associated anomalies to inform us about malfunctions in other proteins that may be responsible for errors in prenatal development of the thyroid and other organs."

According to the American Academy of Pediatrics, other congenital malformations are found in approximately 10% of infants with hypothyroidism, compared to 3% in the general population. Cardiovascular anomalies, including pulmonary stenosis, atrial septal defect, and ventricular septal defect, occur most frequently with congenital hypothyroidism. Down syndrome and congenital anomalies of the nervous system and eyes also have been reported in children born with hypothyroidism.

To identify more genes with mutations that may lead to abnormal thyroid development, Children's Memorial physicians send to Kopp's laboratory DNA samples from infants who have hypothyroidism and also other congenital deficits that are not a result of thyroid hormone deficiency. They also analyze the samples, trying to define a promising phenotype and help identify the genes that may be worthwhile to pursue in closer study. This indirect search for genetic causes of congenital hypothyroidism is a useful strategy, since researchers first need to pinpoint candidate genes before analyzing genetic expression profiles in all infants with hypothyroidism. ■

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