# 1 in 5 patients with suspected congenital hypothyroidism or resistance to thyroid hormone receive a molecular diagnostic result using multi-gene panel testing

Alicia Scocchia,[a] Kimberly Gall,[a] Julie Hathaway,[a] Christèle de Soiuch,[a] Archie Taylor,[a] Johanna Huusko,[b] Manuel Bernal,[b] Inka Saarinen,[b] Jennifer Schleit,[a] Jussi Paananen,[b] Samuel Myllykangas,[b] Juha Koskenvuo[b]

[a] Blueprint Genetics Inc, Seattle, WA USA
[b] Blueprint Genetics, Espoo, Finland

## Introduction and Study Aim

- Congenital hypothyroidism (CH) and resistance to thyroid hormone syndrome (RTH) are conditions impacting production or use of thyroid hormones. Although CH and RTH present differently, some clinical overlap exists, including possible developmental delay if untreated and variation in serum thyroid stimulating hormone and free T4.
- The molecular findings within an unselected referral population receiving genetic testing for an indication of either suspected CH or RTH have not been characterized to date.
- In this study, we assessed the diagnostic utility of next-generation sequencing (NGS) panel tests for individuals with suspected CH or RTH and provide an overview of the molecular diagnostic findings identified in this population.

## Methods

- We reviewed clinical reports for 117 patients who underwent NGS panel testing at Blueprint Genetics. All patient samples were submitted for testing with an indication of suspected CH or RTH (Table). NGS panel testing included sequence and copy number variant (CNV) analyses from a clinically validated exome assay targeting coding exons (+/- 20 bp from the intron/exon boundary) of up to 22 nuclear genes and up to 16 disease-associated non-coding variants.
- Variant interpretation was performed using modified ACMG/AMP guidelines. A molecular diagnosis was defined as the identification of pathogenic (P) or likely pathogenic (LP) variants consistent with the patient's reported phenotype and known associated disease inheritance.

## Results

- A molecular diagnosis was established in 19.7% (23/117) of patients.
- Molecular diagnoses were identified in 7 genes associated with thyroid dysgenesis, dyshormonogenesis, or RTH (Figure 1).
- Diagnostic yield was significantly higher among patients tested in their first 2 years of life (38.9%, 7/18) than among patients tested at age 2 or older (16.2%, 16/99; $X2=4.9812$, $P=.0256$) (Figure 2).
- Two molecular diagnostic results were identified in a 2-year old male patient with reported thyroid hormone resistance and autism: a heterozygous LP missense variant in the *THRB* gene, NM_001128176.2:c.749T>C (p.Ile250Thr), which was thought to be the primary diagnosis for this individual; and a heterozygous LP stop-gained variant in the *DUOX2* gene, NM_014080.4:c.2101C>T (p.Arg701*), which may contribute to disease as monoallelic variants in this gene can cause a milder congenital hypothyroidism phenotype.

**1 in 5 patients** with suspected congenital hypothyroidism (CH) or resistance to thyroid hormone (RTH) who underwent NGS panel testing received a diagnostic result.

Diagnostic yield was higher among patients tested < age 2 than those tested at ≥ age 2

A dual molecular diagnosis of CH and RTH was identified

| Category | Number in total cohort | % of total cohort (n=117) | Number in dx cohort | % of dx cohort (n=23) |
|---|---|---|---|---|
| **Age range at testing** | | | | |
| Infants (newborn- age 2) | 24 | 20.5% | 10 | 43.5% |
| Early childhood (ages 3-6) | 12 | 10.3% | 2 | 8.7% |
| Childhood and adulthood (ages >/=7) | 81 | 69.2% | 11 | 47.8% |
| **Sex** | | | | |
| Male | 55 | 47.0% | 11 | 47.8% |
| Female | 62 | 53.0% | 12 | 52.2% |

Table. Patient cohort demographics by demographic category. The median patient age at time of testing was 22 years (range: newborn to 82 years).
Dx= diagnostic.

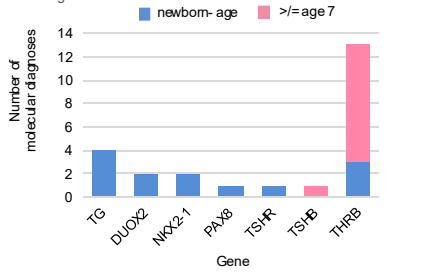


Figure 1. Genes where molecular diagnoses were identified.

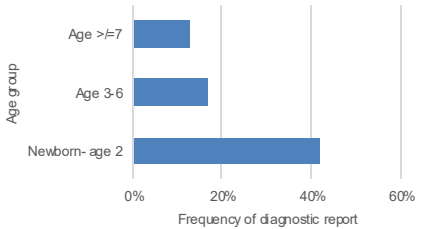


Figure 2. Diagnostic yield by age group. Presumed truncating variants (frameshift, stop-gained, canonical splice donor/acceptor) classified as P/LP in genes associated with CH were accounted for most (71.4%, n=5/7) molecular diagnoses among patients tested < age 2.

Conflict of interest statement: All authors are employed by Blueprint Genetics.

Blueprint Genetics