Variable Clinical Phenotypes in a Family with Homozygous c.1159G>A Mutation in the Thyroid Peroxidase Gene

Ching Chin Lee\textsuperscript{a} Fatimah Harun\textsuperscript{b} Muhammad Yazid Jalaludin\textsuperscript{b} Choon Han Heh\textsuperscript{c} Rozana Othman\textsuperscript{c} In Nee Kang\textsuperscript{a} Sarni Mat Junit\textsuperscript{a}

Departments of \textsuperscript{a}Molecular Medicine, \textsuperscript{b}Paediatrics and \textsuperscript{c}Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Established Facts
- A compound heterozygous of c.1159G>A mutation in exon 8 and a frameshift mutation in exon 5 of the thyroid peroxidase (TPO) gene had been reported to be associated with congenital hypothyroidism (CH).

Novel Insights
- In this study, a homozygous c.1159G>A mutation was detected in a Malaysian-Malay family.
- Three siblings possessing the mutation in a homozygous form have developed goiter, but CH was only detected in the index patient.
- In silico analyses revealed that the mutation interrupts the correct splicing of pre-mRNA and also leads to structural alterations in the functional sites of the mutant TPO.

Key Words
Congenital hypothyroidism · Goiter · Thyroid peroxidase · Homozygous c.1159G>A mutation

Abstract
\textbf{Background}: Defects in the thyroid peroxidase (TPO) gene have been associated with goitrous congenital hypothyroidism (CH). \textbf{Case Report}: In this study, we report 3 siblings possessing a homozygous mutation, c.1159G>A, but exhibiting different clinical phenotypes in a Malaysian-Malay family. The index patient was diagnosed with CH during a routine neonatal screening but the other 2 siblings appeared to be asymptomatic until the ages of 19 and 12.5, respectively, when they started to develop goiter. \textbf{Results and Conclusion}: The mutation was predicted to interrupt the correct splicing of pre-mRNA and also lead to structural alterations in the functional sites of the mutant TPO. The current results...