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International Journal of Neonatal Screening

MDPI

Article

Novel Phenotypic Insights into the *IDS* c.817C>T Variant in Mucopolysaccharidosis Type II from Newborn Screening Cohorts

Éliane Beauregard-Lacroix [1], Caitlin Menello [1], Madeline Steffensen [1], Hsiang-Yu Lin [2,3], Chih-Kuang Chuang [2], Shuan-Pei Lin [2,3] and Can Ficicioglu [1,4,*]

[1] Section of Biochemical Genetics, Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; eliane.beauregard-lacroix@umontreal.ca (É.B.-L.); menelloc@chop.edu (C.M.); steffensem@chop.edu (M.S.)
[2] Department of Pediatrics, Medical Research and International Rare Disease Center, MacKay Memorial Hospital, Taipei 10449, Taiwan; lxc46199@ms37.hinet.net (H.-Y.L.); mmhcck@gmail.com (C.-K.C.); 4535lin@gmail.com (S.-P.L.)
[3] Department of Medicine, MacKay Medical University, New Taipei City 25245, Taiwan
[4] Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
* Correspondence: ficicioglu@chop.edu

Abstract

Mucopolysaccharidosis (MPS) type II, or Hunter syndrome, is an X-linked lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase. Glycosaminoglycan (GAG) accumulation leads to progressive multisystemic involvement, with coarse facial features, hepatosplenomegaly, short stature, recurrent upper respiratory infections, hearing loss, hernias, dysostosis multiplex, joint contractures, and cardiac valve disease. Individuals with the neuronopathic form of the disease also have central nervous system (CNS) involvement with developmental delay and progressive cognitive decline. Enzyme replacement therapy (ERT), idursulfase, is the only FDA-approved treatment for MPS II. MPS II was added to the Recommended Uniform Screening Panel (RUSP) in the United States in 2022, and screening is ongoing in several other countries, including Taiwan. Here, we report seven individuals from four families identified through newborn screening sharing the same *IDS* variant: c.817C>T, p.Arg273Trp. Confirmatory testing demonstrated low iduronate-2-sulfatase activity level and elevated GAGs in every individual, but they had no signs or symptoms of MPS II. They were aged 8 months to 60 years old according to the most recent assessment and all remained asymptomatic. ERT was not initiated for any of them. Our findings suggest that the *IDS* c.817C>T variant is associated with abnormal biochemical findings but no clinical phenotype of MPS II. Newborn screening will likely identify additional cases and provide a better understanding of the clinical significance of this variant.

Keywords: mucopolysaccharidosis type II; Hunter syndrome; lysosomal storage disease; newborn screening

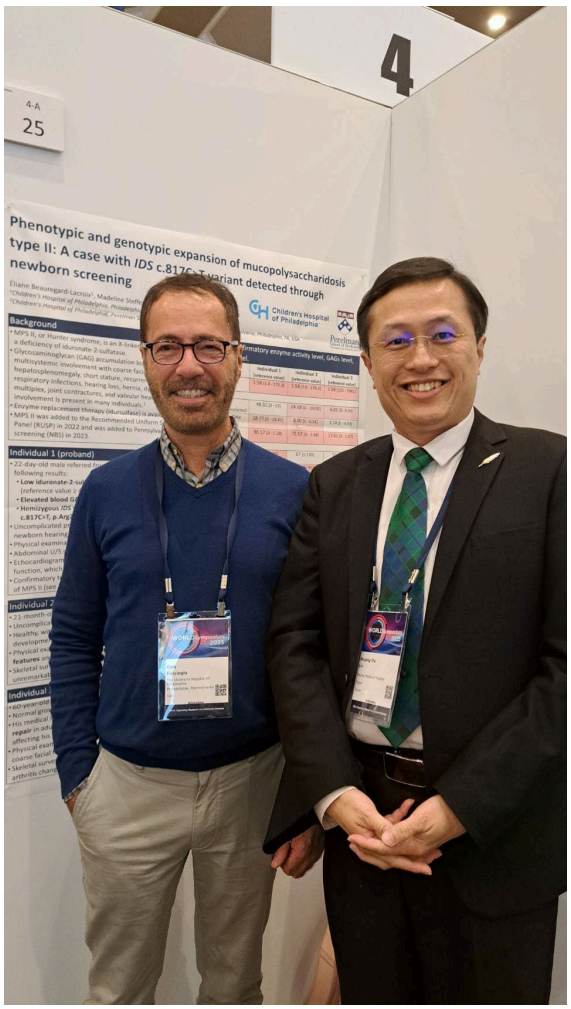
Academic Editor: Barbara K. Burton and Joseph Orsini

Received: 18 July 2025
Revised: 20 August 2025
Accepted: 22 August 2025
Published: 26 August 2025

Citation: Beauregard-Lacroix, É.; Menello, C.; Steffensen, M.; Lin, H.-Y.; Chuang, C.-K.; Lin, S.-P.; Ficicioglu, C. Novel Phenotypic Insights into the *IDS* c.817C>T Variant in Mucopolysaccharidosis Type II from Newborn Screening Cohorts. *Int. J. Neonatal Screen.* **2025**, *11*, 68. https://doi.org/10.3390/ijns11030068

1. Introduction

Mucopolysaccharidosis (MPS) type II, or Hunter syndrome, is an X-linked lysosomal storage disorder (LSD) caused by a deficiency of iduronate-2-sulfatase. This enzyme is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Phenotypic and genotypic expansion of mucopolysaccharidosis type II: A case with IDS c.817C>T variant detected through newborn screening
Children's Hospital of Philadelphia
Background
Individual 1 (proband)