Psychosocial benefits of whole exome sequencing for patients with suspected inherited metabolic disorders

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INTRODUCTION

- **1 in 12** Canadians has a rare disorder, many of which are genetic and remain undiagnosed
- Diagnosis allows clinicians to provide support and anticipatory guidance to families
- Additionally, treatment options are becoming increasingly available for Inherited Metabolic Disorders (IMDs)
- Whole exome sequencing (WES) is increasingly used to establish a diagnosis for rare disease patients, with a diagnostic yield of 20-40%
- However, WES is not typically used as a first-line test for IMDs

HYPOTHESIS

Offering WES early in the diagnostic evaluation of patients suspected to have an IMD will lead to:

Earlier diagnosis

Timely initiation of treatment/ management

Higher patient satisfaction and quality of care

METHODS

Referral

Patients (any age) suspected to have an IMD are referred to the CPMN research study by any health care provider

CPMN Approval

Cases are reviewed by a multidisciplinary team for eligibility for WES

Sample Collected/ WES Analysis

Eligible participants provide an oral sponge sample for WES at Discovery DNA, Inc. (Calgary, AB)

Results/ Counselling

Results are reviewed by the team and/or referring provider and disclosed to the patient

RESULTS: 3 CASE VIGNETTES

Participant 1

27 year old ♂ Congenital cataracts, Muscle weakness

Genomic results:

1. Heterozygous likely pathogenic variant in *WFS1* (c.1243G>T, p.Val415Phe)	**2. Heterozygous variant of uncertain significance in *FLNC*** (c.4970G>A, p.Arg1657Gln)
• *De novo* (not inherited) • Gene associated with: cataracts, optic atrophy; deafness; diabetes Wolfram-like syndrome	• Inherited from healthy dad • Gene associated with: myopathy; cardiomyopathy • No objective evidence of muscle weakness

- ➢ *WFS1* variant is likely the cause of his congenital cataracts
- ➢ Other associated features unlikely given his age

Participant 2

14 year old ♀ Developmental delay, Agenesis of corpus callosum

Genomic results:

1. Heterozygous likely pathogenic variant in *TCF4* (c.655G>C, p.Asp219His)	**2. Heterozygous variant of uncertain significance in *TRIO*** (c.4388G>A, p.Arg1463Gln)
• *De novo* (not inherited) • Gene associated with Pitt-Hopkins syndrome: dev delay/ID non-verbal; facial features; brain anomalies; breathing abnormalities; seizures	• Inheritance unknown • Gene associated with *TRIO*-related intellectual disability: ID; facial features; microcephaly; hand anomalies; dental anomalies

- ➢ Diagnosis of Pitt-Hopkins syndrome, giving the family a name for her symptoms
- ➢ Seizures unlikely given her age

Participant 3

10 year old ♀ Developmental delay, Seizures

Genomic results:

1. Heterozygous likely pathogenic variant in *SYNGAP1* (c.987_988delTG, p.Asp330Feufs*88)
• Inheritance unknown (parentals pending) • Gene associated with *SYNGAP1*-related intellectual disability: dev delay/ID; epilepsy; autism

- ➢ Diagnosis of *SYNGAP1*-related disorder
- ➢ Ruled-out previous working diagnosis, which required significant monitoring
- ➢ Not expected to develop any additional medical issues with this condition

DISCUSSION

- Given that some features of IMDs are non-specific, this study is **expected to identify both metabolic and non-metabolic disorders**
- While the diagnoses in these 3 patients did not lead to changes in clinical management, the team was able to provide **anticipatory guidance and reassurance** that new manifestations are unlikely for each patient
- Anticipatory guidance is known to be an important component of genetic counselling
- *Future Directions:* Qualitative interviews with patients/families and analysis of quality of life data to **gain a better understanding of the psychosocial impact of diagnosis through WES**

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