BAYLOR GENETICS

BAYLOR GENETICS
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PATIENT CASE

WGS and RNA sequencing (RNAseq)

Whole Genome Sequencing with RNAseq reclassified a variant as likely pathogenic and established the patient's diagnosis.

Initial Presentation:

- A 7-year-old male with autism spectrum disorder, intellectual disability, developmental delay, chronic otitis media, irritable bowel syndrome, hypertrichosis, hypotonia, abnormal EEG, low carnitine, and multiple allergies

Genetic Tests Performed:

- Trio WGS
- The patient had previous genetic testing from an outside laboratory, including a large gene panel for ASD and ID, *FMR1* CGG repeat expansion analysis and chromosomal microarray; all returned with negative results

Trio WGS Test Findings:

- A heterozygous variant of uncertain significance (VUS) in the *FOXP4* gene was detected
  - > This variant was maternally inherited
- *FOXP4* has been associated with an autosomal dominant neurodevelopmental disorder with variable congenital anomalies
  - > Symptoms can include delayed speech and language development, delayed motor development, growth abnormalities, facial dysmorphism, infantile hypotonia, skeletal abnormalities, congenital diaphragmatic hernia, cervical spine abnormalities, strabismus, cryptorchidism, and ptosis
  - > Several cases with disease-causing variants being inherited from parents with mild or subclinical features have been reported
  - > This variant has not been described in public databases, but is predicted to disrupt the splicing donor site
- Reflex RNAseq was performed, showing that this variant results in abnormal splicing
- Therefore, RNAseq allowed for this variant to be reclassified as likely pathogenic

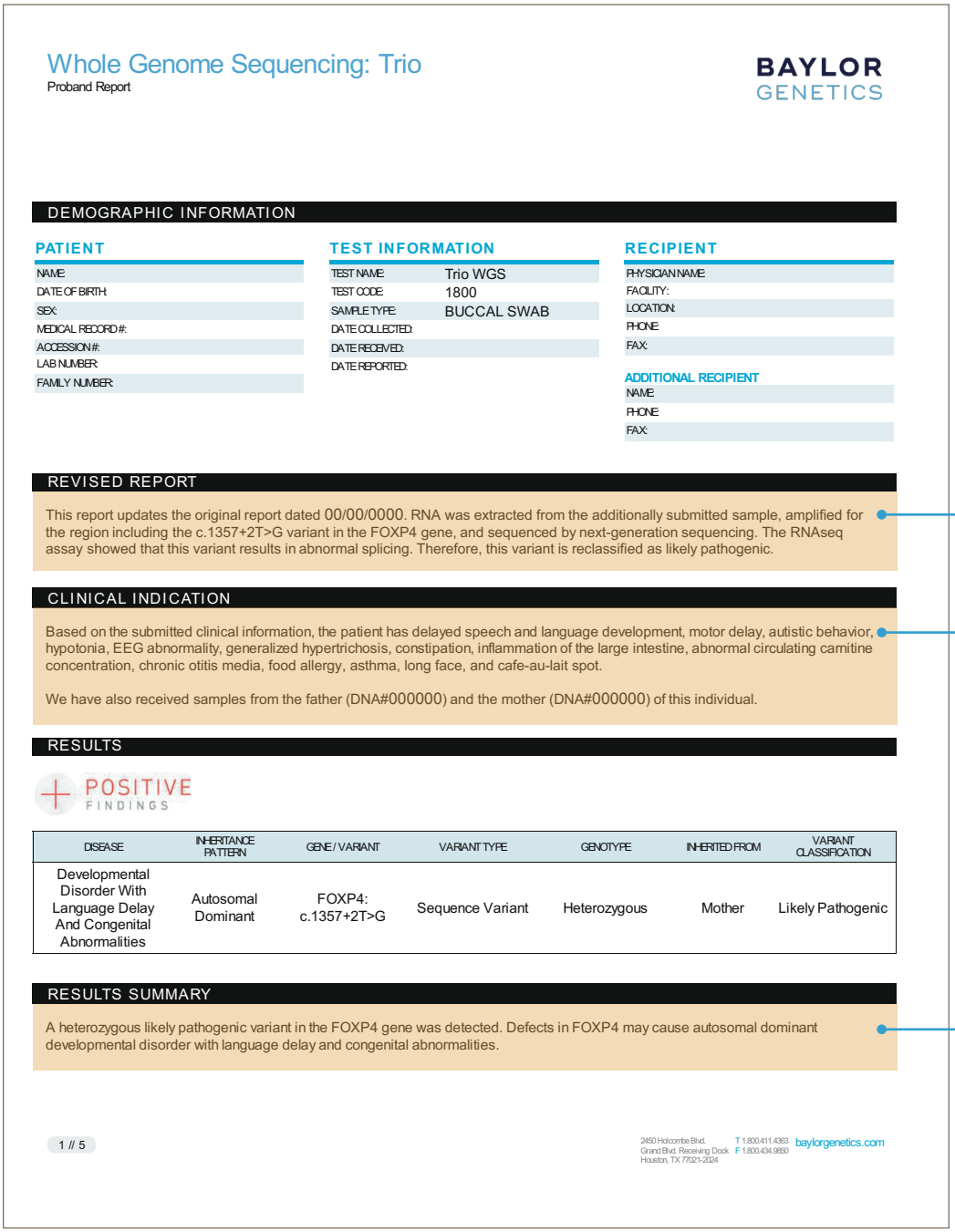
Impact on Medical Management:

- A final diagnosis was established for this patient, allowing them to start antisense oligonucleotide (ASO) therapy
- Additional clinical examinations and surveillance of symptoms associated with *FOXP4*-related neurodevelopmental disorder can be established
- Since this variant was maternally inherited, reproductive risk can be better ascertained for future pregnancies that the parents of this patient may have

Baylor Genetics' WGS includes complimentary RNAseq, and a confirmatory diagnosis was made for this patient using the functional evidence from RNAseq.

Per the American College of Medical Genetics & Genomics (ACMG) guidelines, using WGS as a first-line test for pediatric patients with developmental delays enables the healthcare provider to quickly make a diagnosis. These results concluded the patient's diagnostic odyssey and informed a personalized treatment plan.

WGS with RNAseq confirmed the patient's diagnosis and provided important management information for both the patient and his parents.



Whole Genome Sequencing: Trio

Proband Report

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DEMOGRAPHIC INFORMATION

PATIENT

NAME:	
DATE OF BIRTH:	
SEX:	
MEDICAL RECORD #:	
ACCESSION #:	
LAB NUMBER:	
FAMILY NUMBER:	

TEST INFORMATION

TEST NAME:	Trio WGS
TEST CODE:	1800
SAMPLE TYPE:	BUCCAL SWAB
DATE COLLECTED:	
DATE RECEIVED:	
DATE REPORTED:	

RECIPIENT

PHYSICIAN NAME:	
FACILITY:	
LOCATION:	
PHONE:	
FAX:	

ADDITIONAL RECIPIENT

NAME:	
PHONE:	
FAX:	

REVISED REPORT

This report updates the original report dated 00/00/0000. RNA was extracted from the additionally submitted sample, amplified for the region including the c.1357+2T>G variant in the FOXP4 gene, and sequenced by next-generation sequencing. The RNAseq assay showed that this variant results in abnormal splicing. Therefore, this variant is reclassified as likely pathogenic.

CLINICAL INDICATION

Based on the submitted clinical information, the patient has delayed speech and language development, motor delay, autistic behavior, hypotonia, EEG abnormality, generalized hypertrichosis, constipation, inflammation of the large intestine, abnormal circulating carnitine concentration, chronic otitis media, food allergy, asthma, long face, and cafe-au-lait spot.

We have also received samples from the father (DNA#000000) and the mother (DNA#000000) of this individual.

RESULTS

POSITIVE FINDINGS

DISEASE	INHERITANCE PATTERN	GENE / VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
Developmental Disorder With Language Delay And Congenital Abnormalities	Autosomal Dominant	FOXP4: c.1357+2T>G	Sequence Variant	Heterozygous	Mother	Likely Pathogenic

RESULTS SUMMARY

A heterozygous likely pathogenic variant in the FOXP4 gene was detected. Defects in FOXP4 may cause autosomal dominant developmental disorder with language delay and congenital abnormalities.

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This report was revised to include the functional evidence obtained from RNAseq that allowed for the previously identified *FOPX4* variant to be reclassified as likely pathogenic

The clinical indication for testing was broad, and the provider felt that comprehensive testing was indicated.

Results summary with disease and variant information. A heterozygous variant of uncertain significance was identified in the *FOXP4* gene. This gene has been associated with an autosomal dominant neurodevelopmental disorder with variable congenital anomalies. This variant was maternally inherited. After considering functional evidence from RNAseq, the *FOXP4* variant was upgraded to likely pathogenic.

References:

1. Recurrent *FOXP4* nonsense variant in two unrelated patients: Association with neurodevelopmental disease and congenital diaphragmatic hernia. PMID: 36301021
2. Heterozygous variants that disturb the transcriptional repressor activity of *FOXP4* cause a developmental disorder with speech/language delays and multiple congenital abnormalities. PMID: 33110267