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PATIENT CASE

Rapid Whole Exome Sequencing (rWES)

Rapid Trio Whole Exome Sequencing in the neonatal intensive care unit with a dual diagnosis ends the diagnostic odyssey before it begins.

Initial Presentation:

- 2-week-old baby with seizures, overgrowth, hemimegaloencephaly, cerebellar vermis hypoplasia, single left palmar crease, and worsening respiratory failure.
- Differential diagnoses include mTORopathies, including somatic mutations in *PIK3CA, AKT3, MTOR,* and *RHEB*, and from germline and somatic mutations in mTOR pathway repressors, including *DEPDC5, NPRL2, NPRL3, TSC1* and *TSC2*.

Genetic Tests Performed:

- Rapid Trio WES was ordered by inpatient genetics due to a concern for somatic mosaic overgrowth condition.

Rapid Trio WES Test Findings:

- Rapid Trio WES revealed an unexpected dual diagnosis.
- One paternally inherited pathogenic variant was identified in the *NPRL3* gene associated with autosomal dominant familial focal epilepsy with variable foci type 3.
- An additional diagnosis of Trisomy 21 was made and confirmed by Chromosomal Microarray Analysis. This explains the patient's dysmorphic features that are inconsistent with the diagnosis of familial focal epilepsy.

Impact on Medical Management:

- Targeted treatments for familial focal epilepsy can be initiated based on this diagnosis.
- Results are meaningful for paternal relatives given the variable penetrance of this disorder.
- Affected, or yet asymptomatic but at-risk, family members can be tested. Results also inform recurrence risks for this family.
- Additionally, the American Academy of Pediatrics publishes guidelines for the Health Supervision for Children and Adolescents with Down Syndrome.[1]

Patients with two disorders often present with unusual phenotypes which leave healthcare providers struggling to make a diagnosis.

Approximately 2-7% of patients have a dual diagnosis and comprehensive tests, such as WES and Whole Genome Sequencing, allow for the identification of such cases.[2]

An accurate diagnosis informs genetic counseling, provides information about prognosis, and allows for best clinical management, and testing of at-risk relatives.[3]

Appropriate treatment and medical management could quickly be initiated, and at-risk family members identified because a Rapid Trio WES was performed identifying both diagnoses. WES testing eliminated the diagnostic odyssey before it started for this infant.

References:

1. Bull, M. J., Trotter, T., Santoro, S. L., Christensen, C., Grout, R. W., & Council on Genetics. (2022). Health supervision for children and adolescents with Down syndrome. Pediatrics, 149(5), e2022057010
2. Gonzalez, G. & Montoya, E. (2023). P179: Never two late: A Dual Diagnosis of Noonan Syndrome and Hypophosphatasia in an Adolescent Patient with Unusual Presentation. Genetics in Medicine Open, 1(1). https://doi.org/10.1016/j.gimo.2023.100208
3. Capra, A. P., La Rosa, M. A., Briguori, S., Civa, R., Passarelli, C., Agolini, E., Novelli, A., & Briuglia, S. (2023). Coexistence of Genetic Diseases Is a New Clinical Challenge: Three Unrelated Cases of Dual Diagnosis. Genes, 14(2), 484. https://doi.org/10.3390/genes14020484

WES performed as a trio for this family provided inheritance information for the patient's family members. The pathogenic *NPRL3* variant was also identified in the child's father while the Down Syndrome diagnosis was determined to be de novo.

Whole Exome Sequencing: Rapid Trio

Proband Report

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Test Name

DEMOGRAPHIC INFORMATION

PATIENT

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

TEST INFORMATION

TEST NAME:	Rapid Trio WES
TEST CODE:	1722
SAMPLE TYPE:	BUCCAL SWAB
DATE COLLECTED:	
DATE RECEIVED:	
DATE REPORTED:	

RECIPIENT

PHYSICIAN NAME:	
FACILITY:	
LOCATION:	
PHONE:	
FAX:	
EMAIL:	

ADDITIONAL RECIPIENT

NAME:	
PHONE:	- -
FAX:	- -
EMAIL:	

CLINICAL INDICATION

Based on the submitted clinical information, the patient has seizure, overgrowth, hemimegalencephaly, cerebellar vermis hypoplasia, single left palmar crease, palpebral fissures, respiratory failure.

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

We have also received samples from the father (DNA#1234567) and the mother (DNA# 234568) of this individual.

RESULTS

POSITIVE FINDINGS

DISEASE	INHERITANCE PATTERN	GENE / VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
Epilepsy, Familial Focal, With Variable Foci 3	Autosomal Dominant	NPRL3: c.189-1G>A	Sequence Variant	Heterozygous	Father	Pathogenic
Down Syndrome	Autosomal Dominant	chr21: 10951265-48084286DUP 37133.02(kb)	Copy Number Variant	Heterozygous	De Novo	Pathogenic

Key findings summary with disease and variant information. Two pathogenic variants were identified.

RESULTS SUMMARY

A Heterozygous Pathogenic Variant in the NPRL3 gene was detected, which is consistent with a diagnosis of familial focal epilepsy with variable foci-3 in this individual.

De Novo duplication of entire chromosome 21 was detected, which is consistent with a diagnosis of Down Syndrome in this individual.

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