MAYO CLINIC

1-800-533-1710

Whole Exome Sequencing Reanalysis

WESR

PATIENT NAME				ORDER NUMBER
TESTINGRNV, WESR				**L928000324**
PATIENT ID SA00153406	DATE OF BIRTH 05/15/2021	AGE 13 M	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 6/28/2022, 9:00 AM	RECEIVED 6/28/2022, 2:35 PM	REPORTED 6/29/2022, 3:59 PM		

The collected, received, and reported dates and times on the report are in the time zone of the performing location.

7028846
MCL RochesterCampus
Rochester MN 55901

CLIENT ORDER NUMBER
SA00153406

CLIENT MRN
SA00153406

SPECIMEN

WB Whole Blood

INTERPRETATION

A full copy of the interpretative report is available as a PDF appended to this cover sheet and is ready to review.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

RELEASED BY

Nicole J. Boczek, Ph.D.

Code : MCR Laboratory : Mayo Clinic Laboratories - Rochester Main Campus Address : 200 FIRST STREET SW
Lab Director : WILLIAM G MORICE, II MD, PhD CLIA Certificate : 24D0404292 ROCHESTER MN 55905

TESTINGRNV, WESR

Patient ID: 22-29593| **Family ID:** F4703 | **Date of birth:** 5/15/2021 (13 months old) | Female | **Order number:** L928000324

Requested by: CLIENT, CLIENT
Requesting Institution: 7028846 | MCL RochesterCampus | Rochester, MN 55901

Client MRN: SA00153406
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Clinical Information Summary

Based on information from the ordering provider, the patient's clinical features and history include seizures, developmental regression, and failure to thrive.

Samples were also received from the patient's reportedly unaffected biological mother and father.

Results Summary

Reanalysis was requested on 6/29/2022 due to time elapsed since original analysis. Updated findings were identified and can be reviewed below.

This result is more up to date than the original Whole Exome Sequencing study (L508000294). If the patient wishes for Whole Exome Sequencing Reanalysis (WESR) results to be shared with providers other than the current ordering provider, they will need to share these results directly or sign a release of information form.

A consultation with a genetics professional is recommended. Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Evaluation for additional features and appropriate screening and/or management measures should be considered.

RESULTS

Likely Causative

Pathogenic	WWOX	NM_016373.4 **c.173-1G>T** Associated Condition: Developmental and epileptic encephalopathy, 28, Autosomal recessive	Inherited from **Father, Mother**	Zygosity **Hom**

Possibly Relevant

No reportable possibly relevant variants were identified

Secondary Findings (v3.0)

No reportable secondary findings were identified

INTERPRETATION

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Likely Causative

Pathogenic | WWOX: c.173-1G>T

NM_016373.4 | NC_000016.9:g.78143674G>T

Zygosity	Proband: Hom	Mother: Het	Father: Het

A homozygous variant, c.173-1G>T/p.?, was identified in the WWOX gene. Pathogenic variants in WWOX are associated with autosomal recessive early infantile epileptic encephalopathy, 28 (WWOX-related epileptic encephalopathy (WOREE syndrome); MIM#616211). A recent review of 37 patients suggests WOREE syndrome is a severe epileptic encephalopathy characterized by absence of language development and acquisition of walking, early-onset drug-resistant seizures, ophthalmological involvement, and risk of premature death (Piard et al., 2019). Tentative genotype-phenotype correlation suggests patients with two predicted null alleles are more likely to present with severe phenotype while patients with two missense alleles may present with milder disease (Piard et al., 2019). Of note, biallelic variants are also reportedly associated with spinocerebellar ataxia, type 12 (MIM#614322) however, additional cases are needed to confirm this association.

This variant alters a canonical splice site and may cause skipping of the adjacent exon or use of a cryptic splice site, leading to premature protein truncation. In silico analyses predict a skip of exon 3 is highly likely; a skip of this exon would lead to an out-of-frame product with the resulting protein predicted to be p.[Asp58Alafs*3]. This variant has not been reported in gnomAD (rs1232899835). There is no entry for this variant in ClinVar. This variant has been reported in the literature in at least two individuals with phenotype consistent with early infantile epileptic encephalopathy/WOREE syndrome (Piard et al., 2019 and Tarta-Arsene et al., 2017).

The patient's mother and father are both heterozygous for this variant. Children of this patient's parents would have a 25% chance of inheriting this variant from both parents.

REFERENCES:
1. Piard J, Hawkes L, Milh M, et al. The phenotypic spectrum of WWOX-related disorders: 20 additional cases of WOREE syndrome and review of the literature. Genetics in medicine : official journal of the American College of Medical Genetics. 2018;21(6):1308-1318. [PMID:30356099]
2. Tarta-Arsene O, Barca D, Craiu D, et al. Practical clues for diagnosing WWOX encephalopathy. Epileptic disorders : international epilepsy journal with videotape. 2017;19(3):357-361. [PMID: 28721938]

Possibly Relevant

No reportable variants in genes possibly relevant to the patient's reported clinical features were identified.

Secondary Findings (v3.0)

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No reportable secondary findings were identified in the medically actionable genes analyzed in accordance with ACMG recommendations. Whole exome sequencing is not specifically designed to rule out all pathogenic variants in this list of genes. If there is clinical suspicion for a condition caused by one of these genes, focused genetic testing may be indicated.

Method

Previously generated exome sequence data derived from DNA extracted from the patient and all submitted comparator samples is re-annotated and re-analyzed. The human genome reference GRCh37/hg19 build is used for sequence read alignment. The targeted regions, detected variant types (eg. SNV, CNV), and the average coverage, sensitivity, and specificity values remain the same from the initial analysis. Variants are filtered, annotated using public and proprietary resources, and presented for analysis and interpretation using a vended interpretation tool, Franklin by Genoox. Confirmation of select reportable variants in the proband and submitted comparator samples may be performed by alternate methodologies based on internal laboratory criteria.

Disclaimer

CLINICAL CORRELATIONS
This report contains variants in genes related to the patient's reported clinical features. The interpretation is based upon the clinical information reported by the ordering health care provider(s) at the time of testing. Misinterpretation of results may occur if the clinical information provided is inaccurate or incomplete. Familial segregation analysis may help inform the clinical significance of reported variants. To discuss the availability of further testing options, or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710. Previously reported variants in this patient may not be re-reported or detected for any of the following reasons: insufficient phenotypic overlap, minor allele frequency greater than 1%, outside of the capture region for this assay, genotype quality filters, and/or the variant is currently classified as likely benign or benign. It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome and/or the impact of variants in those genes. Deidentified variant information may be shared in public genetic databases, such as GeneMatcher or ClinVar.

TECHNICAL LIMITATIONS
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some regions. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered. Technical limitations based on variant type and targeted region remain the same from the initial analysis. This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results. If the patient has had an allogeneic marrow transplant or a recent heterologous blood transfusion, these results

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may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

SECONDARY FINDINGS

Patients are evaluated for medically actionable secondary findings as recommended by the published ACMG guidelines unless they opt-out in the initial analysis. Refer to the results and interpretation sections of the report for the ACMG secondary findings gene list version used at the time of testing. Reportable variants include pathogenic variants and likely pathogenic variants. Variants of uncertain significance (VUS) in these genes are not reported unless they overlap with the patient's phenotype. Presence of the variant in comparator samples is stated, unless they opt-out of secondary findings. Variants that are present in a family member but absent from the proband are not evaluated. The absence of a reportable secondary finding does not guarantee that there are no known or expected pathogenic variants in these genes, as portions of the genes may not be adequately covered by this testing methodology. If a patient opts-out of receiving these results, these variants will not be reported unless they occur in a gene that is clinically related to the patient's presenting phenotype.

VARIANT EVALUATION

Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported. Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

RECLASSIFICATION OF VARIANTS

See www.mayocliniclabs.com (Test ID WESDX) for information regarding the laboratory's policy for reclassification of variants.

EXOME REANALYSIS

Healthcare providers may contact the laboratory at 800-533-1710 any time to request reanalysis of the patient's exome; a charge may apply for reanalysis.

TEST CLASSIFICATION

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

Released By

Nicole J. Boczek, PhD on 6/29/2022

Performing Site Legend

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Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories – Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292