MAYO CLINIC

1-800-533-1710

Whole Genome Sequencing

WGSDX

PATIENT NAME				ORDER NUMBER
TESTING, WGSDX A				**M223000129**
PATIENT ID SA00154576	DATE OF BIRTH 07/05/2022	AGE 2 M	SEX Male	REQUESTED BY CLIENT CLIENT
COLLECTED 9/23/2022, 8:30 AM	RECEIVED 9/23/2022, 10:04 AM	REPORTED 9/28/2022, 10:14 AM		

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
SA00154576

CLIENT MRN
SA00154576

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

TESTING, WGSDX A

Patient ID: 22-38980| **Family ID: F4823** | **Date of birth:** 7/5/2022 (2 months old) | Male | **Order number:** M223000129

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

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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

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 (v3.1)

No reportable secondary findings were identified

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INTERPRETATION

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 (v3.1)

No reportable secondary findings were identified in the medically actionable genes analyzed in accordance with ACMG recommendations. Whole genome 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.

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Method

PCR-free next generation sequencing (NGS) is performed on DNA extracted from the patient and all submitted comparator samples to test for the presence of variants. The human genome reference GRCh38/hg38 build is used for sequence read alignment. The revised Cambridge Reference Sequence (rCRS), GenBank accession number NC_012920, is used for mitochondrial variant detection. Variants are called using an optimized bioinformatics package. The average genomic coverage is at or above a read depth of 32X. Sensitivity is estimated above 99% for single nucleotide variants (SNVs) and above 94% for deletion-insertions (delins) less than 50 base pairs (bp). This assay also detects >99% of copy number variants (deletions/duplications) at least 1,000bp in size. Resulting variants are filtered, annotated using public and proprietary resources, and presented for analysis and interpretation using 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.

See technical limitations section for detailed description of additional variant classes detected by this assay (mitochondrial variants, repeat expansions, select spinal muscular atrophy (SMA)-associated variants, balanced structural rearrangements, and mosaic variants).

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 for this patient may not be re-reported or detected for any of the following reasons: insufficient phenotypic overlap, high minor allele frequency, technical limitations, 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 and noncoding regions.

Deidentified variant information may be shared in public genetic databases, such as Matchmaker Exchange or ClinVar. An online research opportunity called GenomeConnect (genomeconnect.org) is available for the recipient of this genetic test. This patient registry collects deidentified genetic and health information to advance knowledge of genetic variants.

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If the patient has had an allogeneic marrow transplant or a recent heterologous blood transfusion, these results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories (1-800-533-1710) for instructions for testing patients who have received a bone marrow transplant.

TECHNICAL LIMITATIONS

Whole genome sequencing may not detect all types of genomic variants; therefore, false negative results are possible. There may be regions of genes that cannot be effectively evaluated by whole genome sequencing as a result of technical limitations of the assay, including variable depth of coverage, regions of homology, and repetitive sequences. 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. In rare cases false-positive results may occur; however, false positive events should be exceedingly rare as confirmation of reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

Additional Variant Classes:
A comprehensive assessment of sensitivity and false negative rate has not been established for mitochondrial variants, repeat expansions, select spinal muscular atrophy (SMA)-associated variants, balanced structural rearrangements, larger delins (51-999 bp), and mosaic variants of all classes. These variants will be evaluated per laboratory protocol, and findings of clinical relevance will be reported following confirmation with validated laboratory methods. Importantly, the sensitivity and performance for these variant classes is not expected to meet that of current gold-standard testing methodologies; therefore, additional testing may be indicated if there is clinical suspicion for a disorder involving these variant classes.

Mitochondrial Genome Variants:
This assay can detect mitochondrial genome SNVs and small delins with heteroplasmy levels above 5%. Detection of large deletion and duplication events involving the mitochondrial genome is not available with the current analysis. Of note, the sensitivity of this assay may be lower in blood samples than in muscle biopsy samples.

Repeat Expansion Variants:
STR loci included in this assay are: AR, ATN1, ATXN1, ATXN2, ATXN3, ATXN7, C9orf72, CACNA1A, CSTB, DMPK, FMR1, FXN, and HTT. Only loci overlapping the patient's (proband's) clinical features will be evaluated and reported.

Spinal Muscular Atrophy (SMA) Variants:
Absence of the definitive C nucleotide in exon 7 of SMN1 (NM_000344.3:c.840C) indicating the homozygous loss of SMN1 exon 7 is detectable by this assay. This assay does not identify SMN1 or SMN2 variants outside of this specific single nucleotide change. This assay does not detect SMN1 carrier status or phase of SMN1/SMN2 alleles.

Balanced Structural Rearrangements:
This assay does not involve comprehensive evaluation of balanced structural rearrangements (e.g., translocations and inversions). However, select genomic regions may be evaluated and balanced events reported when there is a directed clinical focus (e.g., known family history or specific locus of high clinical suspicion communicated to the laboratory).

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Mosaic Variants:
Detected clinically relevant mosaic variants will be reported, however this test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants.

SECONDARY FINDINGS

Patients are evaluated for medically actionable secondary findings as recommended by the published ACMG guidelines unless they opt-out. 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 review is limited to known or highly suspected pathogenic findings, and not all regions of these genes are adequately evaluated by this technology. 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.

RECLASSIFICATION OF VARIANTS

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

GENOME REANALYSIS

Healthcare providers may contact the laboratory at 1-800-533-1710 any time to request reanalysis of the patient's genome (test code WGSR); a charge may apply for reanalysis. It is not a guarantee that patient data will be stored indefinitely. Requests for reanalysis or release of raw data may not be possible, and a new whole genome sequencing order may be required if the original patient data is no longer available or no longer compatible with current bioinformatics processes or analysis tools.

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.

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Released By

Nicole J. Boczek, PhD on 9/28/2022

Performing Site Legend

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