Genetic Testing Report for

OMI RareDx Whole Genome Sequencing (TRIO)

SAMPLE INFORMATION

Date Received	Sample ID	Sample Type	Patient Name	Relationship	Gender	Race	Date of Birth /Age
2024-12-31	2412091	Peripheral blood	Patient A	proband	Male	-	2012-10-04/12
2024-12-31	2412093	Peripheral blood	-	father	Male	-	1975-09-08/49
2024-12-31	2412092	Peripheral blood	-	mother	Female	-	1982-05-01/42

Clinical Manifestation& Family History	2412091	patient; 1. Attention Deficit Hyperactivity Disorder (ADHD) 2. Disorder of Immune System, Unspecified (D89.9) 3. Pervasive Developmental Disorders (F84) o Autism Spectrum Disorder (F84.0; ICD-10: 299.0) 4. Encephalopathy, Unspecified (G93.40; ICD-10: 348.30) 5. Metabolic Disorder, Unspecified (E88.9; ICD-10: 277.9) 6. Sleep Disorder, Unspecified (G47.9; ICD-10: 780.50) Endoscopic Findings: • Scattered superficial jejunal aphthae. • Patchy jejunal mucosal edema and erythema. • Solitary ileal aphthous ulcer. • Biopsy-confirmed chronic intestinal inflammation (non-specific). • Terminal ileum with lymphonodular hyperplasia. MRI Findings: • Evidence of demyelination. Neonatal History: • Swallowing difficulties and asphyxia at birth. • Hyperbilirubinemia post-birth. Growth and Development: • Current height: <3rd percentile. • Intellectual Disability: Mild. • Motor Impairments: o Clumsiness and poor coordination. o Severe deficits in fine motor skills. • Speech and Language Delay: Severe. • Chorea-like body movements. • Severe muscle cramps and generalized muscle weakness. • Hypotonia. Medical and Surgical History: • Severe constipation. • Recurrent severe ear infections. • Enlarged tonsils (removed at age 7). • Macroorchidism. Infectious History: • Epstein-Barr Virus (EBV) infection at 18 months followed by severe regression. Symptoms Present Since Infancy: • Sleep disturbances. • Recurrent stomach pain
	2412092	normal
	2412093	patient; Bechterew's disease ； Sleeping Apnea； Diabetes type 2
HPO	-	

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Clinical Suspicious Diseases or Genes	-

TEST INFORMATION

Test Name	OMI RareDx Whole Genome Sequencing TRIO
Tested strategy	Based on the clinical phenotype of the subject, the clear disease-related genes included in the OMIM database were analyzed.
Method	Whole genome analysis using high-throughput sequencing technology

TEST CONCLUSION

Primary Findings:

1 VUS variant has been detected in *CHD8* gene, known to be associated with {Autism, Susceptibility To, 18}.

1 VUS variant has been detected in *FRMPD4* gene, known to be associated with X-Linked Mental Retardation 104.

Additional Findings:

In additional findings, no variant related to clinical phenotype has been detected as pathogenic/likely pathogenic/VUS.

Mitochondrial Test Results:

In mitochondrial test results, no variant related to clinical phenotype has been detected as pathogenic/likely pathogenic/VUS.

Chromosome large copy number variation:

No pathogenic/likely pathogenic CNVs, chromosomal aneuploidy associated with the subject phenotype were detected.

Secondary Findings in ACMG Recommended Genes:

In incidental findings, no variant related to clinical phenotype has been detected as pathogenic/likely pathogenic/VUS. (SecondaryFinding_Var database)

PRIMARY FINDINGS *

NO.	Gene	Variants Coordinates	Zygosity[1] (proband/father /mother)	Pathogenicity[2]	OMIM Disease /Heredity model[3]	Reference
1	*CHD8*	chr14:21875055 NM_020920.3:c.2030G>A (p.Arg677His)	Het;Het;NA	Uncertain Significance	{Autism, Susceptibility To, 18}(OMIM:615032)/AD	-
2	*FRMPD4*	chrX:12712379 NM_014728.3:c.814-75C>T	Hemi;NA;Het	Uncertain Significance	X-Linked Mental Retardation 104(OMIM:300983)/XL	-

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Notes:

1. Zygosity: Hom represents a homozygous mutation; Het represents a heterozygous mutation; Hemi represents a hemizygous mutation.

2. Pathogenicity: Five categories are set out by ACMG:

***Pathogenic** stands for a disease-causing mutation;*

***Likely pathogenic** stands for a suspected disease-causing mutation;*

***Variant of Uncertain Significance** (VUS) stands for a clinically unknown mutation;*

***Likely benign** stands for a suspected benign mutation;*

***Benign** stands for a benign mutation.*

3. Heredity model: AD is autosomal dominant inheritance, AR is autosomal recessive inheritance, XL is X-linked inheritance, YL is Y-linked inheritance.

**PRIMARY FINDINGS include: 1) pathogenic/likely pathogenic variants which might be associated with patient's clinical manifestation 2) For recessive disorders, Variants of uncertain significance (VUS) detected simultaneously with a pathogenic/likely pathogenic variant, which might be associated with patient's clinical manifestation.*

INTERPRETATION：

1. The Variant *CHD8*;NM_020920.3:c.2030G>A(p.Arg677His) is detected, whose genotype is Het. It has not been reported by the literatures. According to ACMG Standards and Guidelines (appendix), it is classified as Uncertain Significance, PM2+PP2+PP3,the evidence is as follows:

PM2: Absent from controls(or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.

PP2: Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.

PP3: Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.) by SIFT, Condel, MutationTaster, Polyphen2 and dbscSNV softwares,etc.

Disease Description

Gene: *CHD8*

Disease: {Autism, Susceptibility To, 18}(OMIM:615032)

Heredity model: AD

Disease features: Autism, Susceptibility To, 18,also known as Intellectual developmental disorder with autism and macrocephaly (IDDAM) is characterized by impaired intellectual development, a highly penetrant autism spectrum phenotype, and macrocephaly. Other common features include tall stature, gastrointestinal symptoms, distinct facial features, sleep problems, and attention problems.(Source:OMIM)

2. The Variant *FRMPD4*;NM_014728.3:c.814-75C>T is detected, whose genotype is Hemi. It has not been reported by the literatures. According to ACMG Standards and Guidelines (appendix), it is classified as Uncertain Significance, PM2+PP3,the evidence is as follows:

PM2: Absent from controls(or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.

PP3: Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.) by SIFT, Condel, MutationTaster, Polyphen2 and dbscSNV softwares,etc.

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Disease Description

Gene: *FRMPD4*

Disease: X-Linked Mental Retardation 104(OMIM:300983)

Heredity model: XL

Disease features: A form of mental retardation, a disorder characterized by significantly below average general intellectual functioning associated with impairments in adaptive behavior and manifested during the developmental period. Intellectual deficiency is the only primary symptom of non-syndromic X-linked mental retardation, while syndromic mental retardation presents with associated physical, neurological and/or psychiatric manifestations.(Source:OMIM)

ADDITIONAL FINDINGS *

NO.	Gene	Variants Coordinates	Zygosity (proband/father /mother)	Pathogenicity	OMIM Disease /Heredity model	Reference
-	-	-	-	-	-	-

****SECONDARY FINDINGS** include: other variations related to clinical phenotype.*

INTERPRETATION:

No reportable variant has been detected as in secondary findings.

MITOCHONDRIAL TEST RESULTS**

NO.	Gene	Nucleotide changes	Mutation frequency	Pathogenicity	Disease	MtDB frequency	MITO MAP frequency	Reference
-	-	-	-	-	-	-	-	-

*** MITOCHONDRIAL TEST RESULTS** include: reported disease-causing variants associated with clinical phenotypes, referred to the Human Mitochondrial Genome Database: https://www.mitomap.org*

*** Mitochondrial genome reference sequence: NC_012920*

INTERPRETATION:

No reportable variant has been detected as in incidental findings in mitochondrial test result.

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CHROMOSOME LARGE COPY NUMBER VARIATION **

NO.	Test Result	Fragment Length (kb)	Related Genes	Pathogenicity	Variants Origin
-	-	-	-	-	-

**Notes:*

1. Only detect chromosome copy number variation ≥ 30kb

2. Chromosome Large Copy Number Variation pathogenicity include: 1) pathogenic/likely pathogenic variants which might be associated with patient's clinical manifestation 2) Variants of uncertain significance (VUS) only be reported when the variant is associated with patient's clinical manifestation, related to AD inheritance diseases and predicted to be pathogenic by software.

INTERPRETATION：

No pathogenic/likely pathogenic CNVs, chromosomal aneuploidy associated with the subject phenotype were detected.

INCIDENTAL FINDINGS IN ACMG RECOMMENDED GENES*

NO.	Gene	Variants Coordinates	Zygosity	Pathogenicity	OMIM Disease /Heredity model	Reference
-	-	-	-	-	-	-

*****INCIDENTAL FINDINGS IN ACMG RECOMMENDED GENES*** *include: the pathogenic and likely pathogenic variants in SecondaryFinding_Var database. These variants may not be related to the patient's clinical manifestations and diagnosis.*

INTERPRETATION ：

No reportable variant has been detected as in incidental findings in ACMG recommended genes.

REFERENCE

-

RECOMMENDATION

The parents and other members of the family should consider genetic counseling and testing by Sanger sequencing to validate the mutation described above.

METHODOLOGY AND LIMITATIONS

Whole Genome Sequencing Testing uses genomic DNA (derived from the blood of the subject or other kinds of samples) as the detection material, prepares a library after interrupting the DNA, and uses a high-throughput sequencing platform for whole-genome sequencing and mutation detection. This method is suitable for detecting exon mutations, intron mutations (including point mutation or insertion/deletion within 20bp), mitochondrial mutations, and chromosome CNVs larger than 30Kb. This method has limitations in directly detecting complex genome structural variations (e.g. inversion, translocation and large fragment insertion mutation), dynamic mutation, fragment heterozygous insertion (e.g. Alu-induced insertion), epigenetic effects, low ratio chimeric mutation or mutations in intergenic and regulatory regions, but bioinformatics analyses can infer these variations from the sequencing data in supplementary report. This method cannot completely cover highly repetitive

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region, high GC-rich region, high complexity region or pseudogene region, but the overall 20X coverage can reach more than 90%. This detection may not cover all possible pathogenic variants in specific given genes. The above results are for clinical reference purposes only. For all suspected pathogenic mutations, please validate the results with SANGER sequencing or qPCR. If you have any queries, please contact your genetic consultant.

This test is based on the subject main complaint, corresponding to the single-gene hereditary disease-causing genes and mitochondrial genes identified in OMIM (2021.6). Multi-gene susceptible disease-related genes and complex disease-related genes are not included in this analysis. If the subject chooses to analyze the designated gene sets, the non-specified genes are not in the scope of this analysis. Specify the gene name of the gene set and use the formal gene name. Variants found in a patient that are considered benign based on the medical literature are generally not reported; these variants could occur in 5' or 3' untranslated regions. This information can be made available upon request. A negative result from the analysis does not rule out the possibility that the tested individual carries a rare unexamined mutation in an undetectable region. Re-running the data in the future could yield new results and/or diagnosis. The ability to identify variants is dependent on the presence of these variants in the actual sequencing data. Interpretation assumes that any family relationships stated on the sample submission form are accurate.

Testing done and result approved by contractor laboratory Date: 14/02/2025

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APPENDIX

1. EVIDENCE OF PATHOGENICITY & BENIGN CATEGORY AND RULES FOR COMBINING CRITERIA TO CLASSIFY SEQUENCE VARIANTS

Evidence of pathogenicity:

PVS1_Strong: PVS1 downgraded to Strong.

PM2_Supporting: PM2 downgraded to Supporting.

PM3_Very Strong: PM3 upgraded to Very Strong.

PS4_Moderate: PS4 downgraded to Moderate.

PS4: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls.

PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.

PS4_Very Strong: PS4 upgraded to Very Strong.

PS2_Very Strong: PS2 upgraded to Very Strong.

PM3: For recessive disorders, detected in trans with a pathogenic variant. This requires testing of parents (or offspring) to determine phase.

PM5_Strong: PM5 upgraded to Strong.

PP1_Strong: PP1 upgraded to Strong.

PVS1: Null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease.

PP3_Moderate: PP3 upgraded to Moderate.

PS4_Supporting: PS4 downgraded to Supporting.

PS2_Supporting: PS2 downgraded to Supporting.

PM4: Protein length changes as a result of in-frame deletions/insertions in a non-repeat region or stop-loss variants.

PM1: Located in a mutational hot spot and/or critical and well-established functional domain without benign variation.

PM5_Supporting: PM5 downgraded to Supporting.

PM6_Strong: PM6 upgraded to Strong.

PS1_Moderate: PS1 downgraded to Moderate.

PP1: Cosegregation with disease in multiple affected family members in a gene definitively known to cause the Disease.

BP4_Moderate: BP4 upgraded to Moderate.

PVS1_Moderate: PVS1 downgraded to Moderate.

PP2: Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.

PM3_Strong: PM3 upgraded to Strong.

PP1_Moderate: PP1 upgraded to Moderate.

PP3: Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.) by SIFT, Condel, MutationTaster, Polyphen2 and dbscSNV softwares,etc.

PP4_Moderate: PP4 upgraded to Moderate.

PS2: De novo (both maternity and paternity confirmed) in a patient with the disease and no family history.

PM4_Supporting: PM4 downgraded to Supporting.

PM1_Supporting: PM1 downgraded to Supporting.

PS3: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.

BP4_Strong: BP4 upgraded to Strong.

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PM2: Absent from controls(or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.
PS3_Moderate: PS3 downgraded to Moderate.
PS1: Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.
BP4_Very Strong: BP4 upgraded to Very Strong.
PS3_Supporting: PS3 downgraded to Supporting.
PS2_Moderate: PS2 downgraded to Moderate.
PVS1_Supporting: PVS1 downgraded to Supporting.
PM6_Very Strong: PM6 upgraded to Very Strong.
PP4: Patient's phenotype or family history is highly specific for a disease with a single genetic etiology.
PP3_Strong: PP3 upgraded to Strong.
PM6: Assumed de novo, but without confirmation of paternity and maternity.
PM6_Supporting: PM6 downgraded to Supporting.
PM3_Supporting: PM3 downgraded to Supporting.

Evidence of benign:

BP4: Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.) by SIFT, Condel, MutationTaster, Polyphen2 and dbscSNV softwares, etc.
BP5: Variant found in a case with an alternate molecular basis for disease.
BS1: Allele frequency is greater than expected for disorder.
BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern.
BP2_Strong: BP2 upgraded to Strong.
BS3: Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing.
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease.
BP3: In-frame deletions/insertions in a repetitive region without a known function.
BS4_Supporting: BS4 downgraded to Supporting.
BS4: Lack of segregation in affected members of a family.
BS2_Supporting: BS2 downgraded to Supporting.
BS2: Observed twice in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age.
BP7: A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved.
BS1_Supporting: BS1 downgraded to Supporting.
BS3_Supporting: BS3 downgraded to Supporting.
BA1: Allele frequency in one of the controls databases (ESP6500, 1000 Genomes Project, ExAC and GnomAD) are more than 0.05.

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Rules for combining criteria to classify sequence variants:

Classification of variants	NO.	Rules for combining criteria
Pathogenic	1	PVS+≥1(PS)
	2	PVS+≥2(PM)
	3	PVS+1(PM)+1(PP)
	4	PVS+≥2(PP)
	5	≥2(PS)
	6	1(PS)+≥3(PM)
	7	1(PS)+2(PM)+≥2(PP)
	8	1(PS)+1(PM)+≥4(PP)
Likely Pathogenic	1	PVS+1(PM)
	2	1(PS)+1-2(PM)
	3	1(PS)+≥2(PP)
	4	≥3(PM)
	5	2(PM)+≥2(PP)
	6	1(PM)+≥4(PP)
Benign	1	BA1
	2	≥2(BS)
Likely Benign	1	1(BS)+1(BP)
	2	≥2(BP)
Uncertain Significance	1	others

Note:

Reference:

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[13] Zastrow D B, Baudet H, Shen W, et al. Unique aspects of sequence variant interpretation for inborn errors of metabolism (IEM): The ClinGen IEM Working Group and the Phenylalanine Hydroxylase Gene. Human mutation, 2018, 39(11): 1569-1580.

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[15] Brandt T, Sack LM, Arjona D, et al. Adapting ACMG/AMP sequence variant classification guidelines for single-gene copy number variants. Genet Med. 2020, 22(2):336-344.

[16] Wong L J C, Chen T, Wang J, et al. Interpretation of mitochondrial tRNA variants[J]. Genetics in Medicine, 2020, 22(5): 917-926.

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The versions of the frequencies database and the prediction algorithms softs are as follows:

ClinVar(2022-09-17), EPS6500(V2), 1000 human genome Project(Phase3), GnomAD(r2.0.1), ExAC (r0.3.1), BPGD* (V2022Q2), SecondaryFinding_Var*(V1.1_2020.3), dbscSNV(1.1), SpliceAI(1.3), dbNSFP(2.9.1), SIFT, MutationTaster, Polyphen2, Phylop, GERP.

*BPGD (BGI-Phoenix genetic database) is one comprehensive genetic disease database of BGI. Based on the gene-disease information from OMIM database, BPGD integrates the contents from multiple databases (such as OMIM, Genereview, Orphanet, Genetic Home Reference, Uniprot) including genes, disease names, inheritance patterns, clinical characteristics and *etc*.

SecondaryFinding_ Var (V1.1_2020.3) is the internal variation database of BGI, containing 2839 pathogenic and suspected pathogenic variations on 59 genes. The mitochondrial gene reference database and prediction software version are as follows: MtDB: http://www.mtdb.igp.uu.se/ (2019-12), MITOMAP: https://www.mitomap.org/ (2019-12), GnomAD(v.3.1), MitImpact_ db(3.0.6), APOGEE(v.1.0), MitoTIP(3.0.6), HmtVAR: https://www.hmtvar.uniba.it (2019-11). The dbNSFP (2.9.1) contains SIFT, MutationTaster, Polyphen2, Phylop, and GERP.

2. PARAMETERS

Sample ID	Coverage	Mean depth(X)	Proportion (Mean Depth>10X)	Proportion (Mean Depth>20X)
2412091	99.95%	54.36	99.57%	98.01%
2412093	99.95%	57.89	99.61%	98.42%
2412092	99.28%	58.47	98.91%	98.20%

3. FIGURE(S) RELATED TO THE RESULT

Null

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4. LIST OF LOW FREQUENT VARIANT(S) IDENTIFIED ON GENES WITH PHENOTYPE-CAUSING MUTATION

Note：

This report uses hg19 version of the human genome as reference genome.

Only variants detected in this sample with minor allele frequency (MAF) of less than 1% in OMIM disease genes are listed (Reference database including ESP6500, 1000 human genome Project, ExAC, GnomAD).

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