Accession ID:	**599**
Sample Type:	Blood
Patient's Name:	**ABCD**
Gender/Age:	Male/7 Days

CLINICAL EXOME SEQUENCING (CES) EXPANDED PANEL

Data Uploaded On:	26/01/2024	**Report Generated On:**	29/01/2024

CLINICAL INDICATIONS / PHENOTYPE:

Developmental regression, Dyslexia

RESULTS:

List of clinically significant mutations (CSM)

GENE	VARIANT	ZYGOSITY	DISEASE	INHERITANCE	INTERPRETATION
ZBTB20 (NM_001348800.3)	Exon 12 **c.2192A>G (p.Asn731Ser)**	Heterozygous	**Primrose syndrome** (OMIM#259050)	AD	**Uncertain Significance**
ADAR (NM_001111.5)	Exon 2 **c.577C>G (p.Pro193Ala)**	Heterozygous	**Aicardi-Goutieres syndrome 6** (OMIM#615010) **Dyschromatosis symmetrica hereditaria** (OMIM#127400)	AR, AD	**Likely Pathogenic**

***Genetic test results are reported based on the recommendations of American College of Medical Genetics.**
****Sanger validation is recommended for the above listed variants.**
*****The significance/classification of the variant(s) may change based on genetic testing in the parents and other family members.**
******Data revaluation performed upon the up gradation of databases used and results may vary in accordance.**

INTERPRETATION:

ZBTB20;c.2192A>G(p.Asn731Ser)

Genomic location: chr3:114339039 T>C
Variant type: Missense
Depth: total 53; alt 26 (49%);
Frequency: The variant is rare, observed in 1 alleles out of 833,110 (0%) in the gnomAD reference population dataset.
Prediction tools: Computational tools yield conflicting predictions of the impact of the variant on the gene or gene product.
Clinical evidence: This variant has previously been described in ClinVar (VCV1988250) with the following classifications: VUS (1).

ADAR;c.577C>G(p.Pro193Ala)

Genomic location: chr1:154602065 G>C
Variant type: Missense
Depth: total 85; alt 42 (49%);
Frequency: The variant is rare, observed in 5,099 alleles out of 1,614,176 (0.316%) in the gnomAD reference population dataset.
Prediction tools: Multiple lines of computational tools predict a deleterious effect on the gene or gene product.
Clinical evidence: This variant has previously been described in ClinVar (VCV126395) with the following classifications: VUS (3) / LP (7) / P (14) / Other (2).

INCIDENTAL FINDINGS:

GENE	VARIANT	ZYGOSITY	DISEASE	INHERITANCE	INTERPRETATION
FBN1 (NM_000138.5)	Exon 24 **c.2771G>T (p.Gly924Val)**	Heterozygous	**Ectopia lentis 1, isolated, autosomal dominant** (OMIM#129600) **Geleophysic dysplasia 2** (OMIM#614185) **Weill-Marchesani syndrome 2, dominant** (OMIM#608328) **Acromicric dysplasia** (OMIM#102370) **Stiff skin syndrome** (OMIM#184900) **Progeroid and marfanoid aspect-lipodystrophy syndrome** (OMIM#616914) **Marfan syndrome** (OMIM#154700) **MASS syndrome** (OMIM#604308)	AD, AR	Uncertain Significance

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****Sanger validation is recommended for the above listed variants.**
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******Data revaluation performed upon the up gradation of databases used and results may vary in accordance.**

INTERPRETATION:

FBN1;c.2771G>T(p.Gly924Val)
Frequency: The variant is rare, observed in 2 alleles out of 780,646 (0%) in the gnomAD reference population dataset.
Prediction tools: Multiple lines of computational tools predict a deleterious effect on the gene or gene product.
Clinical evidence: This variant has previously been described in ClinVar (VCV457181) with the following classifications: VUS (2).

Genomic location: chr15:48492544 C>A
Variant type: Missense
Depth: total 53; alt 23 (43%);
Frequency: The variant is rare, observed in 2 alleles out of 780,646 (0%) in the gnomAD reference population dataset.
Prediction tools: Multiple lines of computational tools predict a deleterious effect on the gene or gene product.
Clinical evidence: This variant has previously been described in ClinVar (VCV457181) with the following classifications: VUS (2).

RECOMMENDATIONS:

- Genetic counseling is advised for interpretation on the consequences of the variant(s).
- If results obtained do not match the clinical findings, additional testing should be considered as per referring clinician's recommendation.
- Sanger validation is recommended to ascertain the false calls (highly recommended for low sequencing depth variants).
- Variant segregation can be analyzed by assaying for the specific mutation detected in all first-degree relatives. This may be helpful for individualized monitoring and surveillance recommendations for relatives as well as for future pre-implantation/prenatal applications, if desired

METHODOLOGY:

The Genes2Me Clinical Exome Sequencing (CES) Expanded NGS panel was used for sequencing that screens for ~7513 clinically relevant genes (coding regions of the genome) for diseases associated with genetic mutations as well as mitochondrial genome.
It covers all major mutations like SNV, CNV and Indels with hotspot adding up to a target size of 19.5 Mb with hybridization-based target capture technique.
After raw data generation, we follow the GATK best practices framework for identification of variants in the sample, starting with raw data quality check using the FastQC followed by BWA read aligner for mapping/aligning to human reference genome GRCh38.
After the alignment, GATK HaplotypeCaller algorithm is used for variant calling. Annotation of the variants is performed using open-source available software SnpEff. Further, clinically relevant mutations are annotated using published variants in literature and set of diseases databases – ClinVar, OMIM and HPO. The 1000Genome, gnomAD, dbSNP and 100K Genome Asia databases are used for annotation of variants for their minor allele frequency. The dbNSFP database is used for annotation and functional prediction of all potential non-synonymous variants.

TECHNICAL INFORMATION:

Variant	Depth (Total)	Ref	Alt	Variant quality	Mapping quality
ZBTB20;c.2192A>G	53	T	C	122.58	
ADAR;c.577C>G	85	G	C	194.32	
FBN1;c.2771G>T	53	C	A	97.00	

VARIANT CLASSIFICATION AS PER "ACMG GUIDELINES":

Variant is a permanent change in the sequence of DNA that makes up a gene that could be pathogenic – causing a disease or benign – not causing a disease.

1. Pathogenic Variant
   The variant is responsible for causing disease with ample scientific research to support the disease – gene – variant association. These variants are often referred to as mutations.
2. Likely Pathogenic Variant
   The variant is very likely responsible to contribute to the development of disease with insufficient scientific evidences to prove the association. Additional evidences and testing is expected to confirm this assertion of pathogenicity.
3. Variant of Uncertain Significance
   The variant whose impact is difficult to classify based on current available scientific evidences. Further testing of the patient or family members is recommended.

LIMITATIONS:

- Genetic testing is an important part of the diagnostic process however it may not always give a definitive answer. In some cases, a genetic variant may be missed due to the limitations in existing medical

knowledge and testing technology. Accurate interpretation of test results is dependent on the availability of biological & medical information (clinical history) of the family, failing to this may leads to incorrect result interpretation and diagnosis.

- Test results are interpreted in the context of clinical findings, available scientific evidences, family history and other laboratory data. The variation(s) which is/are potentially relevant – significant related to the patient's provided medical history is/are reported.
- Genetic testing is highly accurate but rarely inaccurate results may occur for various reasons like mislabeling of samples, inaccurate clinical/medical family history, rare technical errors or unusual circumstances such as bone marrow transplantation, blood transfusion or the presence of change(s) in such a small percentage of cells that may not be detectable(mosaicism).

DISCLAIMER:

- The interpretation of variants in this report is performed to the best knowledge of the scientific & medical information available at the time of reporting. The classification of variants is based on ACMG (American College of Medical Guidelines) guidelines.
- As of the inherent technological limitations of the sequencing assay, some of the coding regions can't be properly sequenced, so, variations in these regions may not be identified & interpreted. It is possible that variants not identified by the assay may be associated with the provided phenotypes of the patient.
- It is possible due to insufficient phenotypic information, a gene – variant may be present in data but not selected for analysis and interpretation.
- The mutations have not been confirmed by Sanger sequencing.
- Genes2Me clarify that the generated report(s) doesn't provide any kind of diagnosis or opinion or recommendation for any disease and its cure in any manner. It is therefore recommended that the patient and/or the guardian(s) of the patient must take the consultation of the clinician or a certified physician or doctor for further course of action.
- If the provided material quality and/or quantity not up to the desired level so, in that case, test(s) result(s) may be misleading or even wrong. Therefore, Genes2Me hereby disclaims all liability arising in this connection with the test(s) and report(s).
- The analysis pipeline is developed in-house and the performance characteristics of this analysis are determined by Genes2Me only.
- This test result should be used as a reference by the healthcare provider for diagnosis and development of treatment plan.

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***For any further technical queries please contact at contact@genes2me.com**