GenPeima
Precision Medicine

No.4 Niloo St., Valiasr Ave., Tehran, 1434875879,
Iran +982188658752
https://genpeima.com

Whole Exome Sequencing Report_clinical report

Patient Information

Name NA	**Test(s) requested:** NA
Gender NA	**Sample type:** NA
DOB NA	**Collection Date** NA
Patient ID NA	**Report Date** NA

Result Type: Positive

Summary of Results

Primary SNV Findings — Likely pathogenic

CFHR5| Transcript: NM_030787.4
c.1511_1513delinsAA(p.Leu504Glnfs*11)| Zygosity: **HET**

Clinical interpretation:

This variant is consistent with the genetic diagnosis of autosomal dominant **Nephropathy due to CFHR5 deficiency** (OMIM: 614809).

CNV Findings — Pathogenic

Region: **Del:chrX(hg38):?-31929348-31968438-?**
Copy number: **0 (Hemi)**
Classification: **Pathogenic**
Length: **39.1Kb**

Carrier Findings — Carrier

1. *FAH* | Condition: Tyrosinemia, type I | Inheritance: **AR**
c.7786C>T(p.Arg2596*) | Classification: **Pathogenic** | Zygosity: **HET**

2. *CEP295*| Condition: Seckel syndrome 11| Inheritance: **AR**
c.7786C>T(p.Arg2596*) | Classification: **Likely Pathogenic** | Zygosity: **HET**

3. *HFE* | Condition: Hemochromatosis, type 1| Inheritance: **AR**
c.187C>G(p.His63Asp)| Classification: **Pathogenic** | Zygosity: **HET**

4. *FLG*| Condition: Ichthyosis vulgaris| Inheritance: **AR**
c.7837A>T(p.Arg2613*)|Classification: **Pathogenic** | Zygosity: **HET**

Incidental Findings — Actionable

DSG2| c.472del(p.Val158Cysfs*14)
Classification: **Likely pathogenic**
Condition: **Arrhythmogenic right ventricular dysplasia 10**
Inheritance: **AD**

....., PhD
Head of Genetics Department
Human Geneticist

Clinical Indications

The proband is a 12-year-old male. He has muscle weakness. His blood examination showed elevated level of CPK and liver enzymes. Also, he has haemoglobinuria.

HPO Terms Applied: Elevated circulating creatine kinase, Haemoglobinuria, Myoglobinuria, Elevated circulating hepatic transaminase concentration, Pes planus, Muscle weakness, Gait disturbance, Psychomotor deterioration.

Consanguinity of parents: Yes

Detailed Variant Information

1. Primary SNV Findings

Gene / Transcript	Genomic Pos	Zygosity	Associated Disease (OMIM)	Inheritance	Type / Classification*
CFHR5 NM_030787.4	chr1:197004840-CTAG-CAA c.1511_1513delinsAA (p.Leu504Glnfs*11) Exon 9/10	HET	Nephropathy due to CFHR5 deficiency (OMIM: 614809)	AD	**Frameshift Likely pathogenic (Class 2)**

Comment: This variant creates a shift in the reading frame starting at codon 504. The new reading frame ends in a stop codon 11 position downstream. This variant is classified **likely pathogenic** according to ACMG. Pathogenic variants in the CFHR5 gene are associated with autosomal dominant **Nephropathy due to CFHR5 deficiency** (OMIM: 614809).

C3 glomerulopathy-3 (C3G3) is an autosomal dominant kidney disease characterized by the onset of microscopic or macroscopic **hematuria** in the first 3 decades of life, followed by variable progression of renal disease. After age 30, about half of patients continue to have episodic hematuria while maintaining normal renal function, whereas the other half develop proteinuria and progressive renal failure or end-stage renal disease. In some cases, renal dysfunction may be triggered or exacerbated by an infectious disease, often an upper respiratory infection or pharyngitis. Some patients may also develop hypertension. Renal biopsy shows glomerular C3 deposition and mesangial proliferation with glomerulonephritis. Membranoproliferative glomerulonephritis (MPGN) may also be observed on renal biopsy. Males tend to have a more severe phenotype than females and are more likely to develop end-stage renal disease, often necessitating dialysis or renal transplant (PMID: 21566112).

* Variant classification is based on ACMG recommendations: Class 1: Pathogenic, Class 2: Likely pathogenic, Class 3: Variant of uncertain significance (VUS), Class 4: Likely benign, Class 5: Benign.

……., PhD
Head of Genetics Department
Medical Geneticist

2. Copy Number Variants (CNV)

Gene (s)	Region	Chr. Band	CNV Length	Copy Numbers	Type / Classification*
DMD	Del:chrX(hg38):?-31929348-31968438-?	Xp21.1	~39.1Kb	0 (Hemi)	**Deletion Pathogenic (Class 1)**

Comment: By NGS-CNV analysis we detected a CNV of **approximately 39.1 kb** consistent with a single copy loss (hemizygous deletion), encompassing the short arm of the chromosomeX (chrX:?-31929348-31968438-? based on the genomic
assembly hg38) that encompassing exons 45 to 47 in the critical region of **DMD** gene. Defining the breakpoint in the upstream and downstream of the intronic region based on the deleted exons is an estimation.

It is revealed that deletion mutations in the **DMD** gene are correlated with the X-linked recessive of **Duchenne muscular dystrophy** disease (OMIM: 310200), and X-linked **Cardiomyopathy, dilated, 3B** (OMIM: 302045). The detected CNV is classified pathogenic (class 1) according to ACMG recommendation.

Dystrophin-associated muscular dystrophies range from the severe Duchenne muscular dystrophy (DMD) to the milder Becker muscular dystrophy (BMD; 300376). Mapping and molecular genetic studies showed that both are the result of mutations in the huge gene that encodes dystrophin, also symbolized DMD. Approximately two-thirds of the mutations in both forms are deletions of one or many exons in the dystrophin gene. Although there is no clear correlation found between the extent of the deletion and the severity of the disorder, DMD deletions usually result in frameshift.

The most distinctive feature of Duchenne muscular dystrophy is a progressive proximal **muscular dystrophy** with characteristic pseudohypertrophy of the calves. The bulbar (extraocular) muscles are spared but the myocardium is affected. There is massive **elevation of creatine kinase levels** in the blood, myopathic changes by electromyography, and myofiber degeneration with fibrosis and fatty infiltration on muscle biopsy.The onset of Duchenne muscular dystrophy usually occurs before age 3 years, and the victim is chairridden by age 12 and dead by age 20. The onset of Becker muscular dystrophy is often in the 20s and 30s and survival to a relatively advanced age is frequent.

Boland et al. (1996) studied a retrospective cohort of 33 male patients born between 1953 and 1983. The mean age at DMD diagnosis was 4.6 years; wheelchair dependency had a median age of 10 years; cardiac muscle failure developed in 15% of patients with a median age of 21.5 years; smooth muscle dysfunction in the digestive or urinary tract occurred in 21% and 6% of the patients, respectively, at a median age of 15 years. In this cohort, death occurred at a median age of 17 years (PMID: 8652023).

*Variant classification is based on ACMG recommendations: Class 1: Pathogenic, Class 2: Likely pathogenic, Class 3: Variant of uncertain significance (VUS), Class 4: Likely benign, Class 5: Benign

……., PhD
Head of Genetics Department
Medical Geneticist

3. Carrier Findings

Gene / Transcript	Genomic Pos	Zygosity	Associated Disease (OMIM)	Inheritance	Type / Classification*
FAH NM_000137.4	chr15:80180230-G-A c.1062+5G>A Intron 12/13	HET	Tyrosinemia, type I (OMIM: 276700)	AR	**Splice region** **Pathogenic** **(Class 1)**
CEP295 NM_033395.2	chr11:93730249-C-T c.7786C>T (p.Arg2596*) Exon 30/30	HET	Seckel syndrome 11 (OMIM: 620767)	AR	**Stop gain** **Likely pathogenic** **(Class 2)**
HFE NM_000410.4	chr6:26090951-C-G c.187C>G (p.His63Asp) Exon 2/6	HET	Hemochromatosis, type 1 (OMIM: 235200)	AR	**Missense** **Pathogenic** **(Class 1)**
FLG[1] NM_002016.2	chr1:152307049-T-A c.7837A>T (p.Arg2613*) Exon 3/3	HET	Ichthyosis vulgaris (OMIM: 146700)	AD,AR	**Stop gain** **Pathogenic** **(Class 1)**

* Variant classification is based on ACMG recommendations: Class 1: Pathogenic, Class 2: Likely pathogenic, Class 3: Variant of uncertain significance (VUS), Class 4: Likely benign, Class 5: Benign.
1. Please note that this variant is located in a region that is highly similar to another location in the same gene.

……., PhD
Head of Genetics Department
Medical Geneticist

4. Incidental Findings (ACMG SF v3.3)

Gene / Transcript	Genomic Pos	Zygosity	Associated Disease (OMIM)	Inheritance	Type / Classification*
DSG2 NM_001943.5	chr18-31521191-AG-A c.472del(p.Val158Cysfs*14) Exon 5/15	HET	Arrhythmogenic right ventricular dysplasia 10 (OMIM: 610193)	AD	**Frameshift Likely pathogenic (Class 2)**

Comment: This variant creates a shift in the reading frame starting at codon 158. The new reading frame ends in a stop codon 14 positions downstream. This variant is classified **likely pathogenic** according to **ACMG** and **ClinVar**. Pathogenic variants in the DSG2 gene are associated with autosomal dominant inheritance **Arrhythmogenic right ventricular dysplasia 10** (OMIM: 610193) and autosomal recessive **Cardiomyopathy, dilated, 1BB** (OMIM: 612877).

Arrhythmogenic right ventricular cardiomyopathy (ARVC) – previously referred to as arrhythmogenic right ventricular dysplasia (ARVD) – is characterized by progressive fibrofatty replacement of the myocardium that **predisposes to ventricular tachycardia and sudden death in young individuals and athletes.** It primarily affects the right ventricle, and it may also involve the left ventricle. The presentation of disease is highly variable even within families, and some affected individuals may not meet established clinical criteria. The mean age at diagnosis is 31 years (±13; range: 4-64 years).

* Variant classification is based on ACMG recommendations: Class 1: Pathogenic, Class 2: Likely pathogenic, Class 3: Variant of uncertain significance (VUS), Class 4: Likely benign, Class 5: Benign.

Interpretation & Recommendations

- MLPA analysis or any other laboratory test based on the experts' decision is needed to be done for the confirmation of the detected CNV in the **DMD** gene is recommended.
- Sanger sequencing to confirm the detected variants in the proband especially the likely pathogenic one in the **CFHR5** gene as the main cause of the disease.
- Parental carrier testing is recommended to determine whether the detected variant in **CFHR5** gene is inherited or arises de novo.
- Sanger sequencing of the detected variant in the **DMD gene** in the other informative family members in particular affected members.
- Counseling with a cardiologist is strongly recommended to evaluate clinical consequence of detected variant in the **DSG2** gene as incidental finding.
- Genetic counseling is also recommended.

……., PhD
Head of Genetics Department
Medical Geneticist

Statical Analysis

Average Coverage (X)	% Target bp Covered					
	0X	≥ 1X	≥ 5X	≥ 10X	≥ 30X	≥ 50X
129.00	0.90	90.10	99.00	98.05	97.20	96.00

Methodology & Limitations

Methodology: The Twist exome panel V2 Kit was used to enrich the whole human exome. Sequenced on NovaSeq X plus. Aligned to GRCh38/hg38. An in-house bioinformatics pipeline was used for analysis. Variant interpretation follows ACMG/AMP and relevant gene- and phenotype-specific guidance, with internal review by a molecular genetics specialist. CNV calling, if applicable, performed from exome read-depth metrics with orthogonal review for clinically relevant events.

Limitations: Presented test results are interpreted according to the provided clinical reports and family history. Besides, variants of salient health issues are reported in incidental findings according to ACMG guidelines. Current methods detect single rare variants, indels, and CNVs in enriched regions. Please note that, specific genetic events like copy number variants may not be reliably detected with Exome Sequencing and needs further confirmation in the laboratory. Repeat expansions are not within scope. This assay may not detect low-level mosaicism, deep intronic variants, balanced rearrangements, repeat expansions, epigenetic abnormalities, or variants in poorly covered exons. In addition, due to limitations in technology, full coverage on target is not accessible and some regions may not be ideally covered, hence such located variants cannot be confidently detected. A negative result does not exclude a genetic disorder. Clinical correlation and, when indicated, targeted testing or reanalysis are recommended.

Disclaimer: Preparation and processing of samples provided to …. laboratory are performed based on the highest scientific standards. … laboratory is not liable for incomplete or misleading results arising from poor sample quality or inaccurate clinical information provided at the time of testing. Very few cases of inaccurate/incorrect reports may occur due to several reasons, e.g. because of the quality of the material provided to ….. laboratory or in cases where any test provided by ….. laboratory fails for unknown or unforeseeable reasons that cannot be recognized by ….. laboratory in advance. In such cases, ….. laboratory will not be responsible and/or liable for the incomplete, potentially misleading or even wrong result of any testing if such issue could not be prevented by ….. laboratory in advance.

GenPeima
Precision Medicine

No.4 Niloo St., Valiasr Ave., Tehran, 1434875879,
Iran +982188658752
https://genpeima.com

……., PhD
Head of Genetics Department
Medical Geneticist