bioAro

# Whole Genome Sequencing Report

Suite 1020 Calgary Place Tower 1
330- 5th Avenue SW, Calgary, AB

3151 27 St NE Calgary, AB, T1Y 7J8

Tel: 403.250.2221
Email: Info@bioaro.com
www.bioaro.com

## Patient Information:

| | | | |
|---|---|---|---|
| Name | Amrita Arora | Sample Type | WGS |
| Gender | Female | Collection Date | 3 March, 2024 |
| Date of Birth | 27 Aug, 1979 | Report Date | 23 March, 2024 |
| ID | P3626 | Patient's Addres | 159, Birch Road |

## Summary

Variations in multiple genes have been identified in this individual. The report has examined variants that have beenflagged as 'Pathogenic or Likely Pathogenic', as well as some of the VUS variants. Many of these variants have been implicated, by multiple peer-reviewed clinical studies and Genomic databases in different hereditary and acquired diseases. A clinical correlation of these variants with any symptoms or family history of the patient, by a physician isadvised.

***AMPD1, TSFM, MYO15A, LPR2, COL3A1, CACNA1D, FLG, MASP1, DST, COL9A1, TBXAS1, CPT1A, INPPL1, KRT3, KRT4, KRT8, HPD, TNFSF11, NKX2-1, COQ9, GAMT, IFIH1, ITGB2, FOXQ1, MSX2.***

The selection of these key variants has been carefully undertaken, emphasizing their significance and potential implications for gene functioning. This curation process involves a thorough evaluation of each variant's association with observed diseases, ensuring a comprehensive understanding of their role in health and potential impact on the individual.

## Overall Summary of the Genomic test

WGS has identified multiple variants in the individual. As per ACMG guidelines, "Pathogenic' and "Likely Pathogenic" variants are treated as Pathogenic. These variants are likely to alter the normal functioning of a gene, cause disease, and affect the health of an individual. However, an analysis of some variants of unknown significance (VUS), is also included for this patient.

Summary of genes associated with specific disease.

**Table 1: This table provides information on genetic variants identified in cancer-associated genes.**

| Chromosome | Position | Ref | Alt | Variant Identifier | Gene Name | Function |
|---|---|---|---|---|---|---|
| 6 | 1318643 | C | G,T | rs11242675 | FOXQ1 | The FOXQ1 gene, a member of the forkhead transcription factor family, is overexpressed in colorectal cancer (CRC). It promotes tumor growth by upregulating genes associated with positive roles in tumor growth and enhancing angiogenesis and inhibiting apoptosis. FOXQ1's tumorigenic effects are independent of p21 regulation. |
| 5 | 174713048 | C | T | rs192597222 | MSX2 | The MSX2 gene, found on chromosome 5, is associated with craniosynostosis, a condition where cranial sutures fuse prematurely, leading to abnormal skull shape. Mutations in MSX2 have been linked to this disorder, with affected individuals showing specific genetic markers and histidine substitutions |

## Table 2: This table presents genetic variants associated with cardiovascular diseases.

| Chromosome | Position | Ref | Alt | Variant Identifier | Gene Name | Function |
|---|---|---|---|---|---|---|
| 1 | 152313385 | G | A C,T | rs61816761 | FLG | Filaggrin gene defects increase the risk of allergic sensitisation, atopic eczema, allergic rhinitis, and asthma, particularly in individuals with atopic eczema. Restoring skin barrier function in individuals with filaggrin deficiencies may help prevent the development and progression of allergic disease. |
| 2 | 162254026 | A | G | rs2111485 | IFIH1 | The IFIH1 gene codes for MDA5, a sensor detecting viral RNA. Variants in IFIH1 impair MDA5 function, leading to compromised viral sensing in the gut and contributing to Very Early Onset Inflammatory Bowel Disease (VEOIBD). |

Below is a summary of the variant genes identified in this individual. This section has been segregated into two categories:

**TABLE 1:** Contains gene/s, which are Pathogenic or likely pathogenic, which several clinical studies have shown may affect the normal functioning of the gene and cause disease/s.

**TABLE 2:** Contains a list of genes,which the WGS test has shown to be variants of unknown significance (VUS).

**Note:** *The presence of these variants does not imply the individual shall necessarily manifest the disease or its symptoms*

## TABLE 1

## Summary Table of Pathogenic/Likely Pathogenic Genetic Variants from the Screen

| Gene Name | Chr:pos | Variant Identifier | Zygosity | Inheritance | Classification | Associated Disease Risk |
|---|---|---|---|---|---|---|
| *AMPD1* | 1:115216547 | rs749628995 | Heterozygous | Autosomal recessive | Pathogenic | Myopathy (due to AMP deaminase deficiency) |
| *TSFM* | 12:58179944 | . | Heterozygous | Autosomal recessive | Pathogenic | Dilated Cardiomyopathy Combined Oxidative Phosphorylation Deficiency |
| *MYO15A* | 17:18046894 | rs375290498 | Heterozygous | Autosomal recessive | Pathogenic | Deafness Autosomal recessive) |

| Gene Name | Chr:pos | Variant Identifier | Zygosity | Inheritance | Classification | Associated Disease Risk |
|---|---|---|---|---|---|---|
| *FOXQ1* | 1:152313385 | rs61816761 | Heterozygous | Autosomal recessive | Pathogenic | Esophageal cancer, alcohol-related, susceptibility to |

## TABLE 2:

## Summary of VUS / Uncertain significance mutations found in the client include:

These variant genes include those for which firm clinical evidence may not yet be available (VUS or conflicting). These variations need correlation with clinical symptoms or family history to determine risk assessment. Further investigations and monitoring may be prescribed by the physician or geneticist.

| Gene Name | Chr:pos | Variant Identifier | Zygosity | Inheritance | Classification | Associated Disease |
|---|---|---|---|---|---|---|
| *LRP2* | 2:170103277 | rs201299366 | Heterozygous | Autosomal recessive | Uncertain significance | Donnai-Barrow Syndrome Prolactinoma |
| *COL3A1* | 2:189863424 / 189862430 | rs1801183 | Heterozygous | Autosomal recessive, Autosomal dominant | Uncertain significance | Ehlers-Danlos syndrome type 4 Polymicrogyria |
| *CACNA1D* | 3:53766920 / 53779863 | rs186968009 /202058955 | Heterozygous | Autosomal recessive | Uncertain significance | Sinoatrial Node Dysfunction Primary Aldosteronism, Seizures, And Neurologic Abnormalities |
| *FLG* | 1:152313385 | rs61816761 | Heterozygous | Autosomal dominant | Uncertain significance | Rare allergic disease |
| *MASP1* | 3:186943297 | rs556620311 | Heterozygous | Autosomal recessive | Uncertain significance | 3mc Syndrome (Craniofacial-ulnar-renal disease) |
| *DST* | 6:56471615 | rs45442999 | Heterozygous | Autosomal recessive | Uncertain significance | Charcot-Marie-Tooth Disease DST-related epidermolysis bullosa |

| Gene Name | Chr:pos | Variant Identifier | Zygosity | Inheritance | Classification | Associated Disease |
|---|---|---|---|---|---|---|
| *COL9A1* | 6:70990711 | . | Heterozygous | Autosomal dominant, Autosomal recessive | Uncertain significance | Epiphyseal Dysplasia<br>Stickler Syndrome |
| *TBXAS1* | 7:139715531 | rs199422117 | Heterozygous | Autosomal recessive | Uncertain significance | Aregenerative Anemia |
| *CPT1A* | 11:68530124 | rs573452454 | Heterozygous | Autosomal recessive | Uncertain significance | Carnitine palmitoyl transferase IA deficiency |
| *INPPL1* | 11:71943961 | rs61749195 | Heterozygous | Autosomal recessive | Uncertain significance | Opsismodysplasia |
| *KRT3* | 12:53185183 | rs371219499 | Heterozygous | Autosomal dominant | Uncertain significance | Juvenile hereditary epithelial dystrophy of Meesmann |
| *KRT4* | 12:53201474 | rs775355098 | Heterozygous | Autosomal dominant | Uncertain significance | Hereditary mucosal leukokeratosis |
| *KRT8* | 12:53298579 | rs59536457 | Heterozygous | - | Uncertain significance | Cryptogenic Cirrhosis |
| *HPD* | 12:122277904 | rs137852868 | Heterozygous | Autosomal recessive, Autosomal dominant | Uncertain significance | Tyrosinemia Hawkinsinuria |
| *TNFSF11* | 13:43148519 | rs200788562 | Heterozygous | Autosomal recessive | Uncertain significance | Infantile malignant osteopetrosis |
| *NKX2-1* | 14:36987154 | rs575848748 | Heterozygous | Autosomal dominant | Uncertain significance | Chorea<br>Choreoathetosis<br>Thyroid Cancer |
| *MSX2* | 5:174713048 | rs192597222 | Heterozygous | Autosomal dominant | Autosomal dominant | Carcinosarcoma of the corpus uteri |

| Gene Name | Chr:pos | Variant Identifier | Zygosity | Inheritance | Classification | Associated Disease |
|---|---|---|---|---|---|---|
| *COQ9* | 16:57486832 | rs547254482 | Heterozygous | - | Uncertain significance | Coenzyme Q10 Deficiency |
| *GAMT* | 19:1401403 | . | Heterozygous | Autosomal recessive | Uncertain significance | Guanidinoacetate methyltransferase deficiency |
| *IFIH1* | 2:162254026 | rs2111485 | Heterozygous | Autosomal dominant | Uncertain significance | Hypersensitivity pneumonitis |
| *ITGB2* | 21:46330222 | rs552407409 | Heterozygous | Autosomal recessive | Uncertain significance | Leukocyte adhesion deficiency |

## What this result means to you?

*As per the criteria laid out by the American College of Medical Genetics (ACMG), this report has separated genes with alterations, into those which are either* ***"pathogenic" or "likely pathogenic".***

***Pathogenic*** *alterations in a gene imply that the specific alteration is* ***100%*** *associated with the disease observed in the population. While* ***likely pathogenic*** *implies that there is a* ***90%*** *certainty of the variant gene being responsible for the disease in the population.*

*These genetic alterations can compromise the functioning of the listed genes and affect the health of the individual.*

*The presence of these variants does not imply the individual shall necessarily manifest the disease or its symptoms. A clinical correlation of these variants with any symptoms or family history of the patient is required to be performed by a physician or geneticist (and interpretation made by a genetic counselor for the patient).*

Multiple variant genes have been found, which are pathogenic/likely pathogenic or VUS. Many of these are heterozygous recessive (unlikely to produce a disease). However, a clinical correlation with any symptoms or family history is strongly advised to support further investigations or risk assessment.

A few key variants are summarized below:

***AMPD1, TSFM, MYO15A, LPR2, COL3A1, CACNA1D, FLG, MASP1, DST, COL9A1, TBXAS1, CPT1A, INPPL1, KRT3, KRT4, KRT8, HPD, TNFSF11, NKX2-1, COQ9, GAMT, IFIH1, ITGB2, FOXQ1, MSX2.***

## Recommendation / Next step

Variations in multiple genes have been identified in this individual. The report has examined variants that have beenflagged as 'Pathogenic or Likely Pathogenic', as well as some of the VUS variants. Many of these variants have been implicated, by multiple peer-reviewed clinical studies and Genomic databases, in different diseases.

In the case of an autosomal dominant variant, a single copy of the variant gene is sufficient to produce the symptoms/disease in the individual (or modify the response to drugs). Additionally, where both copies of a variant gene are affected (homozygous), the offspring/children have a 50% chance of getting the disease (*and a 100% probability of getting the disease if a similar variant gene is inherited from the other parent*).

The gene alterations identified in this client can lead to the development of associated diseases, however, not all individuals develop actual symptoms. Several studies have shown that positive modifications to diet, gut microbiome, and other environmental factors (e.g. smoking) can ameliorate the effect of genetic variations.

The individual is strongly advised to have a genetic analysis completed for all their siblings/children/grandchildren to help identify variant genes that may have been transmitted to the children (or grandchildren). This wouldallow appropriate counseling and management of children to help prevent (or reduce the severity) of any inflammatory disease in them (*or their children*). The individual is advised to discuss a TRIO analysis.

## Summary of Genomic test performed

Whole genome sequencing (WGS) was carried out on a blood sample obtained from the patient. WGS examines the entire set of known genes present in humans (over 22,000 genes) and compares it with a reference human genome (GRCh37). The test and subsequent analysis of the data, helps identify which genes show alterations or variations, ascompared to the reference genome.

Further analysis (tertiary analysis and clinical correlation) of the data, help to distinguish, which of these **gene variants** may be responsible for:

1. Any diseases (or clinical symptoms) the patient has today.
2. Can be harmful (pathogenic) to the patient, and put her/him at high risk of getting a disease in the future.
3. Which genetic variants and/or associated disease/s could have been inherited from parents?
4. If there is a Proband in the family, how does the individual correlate to the proband clinically and genetically?
5. Adverse effects/correlation with any medication the patient is taking today (Pharmacogenomic Analysis/on demand).

BioAro uses the DNBSEQ G400 for WGS. **All collected data is analyzed in-house and stored locally, without compromising the security or privacy of the data.**

*As per **ACMG guidelines** (American College of Medical Geneticists):*

1. *Alterations in genes are often referred to as 'variations'; altered genes are often called 'variant genes' or simply 'variants'.*
2. *Pathogenic and likely pathogenic variants, carry >90% certainty of being responsible for a disease and hence are accorded the same level of association.*
3. *Variants of unknown significance (VUS) are variations/changes in a person's DNA sequence, which have a yet unknown effect on an individual's health or correlation to the disease/symptoms.*
4. *Autosomal dominant* implies that the variant gene is located on a numbered non-sex chromosome and a single copy of the gene is enough to cause a disease in the individual. A child of a person having an autosomal dominant variant hasa 50% chance of being affected by the same disorder. However, in some cases, it is not possible to determine if the variant gene is dominant or recessive. In such instances, further testing is advised to determine the risk to an offspring.*
5. *BioAro offers a **Genetic monitoring program (GMP)** that monitors published, peer-reviewed scientific literature and clinical studies for new information that may correlate VUS with known diseases or symptoms.*

## Disclaimer

*Genetic testing using the methods applied by BioAro is expected to be accurate but reflex to analysis testing may be sought for confirmation. No diagnostic claims are being made or implied. An absence of definitive pathogenic findings does not rule out the diagnosis of a genetic disorder because there are abnormalities that cannot be detected by this test, and pathogenic classifications are subject to change. It is also possible that a disease-causing variant is located in aregion not covered by the analysis. The chance of a false positive or false negative due to laboratory error cannot be completely excluded. Consultation with a genetics professional is recommended for interpretation of results. This test was performed and developed according to the characteristics of BioAro Inc. following the recommended standards andQC measures by the test manufacturers and industry.*

## Literature references

*All gene references are hyperlinked for convenience.*

*Information has been confirmed from Clinvar, ACMG guidelines and https://www.genecards.org/*