bioAro

Whole Genome Sequencing Report

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Patient Information:

Name:	Akash Lokhande	Sample Type:	WES
Gender:	Male	Collection Date:	05 March, 2024
Date of Birth:	25 May, 1988	Report Date:	15 March, 2024
ID:	P5447	Patient's Address:	134, Pine Street

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.

KCNT2, ATXN3, FOXQ1, ACADSB, FAH, SLC12A3, MTOR , NOTCH2, NOTCH2, PRCC, KCNN3, KCNN3, FN1, RPSA, MCM2, NAF1, MSX1, CHD1, CTNNA1, NQO2 , SAMD9L, ZP3, RP1L1, NEFL, KAT6A, ZNF462, MYOF, CYP2C9, TCF7L2, ELP4, PACS1, TIMELESS, TSC2, IRF8, SLFN14, CYP2A6, CYP2A6, GRIN2D, TCF20, NOS3.

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

WES 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 diseases.

Chromosome	Position	Ref	Alt	Variant Identifier	Gene Name	Function
4	4870660	G	A	rs116521001	MSX1	MSX1 gene's hypomethylation is linked to poor response in high-grade serous ovarian cancer patients. Its decreased expression is associated with resistance, while its overexpression enhances sensitivity, promoting apoptosis and p21 expression
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 regulatio

The following table showing the information of Pathogenic/Likely Pathogenic (Heterozygous + Autosomal dominant) Genetic Variants from the Screen

Gene Name	Chr:pos	Variant Identifier	Zygosity	Inheritance	Classification	Associated Disease Risk
KCNT2	1:196251447	rs780601767	Heterozygous	Autosomal dominant	Likely pathogenic	Developmental and epileptic encephalopathy 57
ATXN3	14:92537354	.	Heterozygous	Autosomal dominant	Likely pathogenic	Azorean disease of the nervous system
FOXQ1	6:1318643	rs11242675	Heterozygous	Autosomal dominant	Pathogenic	Esophageal cancer, alcohol-related, susceptibility to

This table contains gene/s with a combination of (Heterozygous + Autosomal Dominant), which, as indicated by multiple clinical studies, are Pathogenic or likely pathogenic and have been shown to impact the normal functioning of the gene, leading to disease/s.

The following table showing the information of Pathogenic/Likely Pathogenic (Homozygous + Autosomal dominant) mutations found in the client include

Gene Name	Chr:pos	Variant Identifier	Zygosity	Inheritance	Classification	Associated Disease Risk
ACADSB	10:124812634	rs199963793	Homozygous	Autosomal dominant	Likely pathogenic	2-methylbutyryl-CoA dehydrogenase deficiency
FAH	15:80472526	rs11555096	Homozygous	Autosomal dominant	Pathogenic	Tyrosinemia type 1
SLC12A3	16:56919275	rs200697179	Homozygous	Autosomal dominant	Likely pathogenic	Gitelman syndrome

The following table showing the information of VUS/Uncertain significance (Heterozygous + Autosomal dominant) Genetic Variants from the Screen

Gene Name	Chr:pos	Variant Identifier	Zygosity	Inheritance	Classification	Associated Disease
MTOR	1:11169775	rs574378176	Heterozygous	Autosomal dominant	Uncertain significance	MINDS syndrome
NOTCH 2	1:120612013	rs200646249	Heterozygous	Autosomal dominant	Uncertain significance	Alagille-Watson syndrome due to a NOTCH2 point mutation , Alagille-Watson syndrome , Acrodentoosteodysplasia
NOTCH 2	1:120612014	rs782113557	Heterozygous	Autosomal dominant	Uncertain significance	Alagille-Watson syndrome due to a NOTCH2 point mutation , Alagille-Watson syndrome , Acrodentoosteodysplasia
PRCC	1:156756800	rs139572885	Heterozygous	Autosomal dominant	Uncertain significance	Hereditary papillary renal cell carcinoma (HPRCC)
KCNN3	1:154842199	rs3831942	Heterozygous	Autosomal dominant	Uncertain significance	Zimmermann-Laband syndrome 3
KCNN3	1:154842330	rs754856463	Heterozygous	Autosomal dominant	Uncertain significance	Zimmermann-Laband syndrome 3
FN1	2:216288219	rs181283286	Heterozygous	Autosomal dominant	Uncertain significance	Glomerulopathy with fibronectin deposits
RPSA	3:39450225	rs773913524	Heterozygous	Autosomal dominant	Uncertain significance	Familial isolated congenital asplenia
MCM2	3:127323603	rs775995747	Heterozygous	Autosomal dominant	Uncertain significance	Autosomal dominant isolated neurosensory deafness type DFNA
MSX1	4:4870660	rs116521001	Heterozygous	Autosomal dominant	Uncertain significance	Hereditary gastric cancer

Gene Name	Chr:pos	Variant Identifier	Zygosity	Inheritance	Classification	Associated Disease
NAF1	4:164085487	rs200588702	Heterozygous	Autosomal dominant	Uncertain significance	Pulmonary fibrosis and/or bone marrow failure syndrome, telomere-related, 7
CHD1	5:98194709	rs553111541	Heterozygous	Autosomal dominant	Uncertain significance	Pilarowski-Bjornsson syndrome
CTNNA1	5:138261007	rs755724779	Heterozygous	Autosomal dominant	Uncertain significance	Butterfly-shaped pattern dystrophy
NQO2	6:3012778	rs17300141	Heterozygous	Autosomal dominant	Uncertain significance	Familial breast cancer
SAMD9L	7:92764588	rs780573740	Heterozygous	Autosomal dominant	Uncertain significance	Myelocerebellar disorder
ZP3	7:76058857	rs140906109	Heterozygous	Autosomal dominant	Uncertain significance	Oocyte/zygote/embryo maturation arrest 3
RP1L1	8:10464878	rs781237399	Heterozygous	Autosomal dominant	Uncertain significance	OCMD
NEFL	8:24811283	rs372997416	Heterozygous	Autosomal dominant	Uncertain significance	CMT1F, CMT2E
KAT6A	8:41792203	rs201426169	Heterozygous	Autosomal dominant	Uncertain significance	Arboleda-Tham syndrome
ZNF462	9:109688621	rs564684817	Heterozygous	Autosomal dominant	Uncertain significance	Weiss-Kruszka syndrome
MYOF	10:95162056	rs36072133	Heterozygous	Autosomal dominant	Uncertain significance	Angioedema, hereditary, 7
CYP2C9	10:96701991	rs72558189	Heterozygous	Autosomal dominant	Uncertain significance	Tolbutamide poor metabolizer, Warfarin sensitivity
TCF7L2	10:114925408	rs754884239	Heterozygous	Autosomal dominant	Uncertain significance	{Diabetes mellitus, type 2, susceptibility to}

Gene Name	Chr:pos	Variant Identifier	Zygosity	Inheritance	Classification	Associated Disease
ELP4	11:31561287	rs201333718	Heterozygous	Autosomal dominant	Uncertain significance	Isolated aniridia
PACS1	11:66000488	rs767663290	Heterozygous	Autosomal dominant	Uncertain significance	PACS1-related syndrome
TIMELESS	12:56815593	rs200266689	Heterozygous	Autosomal dominant	Uncertain significance	Advance sleep phase syndrome, familial, 4
TSC2	16:2133701	rs45517319	Heterozygous	Autosomal dominant	Uncertain significance	Bourneville syndrome , LAM
IRF8	16:85952388	rs575823888	Heterozygous	Autosomal dominant	Uncertain significance	Mendelian susceptibility to mycobacterial diseases due to partial interferon regulatory factor 8 deficiency
SLFN14	17:33875517	rs562073297	Heterozygous	Autosomal dominant	Uncertain significance	Bleeding disorder, platelet-type, 20
CYP2A6	19:41355876	rs199515342	Heterozygous	Autosomal dominant	Uncertain significance	{Lung cancer, resistance to}, {Nicotine addiction, protection from}, Coumarin resistance
CYP2A6	19:41355885	rs200554095	Heterozygous	Autosomal dominant	Uncertain significance	{Lung cancer, resistance to}, {Nicotine addiction, protection from}, Coumarin resistance
GRIN2D	19:48947132	rs191119443	Heterozygous	Autosomal dominant	Uncertain significance	Developmental and epileptic encephalopathy 46
TCF20	22:42608343	rs758000946	Heterozygous	Autosomal dominant	Uncertain significance	Developmental delay with variable intellectual impairment and behavioral abnormalities

This table contains a list of genes with a combination of (Heterozygous + Autosomal Dominant) identified as variants of unknown significance (VUS) by the WES test.

These variant genes include those for which from 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.

The following table showing the information of VUS/ Uncertain significance (Homozygous + Autosomal dominant) mutations found in the client include

Gene Name	Chr:pos	Variant Identifier	Zygosity	Inheritance	Classification	Associated Disease
NOS3	7:150696111	rs1799983	Homozygous	Autosomal dominant	Uncertain significance	Early-onset familial autosomal dominant Alzheimer disease

This table contains a list of genes with a combination of (Homozygous + Autosomal Dominant) identified as variants of unknown significance (VUS) by the WES test.

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

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. 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:

KCNT2, ATXN3, FOXQ1, ACADSB, FAH, SLC12A3, MTOR , NOTCH2, NOTCH2, PRCC, KCNN3, KCNN3, FN1, RPSA, MCM2, NAF1, MSX1, CHD1, CTNNA1, NQO2 , SAMD9L, ZP3, RP1L1, NEFL, KAT6A, ZNF462, MYOF, CYP2C9, TCF7L2, ELP4, PACS1, TIMELESS, TSC2, IRF8, SLFN14, CYP2A6, CYP2A6, GRIN2D, TCF20, NOS3.

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 exome sequencing (WES) was carried out on a blood sample obtained from the patient. WES 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 WES. **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/