Patient

Name: John Smith
Patient ID: H23/028662
Sex at birth: Male
Date of birth: Nov 20, 1987

Physician

Name: John Doe
Institution:
Heritage Medical Center
Contact: +82-10-0000-0000
Address:
1600 Amphitheatre Parkway,
Mountain View, CA 94043

Specimen

Specimen ID: C346399(9)
Specimen type: Blood
Specimen collection:
Blood draw
Collected: Nov 20, 2023, 11:23
Received: Nov 24, 2023, 13:20
Clinical diagnosis:
Autism spectrum disorder

Test Information

Test name:
Whole genome analysis and interpretation
Quality: Satisfactory
Sequencing mean depth:
48.2x

RESULT SUMMARY

Positive variants detected	***PTEN***
Inconclusive variants detected	***SCN2A, TCF7L2***
Secondary (incidental) findings detected	***BRCA1***

A. POSITIVE VARIANTS

Gene	Variant type	Zygosity	ACMG classification	Related diseases
PTEN	SNV	Heterozygosity	Likely pathogenic	Lhermitte-Duclos disease

B. INCONCLUSIVE VARIANTS

Gene	Variant type	Zygosity	ACMG classification	Related diseases
SCN2A	SNV	Heterozygosity	Pathogenic	Developmental and epileptic encephalopathy 11
TCF7L2	SV	Heterozygosity	-	Diabetes mellitus, type 2, susceptibility to

C. SECONDARY (INCIDENTAL) FINDING

Gene	Variant type	Zygosity	ACMG classification	Related diseases
BRCA2	SNV	Heterozygosity	Likely pathogenic	Breast-ovarian cancer, familial, 2

D. INTERPRETATION

- In *PTEN*, variant ENSP00000278317.6:p.R234H is detected as likely pathogenic, and the variant is identified as heterozygous. And the variant is identified as de novo.
- *PTEN* is known to be associated with the following diseases.
  Lhermitte-Duclos disease (Autosomal dominant) (PMID : 24102544, 21926107).
- Incidentally, in *BRCA2*, variant ENSP00000262426.4:p.F85L is detected as likely pathogenic, and the variant is identified as heterozygous. And the variant is identified as de novo.
- *BRCA2* is known to be associated with the following diseases.
  Breast-ovarian cancer, familial, 2 (Autosomal dominant) (PMID: 17924331).
- Geneticist evaluation for clinical correlation of these results is recommended.

*SNV; Single nucleotide variant, INDEL; Insertion and deletion, SV; Structural variation, TE; Transposable elements, DEL; Deletion, DUP; Duplication, INV; Inversion, BND; Translocation, Chr; Chromosome, AD; Autosomal dominant, AR,Autosomal recessive; XR, X-linked recessive

A. POSITIVE VARIANTS

Variant information - *PTEN*:c.701G>A

Gene	*PTEN*	Locus (GRCh38)	chr11:1,936,982
Variant type	SNV	Category	Missense
cDNA	ENST00000278317.11:c.701G>A	Protein	ENSP00000278317.6:p.R234H
Zygosity	Heterozygosity	Existing variant	rs747756859; COSV53484578
Related diseases	Lhermitte-Duclos disease (AR)		

*SNV; Single nucleotide variant, INDEL; Insertion and deletion, SV; Structural variation, TE; Transposable elements, DEL; Deletion, DUP; Duplication, INV; Inversion, BND; Translocation, Chr; Chromosome, AD; Autosomal dominant, AR,Autosomal recessive; XR, X-linked recessive

Category	Criteria*	Pathogenicity**
Poulation database	PM2 : The variant is very rarely reported (<0.1%) in gnomADv2.1.8 (PMID : 32461654), 1000 genome (PMID : 26432245) & GINS_PM_PON v.1.0 (Inocras database) database.	Likely pathogenic
Computational & predictive data	PP3 : 17 out of the 18 predictive software*** used by Inocras predict the variant as potentially damaging.	
Functional & reported data	-	
Segregation & de novo mutation analysis	PS2 : The variant is de novo variant which is not deteced in the patient's parents.	
Allelic data & other data	PP4 : According to the Human Phenotype Ontology (HPO) database (PMID : 33264411), PTEN has been known to be associated with the developmental delay.	

*The criteria (e.g., PVS1, PS1-4, PM1-6, PP1-5) and pathogenicity of the variant were evaluated according to ACMG guidelines (PMID : 25741868).
**The pathogenicity of the variant was classified as pathogenic, likely pathogenic, benign, likely benign, variant with uncertain significance according to ACMG guidelines (PMID : 25741868). The classification of variant pathogenicity may be subject to change based on additional research results from related literature and databases (refer to TEST INFORMATION).
***18 publicly and commercially available software tools were utilized for *in silico* prediction of the consequences of each variant.

B. INCONCLUSIVE VARIANTS

Variant information - *SCN2A*:c.255C>G

Gene	*SCN2A*	**Locus (GRCh38)**	chr16:86,510,824
Variant type	SNV	**Category**	Missense
cDNA	ENST00000262426.6:c.255C>G	**Protein**	ENSP00000262426.4:p.F85L
Zygosity	Heterozygosity	**Existing variant**	-
Related diseases	Developmental and epileptic encephalopathy 11 (AR)		

*SV, Structural variation; SNV, Singlenucleotide variant; TE, Transposable elements; DEL, Deletion; DUP, Duplication; INV, Inversion; BND, Translocation, Chr; Chromosome, AD; Autosomal dominant, AR; Autosomal recessive, XR; X-linked recessive

Category	Criteria*	Pathogenicity**
Poulation database	PM2 : The variant is very rarely reported (<0.1%) in gnomADv2.1.8 (PMID : 32461654), 1000 genome (PMID : 26432245) & GINS_PM_PON v.1.0(Inocras database) database.	Pathogenic
Computational & predictive data	PM5 : There are reports indicating that variants in the same locus, resulting in different amino acids, are associated with the disease. PP3 : 17 out of the 18 predictive software*** used by Inocras predict the variant as potentially damaging.	
Functional & reported data	-	
Segregation & de novo mutation analysis	PS2 : The variant is de novo variant which is not detected in the patient's parents.	
Allelic data & other data	PP4 : According to the Human Phenotype Ontology (HPO) database (PMID : 33264411), SCN2A has been known to be associated with the developmental delay.	

*The criteria (e.g., PVS1, PS1-4, PM1-6, PP1-5) and pathogenicity of the variant were evaluated according to ACMG guidelines (PMID : 25741868).
**The pathogenicity of the variant was classified as pathogenic, likely pathogenic, benign, likely benign, variant with uncertain significance according to ACMG guidelines (PMID : 25741868). The classification of variant pathogenicity may be subject to change based on additional research results from related literature and databases (refer to TEST INFORMATION).
***18 publicly and commercially available software tools were utilized for in silico prediction of the consequences of each variant.

C. SECONDARY (INCIDENTAL) FINDING

Variant information - *BRCA2*:c.255C>G

Gene	*BRCA2*	Locus (GRCh38)	chr16:86,510,824
Variant type	SNV	Category	Missense
cDNA	ENST00000262426.6:c.255C>G	Protein	ENSP00000262426.4:p.F85L
Zygosity	Heterozygosity	Existing variant	-
Related diseases	Breast-ovarian cancer, familial, 2		

*SV, Structural variation; SNV, Singlenucleotide variant; TE, Transposable elements; DEL, Deletion; DUP, Duplication;INV, Inversion; BND, Translocation; Chr, Chromosome; AD, Autosomal dominant; AR,Autosomal recessive; XR, X-linked recessive

Category	Criteria*	Pathogenicity**
Poulation database	PM2 : The variant is very rarely reported (<0.1%) in gnomADv2.1.8 (PMID : 32461654), 1000 genome (PMID : 26432245) & GINS_PM_PON v.1.0 (Inocras database) database.	Likely pathogenic
Computational & predictive data	PP3 : 17 out of the 18 predictive software*** used by Inocras predict the variant as potentially damaging.	
Functional & reported data	-	
Segregation & de novo mutation analysis	PS2 : The variant is de novo variant which is not deteced in the patient's parents.	
Allelic data & other data	-	

*The criteria (e.g., PVS1, PS1-4, PM1-6, PP1-5) and pathogenicity of the variant were evaluated according to ACMG guidelines (PMID : 25741868).
**The pathogenicity of the variant was classified as pathogenic, likely pathogenic, benign, likely benign, variant with uncertain significance according to ACMG guidelines (PMID : 25741868). The classification of variant pathogenicity may be subject to change based on additional research results from related literature and databases (refer to TEST INFORMATION).
***18 publicly and commercially available software tools were utilized for *in silico* prediction of the consequences of each variant.

TEST INFORMATION

- The RareVision test is a Next Generation Sequencing (NGS) whole genome assay that provides a list of detected single nucleotide variants (SNVs), multiple nucleotide variants (MNVs), small insertions and deletions (indels), copy number alterations (CNAs), structural variations (SVs), and transposable elements (TEs) in patient's sample. The genomic DNA is extracted from the patient˙s sample via the ThermoFisher KingFisher Apex and prepared using the Watchmaker Genomics enzymatic library preparation which includes end repair, purification, adapter ligation and PCR amplification. The libraries are sequenced using the Illumina NovaSeq X+. For whole-genome sequencing, the mean genome-wide read-depth is 30x (deduplicated unique reads). The sequence data are analyzed using various validated bioinformatics tools and a custom data- processing pipeline for NGS platforms. GRCh38 is used for human reference genome.
- Each variant was reported according to the standard nomenclature of the Human Genome Variation Society (www.hgvs.org). Additionally, NCBI IDs were provided.
- The detected SNV, MNVs, and indels were classified into five categories (pathogenic; P , likely pathogenic; LP, likely benign; LB, benign; B, variant with uncertain significance; VUS) according to the 2015 ACMG/AMP guideline (PMID : 25741868). This report focuses on P and LP mutations, but VUS mutations may also be reported for rare mutations in important genes that require further consideration of clinical symptoms. The classification of the mutation may change depending on additional research results from relevant literature and databases. The detected SVs and TEs involving exon region were regarded as pathogenic variants. The detected CNAs were classified into five categories (P, LP, B, LB, VUS) according to the ACMG/ClinGen standards (PMID : 31690835).
- The results are categorized into four categories: positive, inconclusive, negative and secondary.

  - Positive: If a P/LP variant is identified in the gene responsible for AD/XL disease.
    Two or more pathogenic/likely pathogenic variants are identified in the causative gene for AR disease.
  - Inconclusive: If a variant with VUS is identified in the gene responsible for AD/XL disease.
    If more than 1 VUS is identified in the gene responsible for AR disease.
    Only one P/LP variant is identified in the gene causing AR disease.
    Variants are identified in genes of uncertain significance that correspond to the patient's clinical symptoms.
  - Negative: If no clinically relevant meaningful variants are identified.
  - Secondary (Incidental): Per ACMG recommendation, if pathogenic variants are found in genes listed in Appendix I, such variants are reported as secondary findings, even if they are not associated with the patient's symptoms (PMID : 23788249).

- Variant analysis is conducted as follows:

  1. The protein coding region is fully included.
  2. Trio *de novo* analysis includes not only the protein coding region but also regulatory regions and intronic regions.
  3. For important genes that match the clinical symptoms, analysis includes non-coding regions that are known.
  4. SVs are analyzed with priority given to those that include the protein coding region. For important genes, analysis is extended to include known non-coding regions.
  5. For TE gene rearrangements, analysis is centered around important genes that match clinical symptoms.
  6. Copy number profile analysis of chromosomes is included.

- In the assessment of genetic variants, this analysis employs publicly available and reputable *in silico* prediction tools. These tools, totaling 18, are designed to predict the impact of each variant. For SNVs, MNVs, and indels, databases such as the 1000 Genomes Project (PMID: 26432245), gnomAD (PMID: 32461654), ExAC (PMID: 27899611), TOGOVAR (PMID: 36509753), and GASP (PMID: 31802016), along with proprietary in-house databases (GINS_PM_PON v1.0), are utilized. SVs are analyzed using both public databases like gnomAD v2.1.8 and internal resources (GINS_SV_PON v1.0).
- A comprehensive interpretation process was applied to analyze and interpret SNVs, MNVs, indels, CNAs, SVs and TEs. However, there is a possibility that some variants were not discovered or interpreted. Mutations located in regulatory or deep intronic regions that are not close to exons, as well as epigenetic changes and post-zygotic somatic mosaicism, may not have been detected.
- Further inquiries about unreported variants in the report can be directed to Inocras.

DISCLAIMER

- This report is designed to offer valuable insights to the treating physician and serves as an informational resource. It is not intended to deliver a definitive diagnosis, as accurate diagnostic conclusions often depend on more than gene expression alone.
- This test was developed, and quality-assured by Inocras. It has not been cleared or approved by the US Food and Drug Administration. The test has been validated as a Laboratory Developed Test per institutional and applicable CLIA regulation (CLIA# 05D2280195) as qualified to perform high complexity clinical laboratory testing. Data interpretations are based on our current understanding of genes and variants as of the report date. When the report does identify variants with therapeutic implications, this does not promise or guarantee that a particular drug or treatment regimen will be effective or helpful in the treatment of disease in any patient, and the selection of any drug for patient treatment is done at the discretion of the treating physician. Genomic alterations should be considered in the context of the patient's history, risk factors and any previous genomic testing.
- Incidental findings refer to unexpected discoveries made during diagnostic testing that are unrelated to the primary purpose of the examination or study. These findings may include abnormalities, conditions, or other relevant information that was not initially being sought but is discovered by chance during the course of the testing. Inocras shall include these incidental findings in our reports. Please consult your genetic counselor or physician with any questions.
- Proprietary and confidential material disclaimer: This report contains confidential and proprietary information as well as intellectual property owned by Inocras. It is strictly prohibited to use, disclose, or reproduce any of the information within this document, except for the treatment of the specific patient for which it is intended.
- Due to the technical limitations of short-read sequencing, variations in repetitive regions may be difficult to detect or may have lower accuracy.
- For germline alterations, Inocras strongly suggests that the patient receive appropriate genetic counseling to explain the implications of this test result, its residual risks and uncertainties, and the reproductive or medical options it raises for the patient.

TRACKING INFORMATION

Sample tracking ID: 2401-034.001
Analysis ID: GINS-0000-0000-01AD
Pipeline version: Germline 1.0.3

APPENDIX I: GENE LIST FOR SECONDARY (INCIDENTAL) FINDING

ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, COL3A1, DES, DSC2, DSG2, DSP, ENG, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1

This is a sample report

This includes only select key pages