# Whole Exome Sequencing Analysis

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|---|---|---|---|---|---|
| **Patient name** | : | **Mr. XXX** | **PIN** | : | **XX** |
| **Gender/ Age** | : | **XX** | **Sample number** | : | **032327455** |
| **Referring clinician** | : | **XX** | **Sample collection date** | : | **06.11.2023** |
| **Specimen** | : | **XX** | **Sample receipt date** | : | **06.11.2023** |
| | | | **Report date** | : | **01.01.2024** |

## Clinical history

Proband, Mr. XXX was born to non-consanguineous parents. He is a pre-term baby presented with chief complaints of acute onset scholastic decline stereotypic movements muttering to self with abnormal involuntary vigorous movements of head and limbs, delay in speech, head pain, persistent hearing voices, anger burst, uncontrollable and inappropriate laughing and teeth biting. His EEG report indicative of normal findings. His MRI brain indicative of small polyp measuring 1.6*1.1cm in the right maxillary sinus and his whole spine screening indicative of mild anterior spondylotic changes are noted from C3 to C6 levels, disc desiccation is noted from C2 to C6 levels, mild anterior spondylotic changes are seen from L3 to L5 levels, L3-L4, L4-5 and L5-S1 discs show diffuse posterior bulge causing mild indentation on the thecal sac with partial effacement of the anterior subarachnoid spaces. Proband's mother was diagnosed with pre-eclampsia during his pregnancy and his maternal aunt has intellectual disability. Proband, Mr XXX has been evaluated for pathogenic variations.

## Results

**No pathogenic or likely pathogenic variants causative of the reported phenotype was detected**

**List of uncertain significant variant identified:**

| Gene | Region | Variant* | Allele Status | Disease | Classification* | Inheritance pattern |
|---|---|---|---|---|---|---|
| *HTR2A* (-) | Exon 3 | c. 419G>A **(p.Arg140Gln)** | Heterozygous | {Schizophrenia, susceptibility to} **(OMIM#181500)** | **Uncertain significance** | Autosomal Dominant |

*Genetic test results are based on the recommendation of American college of Medical Genetics [1].
No other variant that warrants to be reported for the given clinical indication was identified.

## Interpretation

***HTR2A:* c.419G>A**

**Variant summary:** A heterozygous missense variation in exon 3 of the *HTR2A* gene (chr13:g.46892584C>T, NM_000621.5, Depth: 96x) that results in the amino acid substitution of Glutamine for Arginine at codon 140 (p.Arg140Gln) was detected.

**Population frequency:** This variant has not been reported in gnomAD database and 1000 genomes databases.

**Clinical evidence:** This variant has been previously classified as uncertain significance in ClinVar database [3].

**OMIM phenotype:** {Schizophrenia, susceptibility to} (OMIM#181500) is caused by mutation in the *HTR2A* gene (OMIM*182135). Schizophrenia is a psychosis, a disorder of thought and sense of self. Although it affects emotions, it is distinguished from mood disorders in which such disturbances are primary. Similarly, there may be mild impairment of cognitive function, and it is distinguished from the dementias in which disturbed cognitive function is considered primary. There is no characteristic pathology, such as neurofibrillary tangles in Alzheimer disease. Schizophrenia is a common disorder with a lifetime prevalence of approximately 1%. It is highly heritable but the genetics are complex. This may not be a single entity. This disease follows autosomal dominant pattern of inheritance [2].

**Variant classification:** Based on the evidence, this variant is classified as a variant of uncertain significance. **In this view, clinical correlation and familial segregation analysis are strongly recommended to establish the significance of the finding. If the results do not correlate, additional testing may be considered based on the phenotype observed.**

## Additional Variant(s)

**The additional variants identified may or may not be related to patient's phenotype. Phenotype – genotype correlation is recommended.**
**List of additional uncertain significant variants identified:**

| Gene | Region | Variant* | Allele Status | Disease | Classification* | Inheritance pattern |
|---|---|---|---|---|---|---|
| *GUCY2D* (+) | Exon 10 | c.1978C>T **(p.Arg660Ter)** | Heterozygous | ?Choroidal dystrophy, central areolar 1 **(OMIM#215500)** | **Uncertain significance** | Autosomal Dominant |
| | | | | Cone-rod dystrophy 6 **(OMIM#601777)** | | Autosomal Dominant, Autosomal Recessive |
| | | | | Leber congenital amaurosis 1 **(OMIM#204000)**<br><br>Night blindness, congenital stationary, type 1I **(OMIM#618555)** | | Autosomal Recessive |
| *POLA1* (+) | Exon 14 | c. 1399A>C **(p.Met467Leu)** | Hemizygous | Pigmentary disorder, reticulate, with systemic manifestations, X-linked **(OMIM#301220)** | **Uncertain significance** | X Linked Recessive |
| | | | | Van Esch-O'Driscoll syndrome **(OMIM#301030)** | | |

## Recommendations

- Sequencing the variant(s) in the parents and the other affected and unaffected members of the family is recommended to confirm the significance.
- Alternative test is strongly recommended to rule out the deletion/duplication.
- Genetic counselling is advised.

## Methodology

DNA extracted from the blood was used to perform whole exome using whole exome capture kit. The targeted libraries were sequenced to a targeted depth of 80 to 100X using GenoLab M sequencing platform. This kit has deep exonic coverage of all the coding regions including the difficult to cover regions. The sequences obtained are aligned to human reference genome (GRCh38.p13) using Sentieon aligner and analyzed using Sentieon for removing duplicates, recalibration and re-alignment of indels. Sentieon DNAscope has been used to call the variants. Detected variants were annotated and filtered using the VarSeq software with the workflow implementing the ACMG guidelines for variant classification. The variants were annotated using 1000 genomes (V2), gnomAD (v3.1,2.1.1), ClinVar, OMIM, dbSNP, NCBI RefSeq Genes. *In-silico* predictions of the variant was carried out using VS-SIFT, VS-PolyPhen2, PhyloP, GERP++, GeneSplicer, MaxEntScan, NNSplice, PWM Splice Predictor. Only non-synonymous and splice site variants found in the coding regions were used for clinical interpretation. Silent variations that do not result in any change in amino acid in the coding region are not reported.

## Sequence data attributes

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|---|---|
| Total reads generated | 11.77 Gb |
| Data ≥ Q30 | 94.11% |

Genetic test results are reported based on the recommendations of American College of Medical Genetics [1], as described below:

| Classification | Interpretation |
|---|---|
| Pathogenic | A disease-causing variation in a gene which can explain the patients' symptoms has been detected. This usually means that a suspected disorder for which testing had been requested has been confirmed |

| | |
|---|---|
| Likely Pathogenic | A variant which is very likely to contribute to the development of disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion of pathogenicity. |
| Variant of Uncertain Significance | A variant has been detected, but it is difficult to classify it as either pathogenic (disease causing) or benign (non- disease causing) based on current available scientific evidence. Further testing of the patient or family members as recommended by your clinician may be needed. It is probable that their significance can be assessed only with time, subject to availability of scientific evidence. |

## Disclaimer

- The classification of variants of unknown significance can change over time. Anderson Diagnostics and Labs cannot be held responsible for it.
- Intronic variants, UTR, Promoter region variants and CNV are not assessed using this assay.
- Certain genes may not be covered completely, and few mutations could be missed. Variants not detected by this assay may impact the phenotype.
- The variations have not been validated by Sanger sequencing.
- The above findings and result interpretation was done based on the clinical indication provided at the time of reporting.
- It is also possible that a pathogenic variant is present in a gene that was not selected for analysis and/or interpretation in cases where insufficient phenotypic information is available.
- Genes with pseudogenes, paralog genes and genes with low complexity may have decreased sensitivity and specificity of variant detection and interpretation due to inability of the data and analysis tools to unambiguously determine the origin of the sequence data in such regions.
- Incidental or secondary findings that meet the ACMG guidelines can be given upon request [4].

## References


1. Richards, S, et al. Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine: official journal of the American College of Medical Genetics. 17.5 (2015): 405-424.
2. Amberger J, Bocchini CA, Scott AF, Hamosh A. McKusick's Online Mendelian Inheritance in Man (OMIM). Nucleic Acids Res. 2009 Jan;37(Database issue):D793-6. doi: 10.1093/nar/gkn665. Epub 2008 Oct 8.
3. https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV002223959.1

4. Kalia S.S. et al., Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med., 19(2):249-255, 2017.

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