

## Clinical Exome Sequencing Analysis – Carrier Screening

<b>Patient name</b>	<b>: Mr. XXX</b>	<b>Mrs. YYY</b>
<b>Gender/ Age</b>	<b>: Male/38 years</b>	<b>Female/31 years</b>
<b>PIN</b>	<b>: XX</b>	<b>XX</b>
<b>Sample no</b>	<b>: XX</b>	<b>XX</b>
<b>Specimen</b>	<b>: Peripheral blood</b>	<b>Peripheral blood</b>
<b>Sample collection date</b>	<b>: XX</b>	<b>XX</b>
<b>Sample receipt date</b>	<b>: XX</b>	<b>XX</b>
<b>Report date</b>	<b>: XX</b>	<b>XX</b>
<b>Referring clinician</b>	<b>: XX</b>	
<b>Hospital/Clinic</b>	<b>: XX</b>	

### Clinical history

Mr. XXX and Mrs. YYY are non-consanguineous couple. Mrs. YYY is diagnosed with Oculocutaneous albinism. She is presented with white skin, hair, light brown eyes and has high refractive errors. Female partner's sister has similar diagnosis and her parents are second degree consanguineous marriage. The couple is currently 16 weeks pregnant. Mr. XXX and Mrs. YYY has been evaluated for carrier status of pathogenic variations.

### Results

Mrs. YYY is found to be affected with a likely pathogenic variant in the *OCA2* gene (p.Ser641Leu) and found to be carrier of likely pathogenic variants in the *TH* gene (p.Arg138Ter), *CA5A* gene (p.Glu241Lys), *DNAH1* gene (p.Gln109Ter), *DNAH9* gene (p.Trp1710Ter) and *NLRP7* gene (p.Lys730Ter).

Mr. XXX is found to be carrier of likely pathogenic variants in the *COASY* gene (c.1486-3C>G) and *GRIP1* gene (p.Arg23Ter).

### List of significant variants identified:

Disease	Mr. XXX	Mrs. YYY
Albinism, oculocutaneous, type II (OMIM#203200)  Mode of inheritance: AR	NON - CARRIER	<b>AFFECTED</b>  Gene: <i>OCA2</i> Exon 18, c.1922C>T, p.Ser641Leu, Homozygous  Classification: <b>Likely Pathogenic</b>
Segawa syndrome, recessive (OMIM#605407)  Mode of inheritance: AR	NON - CARRIER	<b>CARRIER</b>  Gene: <i>TH</i> Exon 3, c.412C>T, p.Arg138Ter, Heterozygous  Classification: <b>Likely Pathogenic</b>
Hyperammonemia due to carbonic anhydrase VA deficiency (OMIM#615751)  Mode of inheritance: AR	NON - CARRIER	<b>CARRIER</b>  Gene: <i>CA5A</i> Exon 6, c.721G>A, p.Glu241Lys, Heterozygous  Classification: <b>Likely Pathogenic</b>
Ciliary dyskinesia, primary, 37 (OMIM#617577)  Spermatogenic failure 18 (OMIM#617576)  Mode of inheritance: AR	NON - CARRIER	<b>CARRIER</b>  Gene: <i>DNAH1</i> Exon 2, c.325C>T, p.Gln109Ter, Heterozygous  Classification: <b>Likely Pathogenic</b>
Ciliary dyskinesia, primary, 40 (OMIM#618300)  Mode of inheritance: AR	NON - CARRIER	<b>CARRIER</b>  Gene: <i>DNAH9</i> Exon 24, c.5130G>A, p.Trp1710Ter, Heterozygous  Classification: <b>Likely Pathogenic</b>

Hydatidiform mole, recurrent, 1 (OMIM#231090)	NON - CARRIER	CARRIER Gene: <i>NLRP7</i> Exon 6, c.2188A>T, p.Lys730Ter, Heterozygous
Mode of inheritance: AR		Classification: <b>Likely Pathogenic</b>
Neurodegeneration with brain iron accumulation 6 (OMIM#615643)	CARRIER Gene: <i>COASY</i> Intron 7, c.1486-3C>G, 3' Splice site, Heterozygous	NON - CARRIER
Pontocerebellar hypoplasia, type 12 (OMIM#618266)		
Mode of inheritance: AR	Classification: <b>Likely Pathogenic</b>	
Fraser syndrome 3 (OMIM#617667)	CARRIER Gene: <i>GRIP1</i> Exon 1, c.67C>T, p.Arg23Ter, Heterozygous	NON - CARRIER
Mode of inheritance: AR	Classification: <b>Likely Pathogenic</b>	

\*Genetic test results are reported 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

### Interpretation for the significant variants identified in Mrs. YYY

#### OCA2: c.1922C>T

**Variant summary:** A homozygous missense variation in exon 18 of the *OCA2* gene (chr15:g.27951813G>A, NM\_000275.3, Depth: 81x) that results in the amino acid substitution of Leucine for Serine at codon 641 (p.Ser641Leu) was detected.

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

**Clinical and Literature evidence:** This variant has been previously classified as likely pathogenic in ClinVar database [3]. This variant has been previously reported in patient affected with Nonsyndromic oculocutaneous Albinism [4].

**In-silico prediction:** The *in-silico* predictions of the variant are damaging by SIFT, PolyPhen-2 (HumDiv), LRT and MutationTaster2. The reference codon is conserved across mammals in PhyloP and GERP++ tools.

**OMIM phenotype:** Albinism, oculocutaneous, type II (OMIM#203200) is caused by homozygous or compound heterozygous mutation in the *OCA2* gene (OMIM\*611409). This disease follows autosomal recessive pattern of inheritance [2].

**Variant classification:** Based on the evidence, this variant is classified as a likely pathogenic variant. 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.

#### TH: c.412C>T

**Variant summary:** A heterozygous stop gained variation in exon 3 of the *TH* gene (chr11:g.2168566G>A, NM\_000360.4, Depth: 77x) that results in the premature truncation of the protein at codon 138 (p.Arg138Ter) was detected. This variant is a stop gained variant which occurs in an exon of *TH* upstream of where nonsense mediated decay is predicted to occur. This variant is predicted to cause loss of normal protein function through protein truncation.

**Population frequency:** This variant has a minor allele frequency of 0.0013% in gnomAD database and has not been reported in 1000 genomes databases.

**Clinical and Literature evidence:** This variant has been previously classified as pathogenic in ClinVar database [5]. This variant has been previously identified in a patients affected with Tyrosine hydroxylase (TH) deficiency in compound heterozygous state [6].

**In-silico prediction:** The *in-silico* predictions of the variant are deleterious by Mutationtaster2.

**OMIM phenotype:** Segawa syndrome, recessive (OMIM#605407) is caused by homozygous or compound heterozygous mutation in the *TH* gene (OMIM\*191290). This disease follows autosomal recessive pattern of inheritance [2].

**Variant classification:** Based on the evidence, this variant is classified as a likely pathogenic variant.

#### CA5A: c.721G>A

**Variant summary:** A heterozygous missense variation in exon 6 of the *CA5A* gene (chr16:g.87891852C>T, NM\_001739.2, Depth: 132x) that results in the amino acid substitution of Lysine for Glutamic acid at codon 241 (p.Glu241Lys) was detected.

**Population frequency:** This variant has minor allele frequency of 0.0072% in gnomAD database and has a minor allele frequency of 0.039% in 1000 genomes databases.

**Clinical and Literature evidence:** This variant has been previously classified as pathogenic in ClinVar database [7]. This variant has been previously reported in an Indian patient affected with mitochondrial carbonic anhydrase VA (CAVA) deficiency in homozygous state [8].

**In-silico prediction:** The *in-silico* predictions of the variant are damaging by SIFT, PolyPhen-2 (HumDiv), LRT and MutationTaster2. The reference codon is conserved across mammals in PhyloP tool.

**OMIM phenotype:** Hyperammonemia due to carbonic anhydrase VA deficiency (OMIM#615751) is caused by homozygous mutation in the *CA5A* gene (OMIM\*114761). This disease follows autosomal recessive pattern of inheritance [2].

**Variant classification:** Based on the evidence, this variant is classified as a likely pathogenic variant.

#### ***DNAH1: c.325C>T***

**Variant summary:** A heterozygous stop gained variation in exon 2 of the *DNAH1* gene (chr3:g.52322767C>T, NM\_015512.5, Depth: 92x) that results in the premature truncation of the protein at codon 109 (p.Gln109Ter) was detected. This variant is a stop gained variant which occurs in an exon of *DNAH1* upstream of where nonsense mediated decay is predicted to occur. This variant is predicted to cause loss of normal protein function through protein truncation.

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

**In-silico prediction:** The *in-silico* predictions of the variant is deleterious by MutationTaster2.

**OMIM phenotype:** Ciliary dyskinesia, primary, 37 (OMIM#617577) is caused by homozygous mutation in the *DNAH1* gene (OMIM\*603332). Spermatogenic failure 18 (OMIM#617576) is caused by homozygous or compound heterozygous mutation in the *DNAH1* gene (OMIM\*603332). These diseases follow autosomal recessive pattern of inheritance [2].

**Variant classification:** Based on the evidence, this variant is classified as a likely pathogenic variant.

#### ***DNAH9: c.5130G>A***

**Variant summary:** A heterozygous stop gained variation in exon 24 of the *DNAH9* gene (chr17:g.11701226G>A, NM\_001372.4, Depth: 98x) that results in the premature truncation of the protein at codon 1710 (p.Trp1710Ter) was detected. This variant is a stop gained variant which occurs in an exon of *DNAH9* upstream of where nonsense mediated decay is predicted to occur. This variant is predicted to cause loss of normal protein function through protein truncation.

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

**In-silico prediction:** The *in-silico* predictions of the variant are deleterious by CADD. The reference codon is conserved across mammals in PhyloP and GERP++ tools.

**OMIM phenotype:** Ciliary dyskinesia, primary, 40 (OMIM#618300) is caused by homozygous or compound heterozygous mutation in the *DNAH9* gene (OMIM\*603330). This disease follows autosomal recessive pattern of inheritance [2].

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**Variant classification:** Based on the evidence, this variant is classified as a likely pathogenic variant.

#### ***NLRP7*: c.2188A>T**

**Variant summary:** A heterozygous stop gained variation in exon 6 of the *NLRP7* gene (chr19:g.54936373T>A, NM\_001127255.1, Depth: 118x) that results in the premature truncation of the protein at codon 730 (p.Lys730Ter) was detected. This variant is a stop gained variant which occurs in an exon of *NLRP7* upstream of where nonsense mediated decay is predicted to occur. This variant is predicted to cause loss of normal protein function through protein truncation.

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

**In-silico prediction:** The *in-silico* predictions of the variant are deleterious by CADD.

**OMIM phenotype:** Hydatidiform mole, recurrent, 1 (OMIM#231090) is caused by homozygous or compound heterozygous mutation in the *NLRP7* gene (OMIM\*609661). This disease follows autosomal recessive pattern of inheritance [2].

**Variant classification:** Based on the evidence, this variant is classified as a likely pathogenic variant.

#### **Interpretation for the significance variants identified in Mr. XXX**

#### ***COASY*: c.1486-3C>G**

**Variant summary:** A heterozygous 3' splice site variation in intron 7 of the *COASY* gene (chr17:g.42565656C>G, NM\_025233.7, Depth: 158x) that affects the invariant AG acceptor splice site of exon 8 (c.1486-3C>G) was detected.

**Population frequency:** This variant has a minor allele frequency of 0.002% in gnomAD database and has a minor allele frequency of 0.039% in 1000 genomes databases.

**Clinical and Literature evidence:** This variant has been previously classified as pathogenic in ClinVar database [9]. This variant has been previously reported in an patients affected with Pontocerebellar hypoplasia with prenatal onset of microcephaly, and arthrogryposis in both homozygous and compound heterozygous state [10].

**In-silico prediction:** The reference codon is conserved across mammals in PhyloP tool.

**OMIM phenotype:** Neurodegeneration with brain iron accumulation 6 (OMIM#615643) and Pontocerebellar hypoplasia, type 12 (OMIM#618266) are caused by homozygous or compound heterozygous mutation in the *COASY* gene (OMIM\*609855). These diseases follow autosomal recessive pattern of inheritance [2].

**Variant classification:** Based on the evidence, this variant is classified as a likely pathogenic variant.

### **GRIP1: c.67C>T**

**Variant summary:** A heterozygous stop gained variation in exon 1 of the *GRIP1* gene (chr12:g.66804119G>A, NM\_001379345.1, Depth: 186x) that results in the premature truncation of the protein at codon 23 (p.Arg23Ter) was detected. This variant is a stop gained variant which occurs in an exon of *GRIP1* upstream of where nonsense mediated decay is predicted to occur. This variant is predicted to cause loss of normal protein function through protein truncation.

**Population frequency:** This variant has a minor allele frequency of 0.0007% in gnomAD database and has not been reported in 1000 genomes databases.

**In-silico prediction:** The reference codon is conserved across mammals in PhyloP and GERP++ tools.

**OMIM phenotype:** Fraser syndrome 3 (OMIM#617667) is caused by homozygous mutation in the *GRIP1* gene (OMIM\*604597). This disease follows autosomal recessive pattern of inheritance [2].

**Variant classification:** Based on the evidence, this variant is classified as a likely pathogenic variant.

## **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 counseling is recommended.

## **Methodology**

DNA extracted from the blood was used to perform targeted gene capture using a custom 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 (v3.1.2,2.1.1), ClinVar, OMIM, dbSNP, NCBI RefSeq Genes. *In-silico* predictions of the variant was carried out using VS-SIFT, VS-PolyPhen2, PhyloP, GERP++, CADD, 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

	Mr. Agilan P	Mrs. YYY
Total reads generated	5.90 Gb	4.61 Gb
Data ≥ Q30	88.46%	88.61%

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.
- The variants of uncertain significance and variations with high minor allele frequencies which are likely to be benign will be given upon request.
- Incidental or secondary findings that meet the ACMG guidelines can be given upon request [11].

## 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. PMID: 18842627; PMCID: PMC2686440.
3. <https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000617807.2>
4. Shahzad, Mohsin, et al. "Molecular outcomes, clinical consequences, and genetic diagnosis of Oculocutaneous Albinism in Pakistani population." Scientific reports 7.1 (2017): 44185. PMID: 28266639.
5. <https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV002194153.1>
6. Yeung, Wai Lan, et al. "Galactorrhea—a strong clinical clue towards the diagnosis of neurotransmitter disease." Brain and Development 28.6 (2006): 389-391. PMID: 16376043.
7. <https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000388645.16>
8. Konanki, Ramesh, et al. "Mitochondrial carbonic anhydrase VA deficiency in three Indian infants manifesting early metabolic crisis." Brain and Development 42.7 (2020): 534-538. PMID: 32381389.
9. <https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000599341.2>
10. van Dijk, Tessa, et al. "Biallelic loss of function variants in COASY cause prenatal onset pontocerebellar hypoplasia, microcephaly, and arthrogryposis." European Journal of Human Genetics 26.12 (2018): 1752-1758. PMID: 30089828.
11. 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.

**This report has been reviewed and approved by:**



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**APPENDIX: Current gene list used for carrier screening of pathogenic and likely pathogenic variants:**

AAS, AARS2, ABAT, ABCA1, ABCA12, ABCA3, ABCA4, ABCC4, ABCC8, ABCD1, ABCD4, ABCG5, ABCG8, ACAD9, ACADS, ACADSB, ACADVL, ACAT1, ACD, ACKR1, ACO2, ACOX1, ACOX2, ACP2, ACP5, ACTA1, ADAMTS10, ADAMTS12, ADAMTS14, ADAR, ADAT3, ADCY6, ADD3, ADGRG6, ADGRV1, ADRB2, ADRB3, ADSL, AEBP1, AGA, AGBL5, AGPAT2, AGRP, AGT, AGTR1, AGXT, AGXT2, AHY, AHI1, AHS, AICDA, AIFM1, AIP1, AIRE, AK1, AKR1C4, AKR1D1, ALAD, ALAS2, ALDH18A1, ALDH6A1, ALDOA, ALDOB, ALG1, ALG12, ALG2, ALG3, ALG9, ALMS1, ALOX12B, ALOXE3, ALPL, ALS2, ALX3, ALX4, AMACR, AMBN, AMHR2, AMMECR1, AMN, AMPD1, AMPD2, AMPD3, AMT, ANGPTL3, ANO10, ANOS, ANTXR1, ANTXR2, AP4B1, AP4E1, APS21, APOC2, APOE, APR1, AQP2, AQP7, ARFGEF2, ARHGAP1, ARHGAP2, ARHGAP3, ARHGAP4, ARHGAP5, ARHGAP6, ARHGAP7, ARHGAP8, ARHGAP9, ARHGAP10, ARHGAP11, ARHGAP12, ARHGAP13, ARHGAP14, ARHGAP15, ARHGAP16, ARHGAP17, ARHGAP18, ARHGAP19, ARHGAP20, ARHGAP21, ARHGAP22, ARHGAP23, ARHGAP24, ARHGAP25, ARHGAP26, ARHGAP27, ARHGAP28, ARHGAP29, ARHGAP30, ARHGAP31, ARHGAP32, ARHGAP33, 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