Dr. Emmanouel Kanavakis
Genesis Genoma Lab.
Molecular Genetics
302 Kifissias Ave., Halandri
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Order no.: 63258869
Order received: 20 Sep. 2024
Sample type / Sample collection date: blood, CentoCard® / 16 Sep. 2024
Report date: 06 Nov. 2024
Report type: Final report

Patient no: **1319836**, First Name: **Kevin Anthony Nicolas**, Last Name: **Vlaescu**
DOB: **11 Apr. 2017**, Sex: **male**, Your ref.: **-**

Additional report recipient(s): Dr. Danai Palaiologou, Genesis Genoma Lab., Kifisias Ave. 302, 15232 Chalandri, Greece

Test(s) requested: CentoGenome® MOx 2.0 Solo

CLINICAL INFORMATION

Abnormal facial shape; Abnormality of the face; Atypical behavior; Brain imaging abnormality; Cerebral hypomyelination; Cleft palate; CNS hypomyelination; Decreased body weight; Delayed ability to sit; Delayed ability to walk; Delayed gross motor development; Delayed speech and language development; Episodic vomiting; Esodeviation; Failure to thrive; Gliosis; Global developmental delay; Hyperactivity; Intellectual disability; Microdontia; Micropenis; Microtia; Motor delay; Narrow mouth; Narrow palpebral fissure; Nystagmus; Posteriorly rotated ears; Rod-cone dystrophy; Self-injurious behavior; Sensorineural hearing impairment; Strabismus; Vomiting
(Clinical information indicated above follows HPO nomenclature.)
Previous CENTOGENE testing, results positive: Whole Exome Sequencing (heterozygous *KCNK9*, heterozygous *WDR26*).
Previous external genetic testing, results negative: Array CGH.
Family history: Yes.
Father: Affected.
Consanguineous parents: No.
Clinician suspects: Rod-cone dystrophy, Cone rod dystrophy.

UNCLEAR RESULT
Variant of uncertain significance (VUS) identified
Potentially relevant findings identified

INTERPRETATION

A heterozygous variant of uncertain significance was identified in the *LRP5* gene. Pathogenic variants in this gene are associated with autosomal dominant exudative vitreoretinopathy type 4. **Based on current evidence, the clinical relevance of this variant is unclear.** This result was confirmed by an orthogonal method (Sanger sequencing).

No further clinically relevant variants related to the described phenotype were detected.

Please also note the variants in the potentially relevant findings section.

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The previously detected variant in the *KCNK9* gene was also detected in this analysis in heterozygous state and is classified as likely benign. The familial segregation analysis confirms the variant is inherited from unaffected father, and therefore it is not further reported as it is not considered of clinical significance for the provided phenotype.

The previously detected variant in the *WDR26* gene was also detected in this analysis in heterozygous state and is classified as variant of uncertain significance. The familial segregation analysis confirms the variant is inherited from unaffected father, and therefore it is not further reported as it is not considered of clinical significance for the provided phenotype.

RECOMMENDATIONS

- Clinical evaluation to assess the phenotypic overlap with the detected variant is recommended.
- If the phenotype is considered compatible, parental targeted testing is recommended to establish whether the detected variant is inherited or *de novo*. Additionally, targeted testing for all informative family members to establish whether the detected variant is associated with the disorder should be considered. Basic clinical information and relationship for each analyzed family member are needed for a comprehensive evaluation of the data.
- If the detected variant is not considered to contribute to or fully explain the patient's phenotype, reevaluation of the genome sequence dataset is recommended every 12 months or if there are phenotypic changes.
- Genetic counselling is recommended.

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MAIN FINDINGS

SEQUENCE VARIANTS

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES **	TYPE AND CLASSIFICATION ***
LRP5	NM_002335.2:c.1564G>A	p.(Ala522Thr)	rs80358309	Heterozygous	PolyPhen: Probably damaging Align-GVDG: N/A SIFT: Deleterious MutationTaster: Disease causing Conservation_nt: high Conservation_aa:	gnomAD: 0.0000040 ESP: - 1000 G: - CentoMD: -	Missense Uncertain significance (class 3)

Variant annotation based on CentoCloud Bioinformatics pipeline. * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

VARIANT INTERPRETATION

LRP5, c.1564G>A p.(Ala522Thr)

The *LRP5* variant c.1564G>A p.(Ala522Thr) causes an amino acid change from Ala to Thr at position 522 in exon(s) no. 7 (of 23). According to HGMD Professional 2024.2, this variant has previously been described as disease causing for Familial exudative vitreoretinopathy (PMID:15981244, 31964843, 17955262). ClinVar lists this variant (Interpretation: Pathogenic; Variation ID: 1455445). It is classified as variant of uncertain significance based on CENTOGENE's implementation of the ACMG/AMP/ClinGen SVI guidelines.

Familial exudative vitreoretinopathy (FEVR) is an inherited disorder characterized by the incomplete development of the retinal vasculature. Its clinical appearance varies considerably, even within families, with severely affected patients often registered as blind during infancy, whereas mildly affected patients with few or no visual problems may have such a small area of avascularity in their peripheral retina that it is visible only by fluorescein angiography. It is believed that this peripheral avascularity is the primary anomaly in FEVR and results from defective retinal angiogenesis. The sight-threatening features of the FEVR phenotype are considered secondary to retinal avascularity and develop because of the resulting retinal ischemia; they include the development of hyperpermeable blood vessels, neovascularization, vitreoretinal traction, retinal folds, and retinal detachments (summary by Poulter et al., 2010; PMID:20159112). Mode of Inheritance: Autosomal dominant (OMIM®: 601813)

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NTIALLY RELEVANT FINDINGS

is table we list variants related to disorders without an apparent overlap with the described otype of the patient and/or variants with a zygosity inconsistent with the expected mode of tance. As examples, a variant of uncertain significance (VUS) in a gene with only partial clinical ap, or a single heterozygous pathogenic variant in a gene with a recessive phenotype which has al overlap, may be reported here. These variants are mentioned in this report due to the potential bution to the phenotype of the patient and may help close possible diagnostic gaps. For variants nay be considered clinically relevant, clinical re-evaluation and/or further testing (e.g. familial gation analysis) could clarify their contribution to patient's phenotype.

NCE VARIANTS

VARIANT COORDINATES	AMINO ACID CHANGE	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***	RELATED DISORDER (OMIM®) AND MODE OF INHERITANCE
NM_000350.2:c.5917del	p.(Val1973*)	Heterozygous	PolyPhen: N/A Align-GVDG: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: Conservation_aa:	gnomAD: 0.000028 ESP: - 1000 G: - CentoMD: -	Frameshift Pathogenic (class 1)	*ABCA4*-related disorders (601691), AR
NM_004004.5:c.269T>C	p.(Leu90Pro)	Heterozygous	PolyPhen: Probably damaging Align-GVDG: N/A SIFT: Deleterious MutationTaster: Disease causing Conservation_nt: high Conservation_aa:	gnomAD: 0.00064 ESP: - 1000 G: - CentoMD: -	Missense Pathogenic (class 1)	Deafness, autosomal recessive 1A (220290), AR, DD

tation based on CentoCloud Bioinformatics pipeline. * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database * based on ACMG recommendations.

DARY FINDINGS

nt is provided, in line with ACMG recommendations (ACMG SF v3.2 list for reporting of secondary in clinical exome and genome sequencing; Genetics in Medicine, 2023; PMID: 37347242) we econdary findings, i.e. relevant pathogenic and likely pathogenic variants in the recommended r the indicated phenotypes in this publication.

ot detect any relevant variants in the genes for which secondary findings are reported.

CARRIERSHIP FINDINGS

In this table we list sequence variants previously ascertained or evaluated and classified in CENTOGENE as "pathogenic" and "likely pathogenic", in selected genes associated with recessive severe and early-onset Mendelian diseases. As only in-house classified variants are presented, it should not be considered a comprehensive list of variants in these genes and does not provide a complete list of potentially relevant genetic variants in the patient. The complete gene list can be found at www.centogene.com/carriership-findings (please contact CENTOGENE customer support if the gene list has been updated after this report was issued). Orthogonal validation was not performed for these variants. Therefore, if any variant is used for clinical management of the patient, confirmation by another method needs to be considered. Furthermore, the classification of these variants may change over time, however reclassification reports for these variants will not be issued. CENTOGENE is not liable for any missing variant in this list and/or any provided classification of the variants at a certain point of time. As the identified variants may indicate (additional) genetic risks or diagnoses in the patient and/or family and/or inform about reproductive risks, we recommend discussing these findings in the context of genetic counselling.

SEQUENCE VARIANTS

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION ***
ATP7B	NM_000053.2:c.3207C>A	p.(His1069Gln)	rs76151636	Heterozygous	PolyPhen: - Align-GVDG: N/A SIFT: Deleterious MutationTaster: Disease causing Conservation_nt: moderate Conservation_aa:	gnomAD: 0.0018 ESP: - 1000 G: - CentoMD: -	Missense Pathogenic (class 1)

*Variant annotation based on CentoCloud Bioinformatics pipeline. * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.*

CENTOGENE VARIANT CLASSIFICATION (BASED ON ACMG RECOMMENDATIONS)

Class 1 – Pathogenic
Class 2 – Likely pathogenic
Class 3 – Variant of uncertain significance (VUS)
Class 4 – Likely benign
Class 5 – Benign

Additionally, other types of clinically relevant variants can be identified (e.g. risk factors, modifiers).

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Genetic Diagnostic Laboratory

CentoGenome MOx 2.0

Name/Surname : **VLAESCU KEVIN ANTHONY NICOLAS**
Date of birth : **11/4/2017**
Sample type : **CentoCard**
Referring clinician : **VASILICA PLAIASU - MEDSANA SRL**

Order ID: **65169**
Sample collection date: **16/9/2024**
Sample receipt date: **18/9/2024**
Report date: **12/11/2024**

Indication for testing:

According to the medical history the patient presents with dysmorphic features, cleft palate, global developmental delay (motor, speech, cognitive and behavior), neurosensory deafness, postnatal failure to thrive and suspected cone -rod dystrophy. Whole Exome Sequencing and aCGH analyses have been performed previously.

Method:

Genomic DNA is enzymatically fragmented and tagged with Illumina compatible adapter sequences. The libraries are paired -end sequenced on an Illumina platform to yield an average coverage depth of ~ 30x. A bioinformatics pipeline based on the DRAGEN pipeline from Illumina, as well as CENTOGENE's in-house pipeline is applied. The sequencing reads are aligned to the Genome Reference Consortium Human Build 37 (GRCh37/hg19), as well as the revised Cambridge Reference Sequence (rCRS) of the Human Mitochondrial DNA (NC_012920). Sequence variants (SNVs/indels) and copy number variations (CNVs) are called using DRAGEN, Manta and in -house algorithms. Variants with a minor allele frequency (MAF) of less than 1% in gnomAD database, or disease causing variants reported in HGMD ®, in ClinVar or in CENTOGENE's in-house Biodatabank are evaluated. Although the evaluation is focused on coding exons and flanking intronic regions, the complete gene is interrogated for candidate variants with plausible association to the phenotype. All potential modes of inheritance are considered. In addition, the provided clinical information and family history are used to evaluate identified variants with respect to their pathogenicity and disease causality. Variants are categorized into five classes (pathogenic, likely pathogenic, variant of uncertain significance [VUS], likely benign, and benign) according to ACMG/AMP guidelines for classification of variants in addition to ClinGen recommendations. All relevant variants related to the phenotype of the patient are reported. Likely benign and benign variants are not reported. For CentoGenome ® MOx, if biochemical analysis is applicable, this is performed upon detection of relevant variants by sequencing in specific genes. This enhances the diagnosis of metabolic disorders, optimizes variant classification, and helps to ascertain the eventual contribution to the phenotype; the list of enzyme -activity assays and biomarkers can be obtained at www.centogene.com/mox. CNVs of unknown significance with no apparent relation to the patient's phenotype are not reported. Mitochondrial variants with a heteroplasmy level of 15% or higher are reported. For detection of SNVs and indels in the regions targeted for downstream analysis a sensitivity of 99.9%, a specificity of 99.9%, and an accuracy of 99.9% is achieved. CNV detection software has a sensitivity of more than 95%. CENTOGENE has established stringent quality criteria and validation processes for variants detected by NGS. Variants with low sequencing quality and/or unclear zygosity are confirmed by orthogonal methods. Consequently, a specificity of > 99.9% for all reported variants is warranted. Screening of repeat expansions is performed by the ExpansionHunter algorithm for the following genes: *AR, ATN1, ATXN1, ATXN2, ATXN3, ATXN7, A 8OS, ATXN10, CACNA1A, CNBP, CSTB, C9orf72, DMPK, FMR1, FXN, HTT, JPH3, NOP56, PABPN1, PHOX2B, PPP2R2B, PRNP* and *T*. The technical results of repeat expansion screenings will be correlated with the clinical information provided. Any repeat expansion called and considered relevant to the phenotype will be confirmed by an orthogonal method. *GBA1* screening is performed using Gauchian algorithm to detect recombination events affecting the region encompassing exons 9 -11 (NM_000157.3), a region which has the highest homology to *GBAP1*. Any detected recombination event is reported only when considered relevant to the phenotype. Spinal muscular atrophy (SMA) screening is performed using SMN Caller algorithm to detect the copy number of the *SMN1* gene. Any detected CNV is only confirmed by an orthogonal method and reported when considered relevant to the phenotype. Screening of uniparental disomy (UPD) is performed using an in -house algorithm for Mendelian inheritance errors (MIE) to detect runs of homozygosity (ROH) for the well -known clinically relevant chromosomal regions (6q24, 7, 11p15.5, 14q32, 15q11q13, 20q13 and 20). RNA is isolated from CentoCard ®. Encoding messenger RNA (mRNA) is enriched, fragmented, and transcribed into complementary DNA (cDNA), followed by adapter ligation and amplification of the stranded libraries. The libraries are paired -end sequenced on an Illumina platform. An in-house bioinformatics pipeline is applied to process the sequencing data. Raw sequencing reads are assessed using QC tools to ensure data integrity and to identify any potential issues such as low -quality reads or adapter contamination. Subsequently, the reads are aligned to the GRCh37/hg19 genome assembly using STAR, allowing the accurate determination of splicing events. Quality criteria are applied for acceptance or rejection of the sequencing data. Accepted data is analyzed and used as additional evidence to evaluate the impact of the variant on splicing. The above analysis was performed in CENTOGENE laboratory in Germany.

Result:

The following variant was detected in heterozygosity in the analysed sample:

Gene	Variant coordinates	In silico parameters*	MAF**	Type and classification***
LRP5	NM_002335.2:c.1564G>A **p.(Ala522Thr)** **rs80358309**	PolyPhen: Probably damaging Align-GVDG: N/A SIFT: Deleterious MutationTaster: Disease causing Conservation_nt:high Conservation_aa:-	gnomAD: 0.0000040 ESP: - 1000 G: - CentoMD: -	Missense **Uncertain significance (class 3)**

Variant annotation based on CentoCloud Bioinformatics pipeline. * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function;

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CentoGenome MOx 2.0

Name/Surname : **VLAESCU KEVIN ANTHONY NICOLAS**
Date of birth : **11/4/2017**
Sample type : **CentoCard**
Referring clinician : **VASILICA PLAIASU - MEDSANA SRL**

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splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations

No further clinically relevant variants related to the described phenotype were detected.

Conclusion:

The *LRP5* variant c.1564G>A p.(Ala522Thr) causes an amino acid change from alanine to threonine at aminoacid 522 in exon 7 of 23 of the produced protein. According to HGMD Professional 2024.2, this variant has previously been described as disease causing for Familial exudative vitreoretinopathy with autosomal dominant mode of inheritance. Functional studies have shown that this variant results in 26% reduction in protein signaling, which is usually correlated with a mild clinical phenotype (PMID:15981244, 31964843, 17955262). ClinVar lists this variant with pathogenic clinical significance (Variation ID: 1455445).

It is classified as **variant of uncertain significance** based on CENTOGENE's implementation of the ACMG/AMP/ClinGen SVI guidelines.

Pathogenic/likely pathogenic variants in LRP5 gene are associated with exudative vitreoretinopathy, 4, (OMIM#601813), a disorder that exhibits autosomal dominant and recessive mode of inheritance.

Familial exudative vitreoretinopathy (FEVR) is an inherited disorder characterized by the incomplete development of the retinal vasculature. Its clinical appearance varies considerably, even within families, with severely affected patients often registered as blind during infancy, whereas mildly affected patients with few or no visual problems may have such a small area of avascularity in their peripheral retina that it is visible only by fluorescein angiography. It is believed that this peripheral avascularity is the primary anomaly in FEVR and results from defective retinal angiogenesis. The sight -threatening features of the FEVR phenotype are considered secondary to retinal avascularity and develop because of the resulting retinal ischemia; they include the development of hyperpermeable blood vessels, neovascularization, vitreoretinal traction, retinal folds, and retinal detachments (summary by Poulter et al., 2010; PMID:20159112).

Notes/Comments: Genetic counseling and evaluation of the results by the attending physician are recommended.
Re-evaluation of the sequence dataset upon phenotypic changes of the patient is also recommended.

is advised to perform targeted testing of the parents for the detected variant in *LRP5* gene in order to confirm if it is an inherited ariant or arose *de novo* in the patient.

OTENTIALLY RELEVANT FINDINGS
this table we list variants related to disorders without an apparent overlap with the described phenotype of the patient and/or variants th a zygosity inconsistent with the expected mode of inheritance. As examples, a variant of uncertain significance (VUS) in a gene th only partial clinical overlap, or a single heterozygous pathogenic variant in a gene with a recessive phenotype which has clinical erlap, may be reported here. These variants are mentioned in this report due to the potential contribution to the phenotype of the ient and may help close possible diagnostic gaps. For variants that may be considered clinically relevant, clinical re -evaluation /or further testing (e.g. familial segregation analysis) could clarify their contribution to patient's phenotype.

following variants were detected in heterozygosity in the analysed sample:

Gene	Variant coordinates	In silico parameters*	MAF**	Type and classification***	Related disorder (OMIM®) and mode o inheritance

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ABCA4	NM_000350.2:c.5917del **p.(Val1973*)**	PolyPhen: N/A Align-GVDG: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: Conservation_aa:	gnomAD :0.000028 ESP: - 1000 G: - CentoMD: -	Frameshift **Pathogenic** (class 1)	*ABCA4*-related disorders (601691) Stargardt disease Retinal dystrophy AR
GJB2	NM_004004.5:c.269T>C **p.(Leu90Pro)**	PolyPhen: Probably damaging Align-GVDG: N/A SIFT: Deleterious MutationTaster: Disease causing Conservation_nt: high Conservation_aa:	gnomAD: 0.00064 ESP: - 1000 G: - CentoMD: -	Missense **Pathogenic** (class 1)	Deafness, autosomal recessive 1A (220290) AR, DD

ıriant annotation based on CentoCloud Bioinformatics pipeline. * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; licing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and ntoMD® (latest database available). *** based on ACMG recommendations. AR: autosomal recessive, DD: digenic inheritance

athogenic/likely pathogenic variants in *ABCA4* gene are associated with the development of *ABCA4*-related disorders, such as argardt disease (OMIM#248200), Retinitis pigmentosa 19 (OMIM#601718) and others. They present with autosomal recessive mode inheritance.

athogenic/likely pathogenic variants in *GJB2* gene are associated with the development of deafness (Deafness, autosomal recessive A, OMIM#220290), that presents with autosomal recessive and digenic mode of inheritance in combination with variants in GJB6 and genes.

nce only one variant was detected in ABCA4 and *GJB2* genes, a possible genetic diagnosis of the above conditions can not be onfirmed.

etrospective clinical evaluation is recommended. If there is substantial clinical overlap with the patient's phenotype, dditional genetic analysis using the MLPA method could be performed, in order to screen for a second, deletion variant in *BCA4* and *GJB2* genes.

NCIDENTAL FINDINGS

ccording to the ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (ACMG SF 3.2 list for reporting of secondary findings in clinical exome and genome sequencing; Genetics in Medicine, 2023; PMID: 37347242),

e did not detect any pathogenic and likely pathogenic variants in the genes, for which incidental findings are reported.

ARRIERSHIP FINDINGS

this table sequence variants previously ascertained or evaluated and classified in CENTOGENE as "pathogenic" and "likely athogenic", in selected genes associated with recessive severe and early onset Mendelian diseases. As only in -house classified variants e presented, it should not be considered a comprehensive list of variants in these genes and does not provide a complete list of otentially
levant genetic variants in the patient. The complete gene list can be found at www.centogene.com/carriership -findings (please contact ENTOGENE customer support if the gene list has been updated after this report was issued). Orthogonal validation was not rformed for these variants. Therefore, if any variant is used for clinical management of the patient, confirmation by another method eds to be considered. Furthermore, the classification of these variants may change over time, however reclassification reports for ese variants will not be issued. CENTOGENE is not liable for any missing variant in this list and/or any provided classification of the ıriants at a certain point of time. As the identified variants may indicate (additional) genetic risks or

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iagnoses in the patient and/or family and/or inform about reproductive risks, we recommend discussing these findings in the context of enetic counseling.

he following variant was detected in heterozygosity in the analysed sample:

Gene	Variant coordinates	In silico parameters*	MAF**	Type and classification***
ATP7B	NM_000053.2:c.3207C>A **p.(His1069Gln)** rs76151636	PolyPhen: - Align-GVDG: N/A SIFT: Deleterious MutationTaster: Disease causing Conservation_nt: moderate Conservation_aa:	gnomAD: 0.0018 ESP: - 1000 G: - CentoMD: -	Missense **Pathogenic** (class 1)

ariant annotation based on CentoCloud Bioinformatics pipeline. * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; licing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and ntoMD® (latest database available). *** based on ACMG recommendations.

ccording to the above results the patient is a carrier of Wilson disease. Pathogenic/likely pathogenic variants in *ATP7B* gene are sociated with the development of Wilson disease (OMIM#277900) that presents with autosomal recessive mode of inheritance.

gregation analysis of the detected variant in the patient's parents and complete molecular analysis of the *ATP7B* gene in the on-carrier parent is recommended in the context of prenatal testing.

OTES

previously detected variant in the *KCNK9* gene was also detected in this analysis in heterozygous state and is classified as likely ...gn. The familial segregation analysis confirms the variant is inherited
m unaffected father, and therefore it is not further reported as it is not considered of clinical significance for the provided phenotype.

e previously detected variant in the *WDR26* gene was also detected in this analysis in heterozygous state and is classified as variant uncertain significance. The familial segregation analysis confirms the
iant is inherited from unaffected father, and therefore it is not further reported as it is not considered of clinical significance for the vided phenotype.

MITATIONS

e genetic results are interpreted in the context of the provided clinical findings, family history, and other laboratory data. Only iants in genes potentially related to the proband's medical condition are reported. Misinterpretation of results may occur if the vided genetic data or patient information is inaccurate and/or incomplete. If the obtained genetic results are not compatible with the nical findings, additional testing should be considered. Genes with mapping issues in the genome assembly used, and genomic ions that are hard to sequence by current technology and are without evidenced relevance for monogenic disorders, are excluded n this analysis. More complex genetic events not mentioned in the methods section, such as inversions and translocations, are not lyzed in this test. In addition, due to technology limitations, certain regions may be poorly covered, or not covered at all. In these ions and others encompassing repetitive, high -homology (such as pseudogene homology), and GC -rich sequences, relevant variants be missed. Extremely low coverage calls are expected to be artifacts based on our extensive validations and are consequently not sidered during the analysis. Potential aberrant splicing is assessed with splice prediction tools. Deep intronic variants without strong diction of aberrant splicing may not be reported, with the exception of known pathogenic splicing variants evidenced by external rces. The CNV detection sensitivity is decreased for repetitive regions, homologous regions such as pseudogenes, and for events nning 2 or less exons. Mitochondrial variants with heteroplasmy levels below 15% may not be detected. It is expected that lower lity samples (e.g. prenatal, product of conception, blood from patients with hematologic disorders, and highly degraded DNA) may erate lower quality NGS data; in these cases, CNV analysis, mitochondrial genome analysis, and/or additional integrated screening yses in this test may not be possible to perform. The repeat expansion algorithm used is not designed to handle complex *loci* that or multiple repeats. Repeats are only genotyped if the coverage at the *locus* is at least 10x. The Gauchian algorithm can only detect

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Sample receipt date: **18/9/2024**
Report date: **12/11/2024**

non-recombinant-like variants from a set of 111 known *GBA1* variants and can detect recombination events affecting exons 9 -11 only. Therefore, recombinations affecting other regions are not in the scope of this screening. Silent carriers may be missed with the SMN caller algorithm. The UPD detection is a screening method, and therefore false -positive and false-negative results may occur. The quality of the RNA sequencing data may be significantly impaired by improper sample handling or sample preparation. This could be caused when the instructions for use are not followed (for example, using non -EDTA blood or non-freshly drawn blood for Card® preparation, or extended shipping times). Samples received are extracted and processed only when 7 days or less have passed since blood collection. RNA integrity is evaluated after extraction, and only samples with RIN above 2.5 are processed. In each blood sample the expression of genes is subject to natural variation, leading to varying coverage information per gene. Consequently, genes with low expression in a sample cannot be analyzed if coverage data is not sufficient to evaluate splicing impact. Mapping tools rely on a reference genome, and any discrepancies between the reference and the sample's genome, such as genetic variation or novel transcripts, can result in alignment inaccuracies and potential loss of information (reference genome bias). The presence of highly

References:

1 *et al.* Complexity of the genotype-phenotype correlation in familial exudative vitreoretinopathy with mutations in the LRP5 and/or FZD4 genes. Hum Mutat. 2005 Aug;26(2):104 -12. PMID: 15981244

2 *et al.* Moderate reduction of Norrin signaling activity associated with the causative missense mutations identified in patients with familial exudative vitreoretinopathy. Hum Genet. 2008 Jan;122(6):615 -23.MID: 17955262

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MEDSANA

RAPORT MEDICAL

Specialitate: Genetica
Nume pacient: VLAESCU KEVIN ANTHONY NICOLAS
Sex: Masculin
Vârstă: 7 ani, 3 luni
Data nasterii: 11.04.2017
CNP:
Adresă:

Cod pacient:1009450
Data şi ora examinării: 05.08.2024
Nr. consultaţie: 81,920
Medic: DR. PLAIASU VASILICA
Recomandat de: LA CERERE
Companie/Partener:

MOTIVUL PREZENTARII:
Consult clinic si interpretarea de rezultate genetice efectuate in antecedente

ISTORIC/ANAMNEZA:
Istoric familial negativ, tatal cu sdr Gilbert
Actual:mama cu sarcina in evolutie VG=30 sapt
G=3220g, T=52cm, PC=34cm, APGAR=8
- screening metabolic neonatal extins: N
- palatoschizis complet
VG 39 sapt, cezariana, mama=36 ani, tatal=43cm
- a stat in sezut la 1 an 5 luni
- a mers la v 2 ani 1 luna
- intarziere de limbaj
- fara convulsii
- FA inchisa la v 11 luni
- varsaturi frecvente in primii 2 ani
- RMN cerebral (v 9 luni: plaje de heterosemnal T2 parietale post, zone incomplet mielinizare +/- glioza parietal stg
- Eco cord: N
- Eco abdomen: N
- EEG: normal
- Examen oftalmologic: strabism convergent, nistagmus orizonatal, Rod-cone dystrophy in observatie
- Rf de pumn: VO in limitele varstei cronologice
- Cariotip molecular: N
- WES (Centogene Octombrie 2018): Identificarea unei variante de tip VUS la WDR26, respectiv o varianta heterozigota la nivelul genei KCNK9 mostenite patern
WES prenatal (trio): negativ

EXAMEN CLINIC:
CONSULT GENETICA
G=17kg, T=118cm, PC= 50.5cm
- Falimentul cresterii postnatal
- Trasaturi faciale dismorfice (fante palpebrale inguste, nistagmus, urechi mici, rotate posterior, gura mica, dinti mici, palatoschizis operat)
- Micropenie
- Intarziere de dezvoltare a limbajului
- Intarziere in dezvoltarea cognitiva- autoagresiune (se musca, are leziuni de muscaturi la nivelul mainilor)
- Hiperactivitate
- Nu colaboreaza

MEDSANA

DIAGNOSTIC:

Particularitati fizice. Palatoschizis operat. Intarziere globala de dezvoltare (motor, limbaj, cognitiv, comportamental). Hipoacuzie neurosenzoriala bilaterala. Falimentul cresterii postnatal. Distrofie retiniana in obs (rod-cone distrophy)

Tip afectiune: Monitorizare boala cronica

RECOMANDARI CONFORM DIAGNOSTIC ACUT:

..

RECOMANDARI BOALA CRONICA:

1. monitorizarea curbelor de crestere (G, T, PC)
2. monitorizare neyrologica si psihiatrica
3. continua terapiile de stimulare
4. monitorizarea auzului
5. monitorizarea oftalmologica
6. se va completa investigarea genetica cu analiza WGS (Whole Genome Sequencing)= secventierea intregului genom

Dr. Plaiasu Vasilica

Dr. PLĂIAȘU VASILICA
Medic primar
genetică medicală
doctor în medicină
Cod 036176

Institutul National Pentru Sanatatea Mamei si Copilului "Alessandrescu-Rusescu"
CENTRUL REGIONAL DE GENETICA MEDICALA BUCURESTI
Bd.Lacul Tei nr.120, sector 2, Bucuresti
Telefon: 021/2422713/ interior 1118
Programari online: https://programari.insmc.ro/ Genetica Medicala

Operator date cu caracter personal nr.26683

FISA DE CONSULT GENETIC
REEVALUARE

Nr.inregistrare(reg.cons.) 2/8.01.2026.

I. DATE DESPRE PACIENT

Nume şi prenume: VLĂESCU KEVIN ANTHONY NICOLAS [illegible]
Data naşterii: [illegible].2017 Varsta actuala: 8 ani 9 l. CNP: 51704[illegible]
Domiciliul: Dj, Craiova
Telefon: Email:

II. DIAGNOSTIC CLINIC/ GENETIC

ÎN OBSERVAȚIE PATOLOGIE EREDITARĂ DE ȚESUT CONJUNCTIV (WES, WGS negativ).

III. SOMATOMETRIE:

G= 20 kg (< p 10)
T= 125 cm (p 10-25)
PC= 50 cm (p 5-10)

IV. EXAMEN CLINIC ACTUAL

Particularități fizice: Dificultăți de [illegible] Integrează și [illegible]. [illegible]. Coordonare [illegible]. Hipotrofie [illegible] motorie. Stereotipii motorii. [illegible]. Înțelege. Hiperlaxitate articulară. [illegible]

V. INVESTIGATII EFECTUATE

- EEG: modificări nespecifice
- Analize genetice pt. trombofilie: homozigot MTHFR C677T, heterozigot F XIII
- Polisomnografie: tulb. de respirație în timpul somnului — sdr. de apnee în somn de tip obstructiv.

VI. ALTELE

- dificultăți de somn
- afirmativ un regres de achiziții (ar debut din 2025 la introducerea trat. psihiatric)

VII. RECOMANDARI / OBSERVATII

- [illegible]
- [illegible]
- Analiza genetică de tip WGS (Centogene): negativ

Recomandări de etapă:

1) monitorizarea creșterii (G, T, PC)
2) reevaluare oftalmologică
3) monitorizare digestivă
4) reevaluare psihologică
5) terapii de stimulare; kinetoterapie.
6) au fost discutate cu mama rezultatele testării genetice.

Semnatură si parafa:

1

...contejele şi limitele superioare pentru vârstă.

...au prezentat şi posibilitatea de completare a investigaţiilor

...peutice cu metode complementare (au nu fost de [illegible]

... momentul actual).