MEDICOVER GENETICS

MOLECULAR GENETIC REPORT
GM19.12345

Lochhamer Straße 29, 82152 Martinsried, Germany, Email: info@medicover-genetics.com
Date: 16.03.2023

Report to:

Requesting Physician Name

Address

Contact Information

Order Number	**20 2009 1234**
Born	DD/MM/YYYY
Sex	
Date test requested:	27.02.2023
Sample collected:	27.02.2023
Sample / Specimen:	DNA from EDTA blood

Order: molecular genetic analysis of Neurodegenerative disorders - adult onset_2.31
Additional Information /patient phenotype: Frontotemporal phenotype with parkinsonism.

RESULT SUMMARY:

POSITIVE – Consistent with Ceroid lipofuscinosis, neuronal, 13, Kufs type – homozygous for likely pathogenic variants

Result

The missense variant p.(Tyr231Cys) in *CTSF* has been reported previously as a pathogenic in an individual with Kufs disease type B, where it was found in trans with another pathogenic variant (Smith et al. 2013, Hum Mol Genet 22: 1417). The variant is located in the I29 propeptide inhibitor domain. In silico tools predict it as deleterious.

CTSF encodes cathepsin F, a member of the papain family of cysteine proteases. These enzymes represent a major component of the lysosomal proteolytic system. Pathogenic variants in this gene have been reported as a cause of Kufs disease type B, an autosomal recessive neuronal ceroid lipofuscinosis, characterized by adult onset of progressive cognitive decline and motor dysfunction leading to dementia and often early death (Smith et al. 2013, Hum Mol Genet 22: 1417).

Conclusion

The detected variants in *CTSF* are consistent with the clinical diagnosis of ceroid lipofuscinosis, neuronal, 13, Kufs type and may with a high probability be regarded as causative for the patient's phenotype.

Offspring inherit variants with a probability of 50%, each.

Recommended action

- Offer genetic counselling.
- Offer variant-specific genetic testing of biological relatives for segregation analysis to enable further evaluation of pathogenicity of the likely pathogenic variant.

VARIANT DETAILS

Gene	Variant	Classification	Exon	Location on GRCh38
CTSF	NM_003793.3:c.692A>G p.(Tyr231Cys)	Likely pathogenic	5	Chr11:g.66333791T>C
Consequence	**Zygosity**	**Inheritance**	**ACMG/AMP criteria (Richards et al.; Ellard et al**	**Disorder**
Missense	Homozygous	Autosomal Recessive	PM2,PM1_Supporting,PP3, PM3,PS4_Supporting	Ceroid Lipofuscinosis, Neuronal, 13
GeneID	**#OMIM**	**ClinVarID**	**dbSNP ID**	**Allele Frequency**
8722	615362	60678	rs143889283	11/113730 (0.01%) (gnomAD Non Finnish European)

Report released by

John Doe 16.03.2023

johndoe@medicover.com

TEST METHODOLOGY

Sequencing	Enrichment	SNV and CNV Data analysis	data evaluation	Reference genome
Next Generation Sequencing (Illumina)	Twist Human Core Exome plus RefSeq SpikeIn	Illumina Dragen Bio-IT Platform VarSeq by GoldenHelix	VarSeq by GoldenHelix	hg38, NCBI GR38
Quality criteria	**SNV detection sensitivity**	**Classification of variants**	**in silico algorithms**	**Databases**
>30 (precision >99,9%) in min. 75% of bases	99.92 - 99.93 %; confirmation of reported SNV with Sanger sequencing, data analysis with SeqPilot	Richards et al. 2015, Genet Med 17:405; Ellard et al. "ACGS Best Practice Guidelines for Variant Classification 2020“	MaxEntScan, SpliceSiteFinder-like, REVEL	HGMD Professional release, ClinVar, gnomAD

PERCENTAGE OF SEQUENCED BASES WITH COVERAGE >20X

97.968%

ANALYZED GENES

ABCD1(NM_000033.3), AFG3L2(NM_006796.2), ALS2(NM_020919.3), ANG(NM_001145.4), ANXA11(NM_145868.1), APP(NM_000484.3), ARSA(NM_000487.5), ATP13A2(NM_022089.3), ATP1A3(NM_152296.4), ATP7B(NM_000053.3), AUH(NM_001698.2), C19orf12(NM_031448.4), CACNA1G(NM_018896.4), CCNF(NM_001761.2), CHCHD10(NM_213720.2), CHCHD2(NM_016139.3), CHMP2B(NM_014043.3), CLCN2(NM_004366.5), CLN6(NM_017882.2), COASY(NM_025233.6), CP(NM_000096.3), CSF1R(NM_001288705.2), CTSF(NM_003793.3), CYP27A1(NM_000784.3), CYP7B1(NM_004820.4), DARS2(NM_018122.4), DCTN1(NM_004082.4), DNAJC5(NM_025219.2), DNAJC6(NM_001256864.1), DNMT1(NM_001130823.2), EIF2B1(NM_001414.3), EIF2B2(NM_014239.3), EIF2B3(NM_020365.4), EIF2B4(NM_001034116.1), EIF2B5(NM_003907.2), ELOVL4(NM_022726.3), EPM2A(NM_005670.3), FBXO7(NM_012179.3), FIG4(NM_014845.5), FTL(NM_000146.3), FUS(NM_004960.3), GCH1(NM_000161.2), GFAP(NM_002055.4),

GRN(NM_002087.3), HEXA(NM_000520.5), HEXB(NM_000521.3), HNRNPA1(NM_031157.3), HTRA1(NM_002775.4), ITM2B(NM_021999.4), KCNC3(NM_004977.2), KCND3(NM_004980.4), KIF5A(NM_004984.2), LRRK2(NM_198578.3), LYST(NM_000081.3), MAPT(NM_001123066.3), MYORG(NM_020702.4), NHLRC1(NM_198586.2), NOTCH3(NM_000435.2), NPC1(NM_000271.4), NPC2(NM_006432.3), OPTN(NM_001008212.1), PANK2(NM_153638.3), PARK7(NM_007262.4), PDGFB(NM_002608.3), PDGFRB(NM_002609.3), PFN1(NM_005022.3), PINK1(NM_032409.2), PLA2G6(NM_003560.2), PRKN(NM_004562.2), PRNP(NM_000311.3), PSEN1(NM_000021.3), PSEN2(NM_000447.2), RNF216(NM_207111.3), SETX(NM_015046.5), SLC20A2(NM_001257180.1), SNCA(NM_000345.3), SOD1(NM_000454.4), SPAST(NM_014946.3), SPG11(NM_025137.3), SQSTM1(NM_003900.4), SYNJ1(NM_203446.2), TARDBP(NM_007375.3), TBK1(NM_013254.3), TMEM240(NM_001114748.1), TREM2(NM_018965.3), TTC19(NM_017775.3), TYROBP(NM_003332.3), UBQLN2(NM_013444.3), VAPB(NM_004738.4), VCP(NM_007126.3), VPS13A(NM_033305.2), VPS35(NM_018206.5), WDR45(NM_007075.3), XPR1(NM_004736.3)

LIST OF EXONS WITH COVERAGE <20X

Chr.	Pos.	Gene	Exon	Transcript	Mean Coverage (Min/Max)
Chr1	1475665..1475731	*TMEM240*	Exon 01	NM_001114748.1	39.73 (16/59)
Chr1	20960037..20960433	*PINK1*	Exon 01	NM_032409.2	85.17 (0/144)
Chr6	146056329..146056639	*EPM2A*	Exon 01	NM_005670.3	40.68 (6/99)
Chr10	124221164..124221645	*HTRA1*	Exon 01	NM_002775.4	35.56 (0/80)
Chr12	64890142..64890191	*TBK1*	Exon 16	NM_013254.3	19.22 (18/20)
Chr17	15903158..15903351	*TTC19*	Exon 01	NM_017775.3	57.74 (13/116)
Chr19	10290858..10290915	*DNMT1*	Exon 05	NM_001130823.2	18.22 (13/23)
Chr19	15288331..15288906	*NOTCH3*	Exon 24	NM_000435.2	95.57 (4/180)
Chr19	15311594..15311721	*NOTCH3*	Exon 01	NM_000435.2	23.21 (1/36)
Chr19	50823498..50823611	*KCNC3*	Exon 04	NM_004977.2	31.24 (14/45)
Chr19	50831465..50832344	*KCNC3*	Exon 01	NM_004977.2	54.37 (0/146)

TECHNICAL LIMITATIONS

mosaics (<20%); indels >21bp; repeat expansions; repetitive regions; variants in: homopolymeric regions or regions of high sequence homology, unenriched regions (untranslated regions, introns, promoter and enhancer regions) or enriched but insufficiently covered regions; variants in mt-DNA (VAF<20%); determination of the phase of multiple variants in one gene; balanced genomic rearrangements

CLASSES OF VARIANTS

Class 5: pathogenic variant – are reported, posterior probability >99 %
Class 4: likely pathogenic variant – are reported, posterior probability >90 %
Class 3: uncertain significance – only be listed in the report if posterior probability is >67.5 %
Class 2: likely benign – not reported, posterior probability <10 %
Class 1: benign – not reported, posterior probability <0,1 %

ACMG CRITERIA

1. Criteria for pathogenic evidence
PVS1: Null variant in a gene where loss of function (LOF) is a known mechanism of disease; PS1: same amino acid change as a previously established pathogenic variant regardless of nucleotide change; PS2/PM6: de novo in a patient with the disease and no family history; PS3: well-established functional studies supportive of a damaging effect on the gene or gene product; PS4: the prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls/was identified in unrelated affected individuals; PM1: missense variant located in a mutational hot spot and/or critical and well-established functional domain; PM2: absent from controls (or at extremely low frequency) in Genome Aggregation Database (gnomAD); PM3: for recessive disorders, detected in homozygous state or together with another (not benign or likely benign) variant; PM4: protein length changes as a result of in-frame deletions/insertions in a non- repeat region or stop-loss variants; PM5: missense change at an amino acid residue where a different missense change determined to be (likely) pathogenic has been seen before; PP1: co-segregation with disease in multiple affected family members; PP2: missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease; PP3: multiple lines of computational evidence support a deleterious effect on the gene or gene product; PP4: patient's phenotype or family history is (highly) is specific for variations in the affected gene; PP5: reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.

2. Criteria for benign evidence

BA1: allele frequency is >5% if recessive and 0.5% if dominant in gnomAD; BS1: allele frequency is greater than expected for disorder; BS2: observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age; BS3: well-established functional studies show no damaging effect on protein function or splicing; BS4: lack of segregation with disease; BP1: missense variant in a gene for which primarily truncating variants are known to cause disease OR for loss-of-function variants in a gene where the disease is caused by gain-of-function variants; BP2: observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern; BP3: in-frame deletions/insertions in a repetitive region without a known function; BP4: multiple lines of computational evidence suggest no impact on gene or gene product; BP5: variant found in a case with an alternate molecular basis for disease; BP6: reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation; BP7: a synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved.

According to Ellard et al. 2020, the strength level of criteria PVS1, PS1, PS2, PS3, PS4, PM1, PM3, PM4, PM5, PP1, PP4, BP2, and BP4 can be modified depending on the cogency of the evidence.

ALLELE FREQUENCIES

This value corresponds to the maximum frequency of all reference populations (POPMAX).

Report released by

John Doe 16.3.2023

johndoe@medicover.com