MEDICOVER GENETICS

MOLECULAR GENETIC REPORT
GM19.12345

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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 Inborn errors of metabolism_2.3
Additional Information /patient phenotype: Sudden unexpected death at 1yr. Suspected metabolic disorder.

RESULT SUMMARY:

POSITIVE – Confirmation of Myoglobinuria, acute recurrent, autosomal recessive – homozygous for pathogenic variants

Result

The stop gained .2401C>T p.(Arg801Ter) in the *LPIN1* gene has been reported previously in an individual with myoglobinuria who was compound heterozygous for this variant and a deletion of exons 18 and 19 (Zeharia et al. 2008, Am J Hum Genet 83:489). This variant is expected to result in either an abnormal, truncated protein product or loss of protein from this allele through nonsense-mediated mRNA decay.

LPIN1 encodes lipin 1, a magnesium-ion-dependent phosphatidic acid phosphohydrolase enzyme that catalyzes the penultimate step in triglyceride synthesis including the dephosphorylation of phosphatidic acid to yield diacylglycerol. Expression of this gene is required for adipocyte differentiation and it also functions as a nuclear transcriptional coactivator with some peroxisome proliferator-activated receptors to modulate expression of other genes involved in lipid metabolism. Pathogenic variants in this gene are associated with autosomal recessive recurrent acute myoglobinuria. It is characterized by recurrent attacks of rhabdomyolysis associated with muscle pain and weakness and followed by excretion of myoglobin in the urine. About one-third of patients die from cardiac arrest during a crisis episode (Legendre et al. 2018, Mol Genet Metab 123:375; Schönfelder et al. 2011, Neuropediatrics 42:118).

Conclusion

The detected variants in *LPIN1* confirm the myoglobinuria, acute recurrent, autosomal recessive. To what extent the detected variants can be regarded as the cause for the patient's phenotype must be evaluated in consideration of the clinical findings.

Offspring inherit variant, each.

Recommended action

- Offer genetic counselling.
- Offer variant-specific genetic testing of biological relatives.

VARIANT DETAILS

Gene	Variant	Classification	Exon	Location on GRCh38
LPIN1	NM_145693.2:c.2401C>T p.(Arg801Ter)	Pathogenic	18	Chr2:g.11959716C>T
Consequence	**Zygosity**	**Inheritance**	**ACMG/AMP criteria (Richards et al.; Ellard et al.)**	**Disorder**
Stop Gained	Homozygous	Autosomal Recessi	PM2,PVS1,PM3,PS4_Supporting	Myoglobinuria, acute rec autosomal recessive
GeneID	**#OMIM**	**ClinVarID**	**dbSNP ID**	**Allele Frequency**
23175	268200	4912	rs119480073	1/16256 (0.006%) (gnomAD African)

Report released by

John Doe 16.03.2023

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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

97.856%

ANALYZED GENES

BCS1L(NM_001079866.1), RPIA(NM_144563.2), RPL10(NM_001256577.2), CNNM2(NM_017649.4), MRPL3(NM_007208.3), SACS(NM_014363.5), SAR1B(NM_016103.3), MSMO1(NM_006745.4), SC5D(NM_006918.4), SCO1(NM_004589.3), SCO2(NM_005138.2), SCP2(NM_002979.4), SDHA(NM_004168.3), SDHB(NM_003000.2), SDHD(NM_003002.3), SEC23B(NM_006363.4), SGSH(NM_000199.3), SI(NM_001041.3), ST3GAL3(NM_006279.3), ST3GAL5(NM_003896.3), SKIV2L(NM_006929.4), SLC40A1(NM_014585.5), SLC12A3(NM_000339.2), SLC16A1(NM_003051.3), SLC17A5(NM_012434.4), SLC18A2(NM_003054.4), SLC19A2(NM_006996.2), SLC22A5(NM_003060.3), SLC25A1(NM_005984.4), SLC25A12(NM_003705.4), SLC25A13(NM_014251.2), SLC25A15(NM_014252.3), SLC25A3(NM_005888.3), SLC25A4(NM_001151.3), SLC2A1(NM_006516.2), SLC2A2(NM_000340.1), SLC35A1(NM_006416.4), SLC35A2(NM_001042498.2), SLC3A1(NM_000341.3), SLC5A1(NM_000343.3), SLC6A3(NM_001044.4), SLC6A8(NM_005629.3), SLC7A7(NM_001126106.2), SLC7A9(NM_014270.4),

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APOA1(NM_000039.2), APOB(NM_000384.2), APOC2(NM_000483.4), ABCD1(NM_000033.3), APOE(NM_000041.3), ITPA(NM_033453.3), IVD(NM_002225.3), KARS1(NM_001130089.1), APRT(NM_000485.2), KYNU(NM_003937.2), LAMP2(NM_002294.2), LARGE1(NM_004737.5), LARS1(NM_020117.10), LBR(NM_002296.3), LCAT(NM_000229.1), LCT(NM_002299.3), LDHA(NM_005566.3), COG1(NM_018714.2), LDLR(NM_000527.4), LIPA(NM_000235.3), ARG1(NM_000045.3), LPL(NM_000237.2), ABCD4(NM_005050.3), MAN1B1(NM_016219.4), MAN2B1(NM_000528.3), MANBA(NM_005908.3), MAOA(NM_000240.3), MAT1A(NM_000429.2), MCCC1(NM_020166.4), MCCC2(NM_022132.4), CHST6(NM_021615.4), MDH2(NM_005918.3), MGAT2(NM_002408.3), MIPEP(NM_005932.3), ARSA(NM_000487.5), ARSB(NM_000046.3), MLYCD(NM_012213.2), ALDH6A1(NM_005589.3), ARSL(NM_000047.2), MOCS1(NM_005943.5), MOCS2(NM_176806.3), MPDU1(NM_004870.3), MPI(NM_002435.2), MPV17(NM_002437.4), ASAH1(NM_177924.4), MT-ATP6(MT-ATP6), MT-ATP8(MT-ATP8), MT-CO1(MT-CO1), MT-CO2(MT-CO2), MT-CO3(MT-CO3), MT-CYB(MT-CYB), MTHFR(NM_005957.4), MT-ND1(MT-ND1), MT-ND2(MT-ND2), MT-ND3(MT-ND3), MT-ND4(MT-ND4), ASL(NM_000048.3), MT-ND4L(MT-ND4L), MT-ND5(MT-ND5), MT-ND6(MT-ND6), MTTP(NM_000253.3), MTR(NM_000254.2), MT-RNR1(No Transcript), MTRR(NM_002454.2), MT-TA(No Transcript), MT-TC(No Transcript), MT-TD(No Transcript), MT-TE(No Transcript), MT-TF(No Transcript), MT-TG(No Transcript), MT-TH(No Transcript), MT-TI(No Transcript), MT-TK(No Transcript), MT-TL1(No Transcript), MT-TL2(No Transcript), MT-TM(No Transcript), MT-TN(No Transcript), MT-TP(No Transcript), MT-TQ(No Transcript), MT-TR(No Transcript), MT-TS1(No Transcript), MT-TS2(No Transcript), MT-TV(No Transcript), MT-TW(No Transcript), MT-TY(No Transcript), TRIM37(NM_015294.4), MMUT(NM_000255.3), MVK(NM_000431.3), ASPA(NM_000049.2), ASS1(NM_000050.4), NAGA(NM_000262.2), NAGLU(NM_000263.3), NDUFA1(NM_004541.3), NDUFA10(NM_004544.3), NDUFA2(NM_002488.4), NDUFA4(NM_002489.3), NDUFA6(NM_002490.4), NDUFA9(NM_005002.4), NDUFB3(NM_002491.2), NDUFB8(NM_005004.3), NDUFS1(NM_005006.6), NDUFS2(NM_004550.4), NDUFS3(NM_004551.2), NDUFS4(NM_002495.3), NDUFS6(NM_004553.4), NDUFS7(NM_024407.4), NDUFS8(NM_002496.3), NDUFV1(NM_007103.3), NDUFV2(NM_021074.4), NEU1(NM_000434.3), NNT(NM_012343.3), PNP(NM_000270.3), NPC1(NM_000271.4), ATIC(NM_004044.6), OAT(NM_000274.3), OCRL(NM_000276.3), OPA1(NM_015560.2), OPA3(NM_025136.3), ATP5F1D(NM_001687.4), OTC(NM_000531.5), OXCT1(NM_000436.3), PAH(NM_000277.1), PC(NM_001040716.1), PCBD1(NM_000281.3), PCCA(NM_000282.3), PCCB(NM_000532.4), ATP6AP1(NM_001183.5), ATP7A(NM_000052.6), ACAD8(NM_014384.2), ATP7B(NM_000053.3), PCK1(NM_002591.3), AIFM1(NM_004208.3), ALDH7A1(NM_001182.4), PDHA1(NM_000284.3), PDHB(NM_000925.3), PEPD(NM_000285.3), PEX1(NM_000466.2), PEX10(NM_153818.1), PEX11B(NM_003846.2), PEX12(NM_000286.2), PEX13(NM_002618.3), PEX14(NM_004565.2), PEX16(NM_057174.2), PEX3(NM_003630.2), PEX6(NM_000287.3), PEX7(NM_000288.3), PFKM(NM_000289.5), PGAM2(NM_000290.3), PGK1(NM_000291.3), ACADM(NM_000016.5), AUH(NM_001698.2), PGM1(NM_002633.2), PGM3(NM_001199917.1), PHGDH(NM_006623.3), PHKA1(NM_002637.3), PHKA2(NM_000292.2), PHKB(NM_000293.2), PHKG2(NM_000294.2), PHYH(NM_006214.3), PIGA(NM_002641.3),

PIGL(NM_004278.3), PIGN(NM_176787.4), ACADS(NM_000017.3), PLA2G6(NM_003560.2), ACADSB(NM_001609.3), PMM2(NM_000303.2), PMPCB(NM_004279.2), POLG(NM_002693.2), POLG2(NM_007215.3), ACADVL(NM_000018.3), POMT1(NM_007171.3), POR(NM_000941.2), B3GAT3(NM_012200.3), B4GALT1(NM_001497.3), CTSA(NM_000308.3), PDP1(NM_018444.3), PPOX(NM_000309.3), ACAT1(NM_000019.3), B4GALT7(NM_007255.2), BAAT(NM_001701.3), PPT1(NM_000310.3), PRKAG2(NM_016203.3), PRODH(NM_016335.4), PRPS1(NM_002764.3), LONP1(NM_004793.3), PSAP(NM_002778.3), PTS(NM_000317.2), PEX19(NM_002857.3), PEX2(NM_000318.2), PEX5(NM_001131025.1), PYCR1(NM_006907.3), ALDH18A1(NM_002860.3), PYGL(NM_002863.4), PYGM(NM_005609.3), QDPR(NM_000320.2), BCAT2(NM_001190.3), BCKDHA(NM_000709.3), BCKDHB(NM_183050.3), RBP4(NM_006744.3)

LIST OF EXONS WITH COVERAGE <20X

Chr.	Pos.	Gene	Exon	Transcript	Mean Coverage (Min/Max)
Chr1	1167654..1168653	*B3GALT6*	Exon 01	NM_080605.3	37.78 (0/83)
Chr1	1447644..1447858	*ATAD3A*	Exon 01	NM_001170535.1	14.27 (6/22)
Chr1	1453091..1453160	*ATAD3A*	Exon 04	NM_001170535.1	23.23 (14/36)
Chr1	20960037..20960433	*PINK1*	Exon 01	NM_032409.2	57.10 (2/100)
Chr1	25870185..25870282	*LDLRAP1*	Exon 01	NM_015627.2	30.02 (17/38)
Chr1	155580035..155580128	*MSTO1*	Exon 01	NM_018116.3	22.66 (15/31)
Chr1	155580211..155580356	*MSTO1*	Exon 02	NM_018116.3	19.15 (16/22)
Chr1	155580825..155580904	*MSTO1*	Exon 03	NM_018116.3	10.16 (9/13)
Chr1	155581475..155581623	*MSTO1*	Exon 06	NM_018116.3	10.21 (5/17)
Chr1	155581769..155581896	*MSTO1*	Exon 07	NM_018116.3	33.05 (16/52)
Chr1	155583845..155584069	*MSTO1*	Exon 14	NM_018116.3	27.94 (10/60)
Chr1	235667436..235667557	*B3GALNT2*	Exon 01	NM_152490.4	32.18 (12/47)
Chr2	21266731..21266822	*APOB*	Exon 01	NM_000384.2	12.09 (6/16)
Chr2	86115942..86116033	*ST3GAL5*	Exon 01	NM_003896.3	20.15 (14/26)
Chr2	191745806..191746201	*GLS*	Exon 01	NM_014905.4	46.45 (8/82)
Chr2	207018337..207018407	*NDUFS1*	Exon 02	NM_005006.6	29.62 (18/36)
Chr4	996819..996950	*IDUA*	Exon 10	NM_000203.4	25.52 (16/36)
Chr5	36241596..36241905	*NADK2*	Exon 01	NM_001085411.2	32.61 (4/65)
Chr5	161529555..161529684	*GABRG2*	Exon 06	NM_198903.2	0.82 (0/1)
Chr5	177027207..177027266	*B4GALT7*	Exon 01	NM_007255.2	22.67 (16/27)
Chr6	137143799..137143938	*PEX7*	Exon 01	NM_000288.3	62.17 (17/89)
Chr6	146056329..146056639	*EPM2A*	Exon 01	NM_001018041.1	29.07 (5/66)
Chr6	146056329..146056639	*EPM2A*	Exon 01	NM_005670.3	29.07 (5/66)
Chr7	16460686..16460952	*CRPPA*	Exon 01	NM_001101426.3	53.56 (13/85)
Chr8	42995635..42995762	*HGSNAT*	Exon 01	NM_152419.2	8.38 (2/12)
Chr8	145149998..145150136	*CYC1*	Exon 01	NM_001916.4	25.37 (8/36)
Chr9	6645240..6645504	*GLDC*	Exon 01	NM_000170.2	62.78 (4/127)
Chr9	136223271..136223334	*SURF1*	Exon 01	NM_003172.3	14.55 (13/19)
Chr9	138393685..138393824	*MRPS2*	Exon 03	NM_016034.4	27.18 (19/32)
Chr10	26986636..26986774	*PDSS1*	Exon 01	NM_001321978.1	16.35 (12/19)
Chr10	26986636..26986774	*PDSS1*	Exon 01	NM_014317.4	16.35 (12/19)
Chr10	26991086..26991128	*PDSS1*	Exon 02	NM_001321978.1	0.00 (0/0)
Chr10	26991086..26991128	*PDSS1*	Exon 02	NM_014317.4	0.00 (0/0)
Chr11	763339..763524	*TALDO1*	Exon 05	NM_006755.1	39.26 (17/52)
Chr11	797621..798278	*PANO1*	Exon 01	NM_001293167.1	64.84 (10/102)
Chr11	77813935..77813999	*ALG8*	Exon 13	NM_001007027.2	1.69 (0/2)
Chr11	116660839..116661788	*APOA5*	Exon 04	NM_001166598.1	73.75 (16/117)
Chr11	116660839..116661788	*APOA5*	Exon 04	NM_052968.4	73.75 (16/117)
Chr11	118897642..118897810	*SLC37A4*	Exon 07	NM_001164277.1	23.37 (16/31)
Chr11	118897642..118897810	*SLC37A4*	Exon 07	NM_001164278.1	23.37 (16/31)
Chr11	118897642..118897810	*SLC37A4*	Exon 07	NM_001164279.1	23.37 (16/31)
Chr11	118897642..118897810	*SLC37A4*	Exon 05	NM_001164280.1	23.37 (16/31)
Chr11	118897642..118897810	*SLC37A4*	Exon 06	NM_001467.5	23.37 (16/31)
Chr12	58185743..58185815	*TSFM*	Exon 05	NM_001172696.1	1.99 (1/2)
Chr12	132414447..132414685	*PUS1*	Exon 02	NM_025215.5	38.59 (16/60)
Chr13	31774217..31774296	*B3GLCT*	Exon 01	NM_194318.3	19.14 (15/22)
Chr13	111358212..111358445	*CARS2*	Exon 01	NM_024537.3	38.94 (6/67)
Chr14	96001422..96001726	*GLRX5*	Exon 01	NM_016417.2	37.29 (7/69)
Chr14	103396497..103396669	*AMN*	Exon 10	NM_030943.3	27.57 (13/44)
Chr15	40763408..40764548	*CHST14*	Exon 01	NM_130468.3	83.58 (15/130)
Chr15	101791337..101791666	*CHSY1*	Exon 01	NM_014918.4	19.84 (4/47)

Chr16	1401962..1402023	*GNPTG*	Exon 01	NM_032520.4	25.31 (12/38)
Chr16	2034215..2034482	*GFER*	Exon 01	NM_005262.2	44.87 (14/56)
Chr16	17564286..17564658	*XYLT1*	Exon 01	NM_022166.3	13.72 (0/33)
Chr16	31120540..31120744	*BCKDK*	Exon 02	NM_005881.3	43.20 (18/54)
Chr16	56936280..56936425	*SLC12A3*	Exon 24	NM_000339.2	42.96 (17/56)
Chr16	66581869..66581887	*TK2*	Exon 03	NM_001271934.1	6.00 (6/6)
Chr16	83932745..83933282	*MLYCD*	Exon 01	NM_012213.2	58.39 (8/102)
Chr16	88888992..88889123	*GALNS*	Exon 12	NM_000512.4	24.24 (19/28)
Chr16	89574821..89575013	*SPG7*	Exon 01	NM_003119.3	50.95 (15/69)
Chr16	89574821..89575013	*SPG7*	Exon 01	NM_199367.2	50.95 (15/69)
Chr17	15903158..15903351	*TTC19*	Exon 01	NM_017775.3	53.59 (14/134)
Chr17	40688286..40688678	*NAGLU*	Exon 01	NM_000263.3	15.56 (3/45)
Chr19	1241845..1241995	*ATP5F1D*	Exon 01	NM_001687.4	23.60 (14/29)
Chr19	12767758..12767875	*MAN2B1*	Exon 12	NM_000528.3	21.81 (16/25)
Chr19	12767758..12767875	*MAN2B1*	Exon 12	NM_001173498.1	21.81 (16/25)
Chr19	47249401..47249692	*STRN4*	Exon 01	NM_013403.2	18.51 (0/42)
Chr19	47258703..47260200	*FKRP*	Exon 04	NM_001039885.2	55.60 (19/110)
Chr19	47258703..47260200	*FKRP*	Exon 04	NM_024301.4	55.60 (19/110)
Chr20	25371144..25371344	*ABHD12*	Exon 01	NM_001042472.2	25.98 (15/31)
Chr20	25371144..25371344	*ABHD12*	Exon 01	NM_015600.4	25.98 (15/31)
Chr20	49557637..49557751	*DPM1*	Exon 07	NM_001317034.1	18.98 (14/24)
Chr20	49557661..49557751	*DPM1*	Exon 07	NM_001317035.1	17.90 (14/23)
Chr22	19166088..19166191	*SLC25A1*	Exon 01	NM_005984.4	8.55 (1/15)
ChrX	152954025..152954296	*SLC6A8*	Exon 01	NM_001142805.1	28.57 (6/43)
ChrX	152954025..152954296	*SLC6A8*	Exon 01	NM_005629.3	28.57 (6/43)

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

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