HK LONGEVITY MEDICAL CENTRE

Genetic Risk Carriers Screening and Analysis Report

PATIENT NAME John Doe	**GENDER** Male
DATE OF BIRTH 01/11/1990	**SAMPLE TYPE** Whole Blood
COLLECTION DATE 01/01/2023	**SAMPLE ID** A123456
ACCESSION # 4316546	**REPORT DATE** 07/08/2023

Overview

Your genetic blueprint, steeped in your DNA, is the most critical factor in determining who you are. From the beginning of life to your golden years, it is these unique genetic variants that set you apart from your relatives and acquaintances. As you navigate through the later stages of life, an interplay of these inherent genetic traits, your lifestyle choices, and environmental factors, collectively contribute to the pace at which you age. This complex interaction also influences your susceptibility to various age-related health conditions and consequently how long you live.

Here at HK Longevity Medical Centre, our expertise lies in conducting comprehensive Genetic Risk Carriers Screening and Analysis. Our principal objective is to deliver personalized genomic data that can illuminate your genetic predisposition towards hereditary health conditions and diseases and provide insights into your potential physical fitness.

In our pursuit of this mission, we employ Whole Genome Sequencing (WGS), a state-of-the-art technology that deciphers an individual's DNA sequence, comprising approximately three billion base pairs. WGS grants us a panoramic view of the entire genome, enabling the detection of genetic variants that could potentially influence your health and disease susceptibility.

Armed with this knowledge, you gain the power to make well-informed decisions concerning your health, lifestyle, and preventive care. Our services aim to demystify the intricate realm of genomics, forging a clear path from raw genetic information to actionable health insights. At HK Longevity Medical Centre, we are your trusted partner in navigating the complex life journey from genetic understanding to your life goal Healthy Aging and Longevity.

Finding Summary

This is a brief summary of the WGS screening and analysis.

Category	Test Results	Your Risk
Genome sequenced	3.2 Billion base pairs analyzed	nan
Variants detected	5.3 millions	nan
Total genes assessed	1519	Carrying 5 disease-causing variants
Total hereditary diseases assessed	1652	1 hereditary cancer, 2 metabolic disorders, 1 endocrine disorder, and 1 respiratory disorder
Total pharmacogenetic genes assessed	1234	nan
Total drugs assessed	120	51 drugs potentially impacted
Total age-related phenotypes/traits assessed	25	High risk of developing muscle degeneration condition, one neurological condition
Total physical fitness traits assessed	12	Physically active, risk in developing cardiovascular conditions

Section 1: Hereditary Disease Risk

This section includes variants that, when found by themselves, are associated with high and moderate genetic risk of developing a disease. Depending on a variant zygosity and disease inheritance, the disease can affect you or represent a risk for the next generation (carrier variants).

Subsection 1.1: Variant Summary

Gene	Variant	Zygosity	Classification	Disease associated	Inheritance
APC	rs2229992 ENST00000257430.9 c.1458T>C (p.Tyr486=)	homozygous	Benign	familial adenomatous polyposis 1	Autosomal dominant inheritance
APC	rs351771 ENST00000257430.9 c.1635G>A (p.Ala545=)	homozygous	Benign	familial adenomatous polyposis 1	Autosomal dominant inheritance
APC	rs459552 ENST00000257430.9 c.5465T>A (p.Val1822Asp)	homozygous	Benign	familial adenomatous polyposis 1	Autosomal dominant inheritance
BRAF	rs9648696 ENST00000644969.1 c.2049A>G (p.Gly683=)	heterozygous	Benign	RASopathy	Autosomal dominant inheritance
PTEN	rs11202592 ENST00000371953.8 c.-9C>G ()	heterozygous	Benign	PTEN hamartoma tumor syndrome	Autosomal dominant inheritance
TECTA	rs612969 ENST00000264037.2 c.1111A>G (p.Arg371Gly)	heterozygous	Benign	nonsyndromic genetic deafness	nan
KRAS	rs1137282 ENST00000256078.9 c.*73T>C ()	heterozygous	Benign	RASopathy	Autosomal dominant inheritance
PAH	rs772897 ENST00000553106.6 c.1155C>G (p.Leu385=)	heterozygous	Benign	phenylketonuria	Autosomal recessive inheritance
PAH	rs12580432 ENST00000553106.6 c.1065+97G>A ()	heterozygous	Benign	phenylketonuria	Autosomal recessive inheritance
PAH	rs1042503 ENST00000553106.6 c.735G>A (p.Val245=)	heterozygous	Benign	phenylketonuria	Autosomal recessive inheritance
PAH	rs10860933 ENST00000553106.6 c.509+101A>C ()	heterozygous	Benign	phenylketonuria	Autosomal recessive inheritance
PAH	rs2037639 ENST00000553106.6 c.353-22C>T ()	heterozygous	Benign	phenylketonuria	Autosomal recessive inheritance
PAH	rs1522296 ENST00000553106.6 c.60+62C>T ()	heterozygous	Benign	phenylketonuria	Autosomal recessive inheritance
PAH	rs2280615 ENST00000553106.6 c.-71A>C ()	heterozygous	Benign	phenylketonuria	Autosomal recessive inheritance
HNF1A	rs1169305 ENST00000257555.10 c.1720A>G (p.Ser574Gly)	homozygous	Benign	monogenic diabetes	Autosomal dominant inheritance
MYH7	rs7157716 ENST00000355349.4 c.2967T>C (p.Ile989=)	heterozygous	Benign	cardiomyopathy	Autosomal dominant inheritance
MYH7	rs2069540 ENST00000355349.4 c.189C>T (p.Thr63=)	heterozygous	Benign	cardiomyopathy	Autosomal dominant inheritance

GATM	rs1049518 ENST00000396659.8 c.*940C>T ()	homozygous	Benign	AGAT deficiency	Autosomal recessive inheritance
GATM	rs1049503 ENST00000396659.8 c.*600A>G ()	homozygous	Benign	AGAT deficiency	Autosomal recessive inheritance
GATM	rs1145086 ENST00000396659.8 c.1252T>C (p.Leu418=)	homozygous	Benign	AGAT deficiency	Autosomal recessive inheritance
POLG	rs3176174 ENST00000268124.10 c.1250+188A>G ()	heterozygous	Benign	mitochondrial disease	Autosomal recessive inheritance
PALB2	rs183489969 ENST00000261584.9 c.3054G>C (p.Glu1018Asp)	heterozygous	Benign	hereditary breast cancer	Autosomal dominant inheritance
CDH1	rs3743674 ENST00000261769.10 c.48+6C>T ()	heterozygous	Benign	hereditary diffuse gastric cancer	Autosomal dominant inheritance
CDH1	rs1801552 ENST00000261769.10 c.2076T>C (p.Ala692=)	homozygous	Benign	hereditary diffuse gastric cancer	Autosomal dominant inheritance
CDH1	rs33964119 ENST00000261769.10 c.2253C>T (p.Asn751=)	homozygous	Benign	hereditary diffuse gastric cancer	Autosomal dominant inheritance
CDH1	rs1801026 ENST00000261769.10 c.*54C>T ()	homozygous	Benign	hereditary diffuse gastric cancer	Autosomal dominant inheritance
CDH1	rs13689 ENST00000261769.10 c.*1120T>C ()	heterozygous	Benign	hereditary diffuse gastric cancer	Autosomal dominant inheritance
ACADVL	rs370388543 ENST00000356839.10 c.478-106del ()	heterozygous	Benign	very long chain acyl-CoA dehydrogenase deficiency	Autosomal recessive inheritance
MYO15A	rs854777 ENST00000647165.2 c.5929T>C (p.Cys1977Arg)	homozygous	Benign	nonsyndromic genetic deafness	Autosomal recessive inheritance
ITGB3	rs15908 ENST00000559488.6 c.1143A>C (p.Val381=)	heterozygous	Benign	Glanzmann's thrombasthenia	Autosomal recessive inheritance
ITGB3	rs4634 ENST00000559488.6 c.1545G>A (p.Arg515=)	heterozygous	Benign	Glanzmann thrombasthenia	Autosomal recessive inheritance
GAA	rs1800300 ENST00000302262.8 c.324T>C (p.Cys108=)	homozygous	Benign	glycogen storage disease II	Autosomal recessive inheritance
GAA	rs3816256 ENST00000302262.8 c.547-4C>G ()	homozygous	Benign	glycogen storage disease II	Autosomal recessive inheritance
GAA	rs1042395 ENST00000302262.8 c.668G>A (p.Arg223His)	homozygous	Benign	glycogen storage disease II	Autosomal recessive inheritance
GAA	rs1800304 ENST00000302262.8 c.1203G>A (p.Gln401=)	homozygous	Benign	glycogen storage disease II	Autosomal recessive inheritance
GAA	rs1126690 ENST00000302262.8 c.2338G>A (p.Val780Ile)	homozygous	Benign	glycogen storage disease II	Autosomal recessive inheritance
GAA	rs1042397 ENST00000302262.8 c.2553G>A (p.Gly851=)	homozygous	Benign	glycogen storage disease II	Autosomal recessive inheritance

MAP2K2	rs10250 ENST00000262948.9 c.660C>A (p.Ile220=)	homozygous	Benign	RASopathy	Autosomal dominant inheritance
ETHE1	rs3810381 ENST00000292147.7 c.6G>A (p.Ala2=)	heterozygous	Benign	ethylmalonic encephalopathy	Autosomal recessive inheritance
RUNX1	rs73900787 ENST00000300305.7 c.58+265G>A ()	heterozygous	Benign	hereditary thrombocytopenia and hematologic cancer predisposition syndrome	Autosomal dominant inheritance
PDHA1	rs2229137 ENST00000422285.7 c.844A>C (p.Met282Leu)	heterozygous	Benign	pyruvate dehydrogenase deficiency	X-linked inheritance

Subsection 1.2: Variant Details

Variant detected

rsID	Gene	Variant
rs2229992	APC	c.1458T>C (p.Tyr486=)

Detailed interpretation

The c.1458T>C (p.Tyr486=) variant in APC is a synonymous (silent) variant that is not predicted to impact splicing (BP4, BP7). The highest population minor allele frequency (non-cancer) in gnomAD v2.1.1 is 69.75% in Latino/Admixed American population, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (HCCP VCEP) threshold (â‰¥ 0.1%) for BA1, and therefore meets this criterion (BA1). In summary, this variant meets the criteria to be classified as Benign for FAP based on the ACMG/AMP criteria applied, as specified by the HCCP VCEP: BA1, BP4, BP7 (VCEP specifications Version 1.0, date of approval: 12/12/2022).

Variant detected

rsID	Gene	Variant
rs351771	APC	c.1635G>A (p.Ala545=)

Detailed interpretation

The c.1635G>A (p.Ala545=) variant is a synonymous (silent) variant that is not predicted to impact splicing (BP4, BP7). The highest population minor allele frequency in gnomAD v2.1.1 is 0.82 (15756 in 19198 alleles) in the East Asian population, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (HCCP VCEP) threshold (â‰¥ 0.001) for BA1, and therefore meets this criterion (BA1). In summary, this variant meets the criteria to be classified as Benign for FAP based on the ACMG/AMP criteria applied, as specified by the HCCP VCEP: BA1, BP4, and BP7. (VCEP specifications version 1; date of approval: 12/12/2022).

Variant detected

rsID	Gene	Variant
rs459552	APC	c.5465T>A (p.Val1822Asp)

Detailed interpretation

The c.5465T>A variant in APC is a missense variant predicted to cause the substitution of Valine by Asparagine at amino acid position 1822 (p.Val1822Asp). APC is defined by the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (HCCP VCEP) as a gene for which primarily truncating variants are known to cause disease (BP1). The highest population minor allele frequency in gnomAD v2.1.1 is 0.9598 (23897/24898 alleles) in the African/African American population, which is higher than the ClinGen APC VCEP threshold (>0.1%) for BA1, and therefore meets this criterion (BA1). In summary, this variant meets the criteria to be classified as Benign for FAP based on the ACMG/AMP criteria applied, as specified by the HCCP VCEP: BA1 and BP1 (VCEP specifications version 1; date of approval: 12/12/2022).

Variant detected

rsID	Gene	Variant
rs9648696	BRAF	c.2049A>G (p.Gly683=)

Detailed interpretation

The filtering allele frequency of the c.1929A>G (p.Gly643=) variant in the BRAF gene is 66.117% (6984/10356) of African chromosomes by the Exome Aggregation Consortium, which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen RASopathy Expert Panel (BA1; PMID:29493581)

Variant detected

rsID	Gene	Variant
rs11202592	PTEN	c.-9C>G ()

Detailed interpretation

PTEN c.-9C>G (NC_000010.10:g.89624218C>G) meets criteria to be classified as benign for PTEN Hamartoma Tumor syndrome in an autosomal dominant manner using modified ACMG criteria (Mester et al. 2018; manuscript in preparation). Please see a summary of the rules and criteria codes in the â€œPTEN ACMG Specifications Summaryâ€ document (assertion method column).BA1: Allele frequency of 0.048 (4.8%, 903/18,870 alleles) in the East Asian subpopulation of the gnomAD cohort. (PMID 27535533)

Variant detected

rsID	Gene	Variant
rs612969	TECTA	c.1111A>G (p.Arg371Gly)

Detailed interpretation

The filtering allele frequency of the p.Arg317Gly variant in the TECTA gene is 67.5% (16434/24006) of African chromosomes by the Genome Aggregation Database (http://gnomad.broadinstitute.org; calculated by using inverse allele frequency at https://www.cardiodb.org/allelefrequencyapp/), which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal dominant and autosomal recessive hearing loss variants (BA1).

Variant detected

rsID	Gene	Variant
rs1137282	KRAS	c.*73T>C ()

Detailed interpretation

The filtering allele frequency of the c.519T>C (p.Asp173=) variant in the KRAS gene is 22.2% for European (non-Finnish) chromosomes by the Exome Aggregation Consortium (14553/65674 with 95% CI), which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen RASopathy Expert panel for autosomal dominant RASopathy variants (BA1).

Variant detected

rsID	Gene	Variant
rs772897	PAH	c.1155C>G (p.Leu385=)

Detailed interpretation

This c.1155C>G (p.Leu385=) synonymous variant in PAH is not predicted to have a splice-altering consequence. This variant was present at a high frequency of 0.840256 in 1000 genomes and 0.858145 in ExAC. In summary, this variant meets criteria to be classified as a benign for PAH. PAH-specific ACMG/AMP criteria applied: BP7, BA1.

Variant detected

rsID	Gene	Variant
rs12580432	PAH	c.1065+97G>A ()

Detailed interpretation

The c.1065+97G>A variant in PAH has a MAF of 0.2430 in the gnomAD non-Finnish European population. This intronic variant does not have a predicted impact on splicing. In summary this variant meets criteria to be classified as benign. PAH-specific ACMG/AMP criteria applied: BA1, BP7

Variant detected

rsID	Gene	Variant
rs1042503	PAH	c.735G>A (p.Val245=)

Detailed interpretation

The c.735G>A (p.Val245=) variant in PAH has a MAF of 0.29058 in ExAC (BA1; http://exac.broadinstitute.org) with 6,524 homozygotes (BS2). This is a synonymous variant, predicted tolerated and benign in SIFT, Polyphen. MutationTaster predicted polymorphism with no abrogation of splice sites (BP4). In summary, this variant meets criteria to be classified as benign.

Variant detected

rsID	Gene	Variant
rs10860933	PAH	c.509+101A>C ()

Detailed interpretation

The c.509+101A>C variant in PAH has a MAF of 0.2325 in the gnomAD European (Non-Finnish) population. This intronic variant does not have a predicted impact on splicing. In summary this variant meets criteria to be classified as benign. PAH-specific ACMG/AMP criteria applied: BA1, BP7

Variant detected

rsID	Gene	Variant
rs2037639	PAH	c.353-22C>T ()

Detailed interpretation

The c.353-22C>T variant in PAH has a MAF of 0.7066 in the gnomAD East Asian population. This intronic variant does not have a predicted impact on splicing. In summary this variant meets criteria to be classified as benign. PAH-specific ACMG/AMP criteria applied: BA1, BP7

Variant detected

rsID	Gene	Variant
rs1522296	PAH	c.60+62C>T ()

Detailed interpretation

The c.60+62C>T intronic variant in PAH has a MAF of 0.3441 in gnomAD with 2,014 homozygotes.In summary, this variant meets criteria to be classified as benign for PAH. PAH-specific ACMG/AMP criteria applied: BA1, BS2, BP7.

Variant detected

rsID	Gene	Variant

rs2280615	PAH	c.-71A>C ()

Detailed interpretation

The c.-71A>Cvariant in PAH has a MAF of 0.16686 in the gnomAD African population. In summary this variant meets criteria to be classified as benign. PAH-specific ACMG/AMP criteria applied: BA1.

Variant detected

rsID	Gene	Variant
rs1169305	HNF1A	c.1720A>G (p.Ser574Gly)

Detailed interpretation

The c.1720A>G variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of serine to glycine at codon 574 (p.(Ser574Gly)) of NM_000545.8. This variant has a Popmax Filtering allele frequency in gnomAD 2.1.1 of 0.996; however, given that the G (Gly) alternate allele has frequencies â‰¥95% in all subpopulations, we have recalculated the Popmax Filtering allele frequency based on the highest prevalence of the A (Ser) reference allele being found in the African/African-American subpopulation (1144/24164 = 0.0473). The newly calculated Popmax Filtering allele frequency is 0.0447, which is greater than the MDEP threshold for BA1 (â‰¥0.0001) (BA1). Additionally, this variant was identified in a patient with an alternate molecular basis for disease (BP5; internal lab contributors). In summary, c.1720A>G meets the criteria to be classified as benign for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.1, approved 9/30/2021): BA1, BP5.

Variant detected

rsID	Gene	Variant
rs7157716	MYH7	c.2967T>C (p.Ile989=)

Detailed interpretation

The filtering allele frequency of the c.2967T>C (p.Ile989=) variant in the MYH7 gene is 70.48% (7476/10406) of African chromosomes by the Exome Aggregation Consortium (http://exac.broadinstitute.org), which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen Inherited Cardiomyopathy Expert Panel (BA1; PMID: 29300372).

Variant detected

rsID	Gene	Variant
rs2069540	MYH7	c.189C>T (p.Thr63=)

Detailed interpretation

The filtering allele frequency of the c.189C>T (p.Thr63=) variant in the MYH7 gene is 61.57% (6532/10394) of African chromosomes by the Exome Aggregation Consortium (http://exac.broadinstitute.org), which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen Inherited Cardiomyopathy Expert Panel (BA1; PMID: 29300372).

Variant detected

rsID	Gene	Variant
rs1049518	GATM	c.*940C>T ()

Detailed interpretation

The NM_001482.3:c.*940C>T variant is a single nucleotide substitution in the 3'UTR of GATM. Because the variant is located in the 3'UTR, it is not expected to alter the amino acid sequence. The highest population minor allele frequency in gnomAD v2.1.1, in a population with >2000 alleles, is 0.8433 (7330/8692 alleles) in the African population, which is higher than the ClinGen CCDS VCEPâ€™s threshold for BA1 (>0.0005), and therefore meets this criterion (BA1). There is a ClinVar entry for this variant (Variation ID: 316200, 1 star review status) with one submitter classifying the variant as benign. In summary, this

variant meets the criteria to be classified as benign for AGAT deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.0, ; classification approved June 6, 2022): BA1.

Variant detected

rsID	Gene	Variant
rs1049503	GATM	c.*600A>G ()

Detailed interpretation

The NM_001482.3:c.*600A>G variant is a single nucleotide substitution in the 3'UTR of GATM. Because the variant is located in the 3'UTR, it is not expected to alter the amino acid sequence. The highest population minor allele frequency in gnomAD v2.1.1, in a continental population with >2000 alleles, is 0.2934 (2554/8704 alleles) in the African population, which is higher than the ClinGen CCDS VCEPâ€™s threshold for BA1 (>0.0005), and therefore meets this criterion (BA1). There is a ClinVar entry for this variant (Variation ID: 316206). In summary, this variant meets the criteria to be classified as benign for AGAT deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.1.0): BA1.(Classification approved by the ClinGen CCDS VCEP on June 6, 2022).

Variant detected

rsID	Gene	Variant
rs1145086	GATM	c.1252T>C (p.Leu418=)

Detailed interpretation

The NM_001482.3:c.1252T>C (p.Leu418=) variant in GATM is a synonymous (silent) variant that is not predicted by SpliceAI to impact splicing. In addition, it occurs at a nucleotide that is not conserved as shown by PhyloP (BP7). The highest population minor allele frequency in gnomAD v2.1.1 is 0.9186 (18317/19940 alleles) in the East Asian population, which is higher than the ClinGen CCDS VCEPâ€™s threshold for BA1 (>0.0005), and therefore meets this criterion (BA1). The computational splicing predictor SpliceAI gives a score of 0.0 for donor and acceptor loss suggesting that the variant has no impact on splicing, and the nucleotide is not highly conserved (BP4, BP7). There is a ClinVar entry for this variant (Variation ID: 129137). In summary, this variant meets the criteria to be classified as benign for AGAT deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.1.0): BA1, BP4, BP7.(Classification approved by the ClinGen CCDS VCEP on June 6, 2022).

Variant detected

rsID	Gene	Variant
rs3176174	POLG	c.1250+188A>G ()

Detailed interpretation

The c.1250+188A>G variant in POLG has been reported with an allele frequency in the population of 58% in gnomAD (BA1). In summary, this variant meets criteria to be classified as benign for primary mitochondrial disease inherited in a recessive manner. ntDNA Mitochondrial ACMG-AMP Criteria for POLG applied: BA1.

Variant detected

rsID	Gene	Variant
rs183489969	PALB2	c.3054G>C (p.Glu1018Asp)

Detailed interpretation

The c.3054G>C variant in PALB2 is a missense variant predicted to cause substitution of glutamate by aspartate at amino acid 1018 (p.Glu1018Asp). The filtering allele frequency in gnomAD v2.1.1 is 0.004 in the East Asian population, which is higher than the ClinGen HBOP threshold (>0.001) for BA1, and therefore meets this criterion. This variant has been observed in a homozygous state and phase unknown with numerous other PALB2 variants that are tentatively classified as likely pathogenic or pathogenic by the HBOP VCEP in individuals without Fanconi Anemia (GeneDx, Ambry Genetics, Invitae). This variant is functional in multiple different protein assays (PMID 31757951); however due to a lack of positive missense controls with

known clinical impact, these protein assays do not meet the requirements for use by the HBOP VCEP. PALB2, in which the variant was identified, is defined by the HBOP VCEP as a gene for which primarily truncating variants are known to cause disease. In summary, this variant meets the criteria to be classified as benign for autosomal dominant hereditary breast and pancreatic cancer and autosomal recessive FANCN based on the ACMG/AMP criteria applied, as specified by the HBOP VCEP. (BA1, BP2_Moderate, BP1)

Variant detected

rsID	Gene	Variant
rs3743674	CDH1	c.48+6C>T ()

Detailed interpretation

The c.48+6C>T variant has an allele frequency of 0.81161 (81%, 129,383/159,416 alleles) in the gnomAD cohort (BA1). Therefore, this variant meets criteria to be classified as benign. ACMG/AMP criteria applied, as specified by the CDH1 Variant Curation Expert Panel: BA1.

Variant detected

rsID	Gene	Variant
rs1801552	CDH1	c.2076T>C (p.Ala692=)

Detailed interpretation

The NM_004360.5(CDH1):c.2076T>C (p.Ala692=) variant has an allele frequency of 0.88894 (88.89%, 22156/24924 alleles, 9856 homozygotes) in the African subpopulation of the gnomAD v2.1.1 cohort (BA1; BP2_Strong). Therefore, this variant meets criteria to be classified as benign. ACMG/AMP criteria applied, as specified by the CDH1 Variant Curation Expert Panel: BA1, BP2_Strong.

Variant detected

rsID	Gene	Variant
rs33964119	CDH1	c.2253C>T (p.Asn751=)

Detailed interpretation

The NM_004360.5(CDH1):c.2253C>T (p.Asn751=) variant has an allele frequency of 0.10006 (10%, 3546/35438 alleles, 185 homozygotes) in the Latino subpopulation of the gnomAD v2.1.1 cohort (BA1; BP2_Strong). Therefore, this variant meets criteria to be classified as benign. ACMG/AMP criteria applied, as specified by the CDH1 Variant Curation Expert Panel: BA1, BP2_Strong

Variant detected

rsID	Gene	Variant
rs1801026	CDH1	c.*54C>T ()

Detailed interpretation

The NM_004360.5(CDH1):c.*54C>T variant has an allele frequency of 0.18763 (18.76%, 1629/8682 alleles, 147 homozygotes) in the African subpopulation of the gnomAD v2.1.1 cohort (BA1; BP2_Strong). Therefore, this variant meets criteria to be classified as benign. ACMG/AMP criteria applied, as specified by the CDH1 Variant Curation Expert Panel: BA1, BP2_Strong.

Variant detected

rsID	Gene	Variant
rs13689	CDH1	c.*1120T>C ()

Detailed interpretation

The NM_004360.5(CDH1):c.*1120T>C variant has an allele frequency of 0.21013 (21%, 730/3474 alleles, 79 homozygotes) in the African subpopulation of the gnomAD v2.1.1 cohort (BA1; BP2_Strong). Therefore, this variant meets criteria to be classified as benign. ACMG/AMP criteria applied, as specified by the CDH1 Variant Curation Expert Panel: BA1, BP2_Strong.

Variant detected

rsID	Gene	Variant
rs370388543	ACADVL	c.478-106del ()

Detailed interpretation

The c.478-106del variant in ACADVL is an intronic variant. The highest population minor allele frequency in gnomAD v2.1.1 is 0.62 in the European Finnish population, which is higher than the ClinGen ACADVL Variant Curation Expert Panel threshold (â‰¥0.007) for BA1, and therefore meets this criterion (BA1). In summary, this variant meets the criteria to be classified as benign for autosomal recessive very long chain acyl-CoA dehydrogenase (VLCAD) deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen ACADVL Variant Curation Expert Panel: BA1

Variant detected

rsID	Gene	Variant
rs854777	MYO15A	c.5929T>C (p.Cys1977Arg)

Detailed interpretation

The filtering allele frequency (the lower threshold of the 95% CI of 15730/17934) of the p.Cys1977Arg variant in the MYO15A gene is 86.6% for African chromosomes (including 6913 homozygous observations) by gnomAD v2.1, which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss variants (BA1). ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel : BA1.

Variant detected

rsID	Gene	Variant
rs15908	ITGB3	c.1143A>C (p.Val381=)

Detailed interpretation

The ITGB3 synonymous variant NM_000212.2:c.1143A>C is very common in control population databases, with an overall allele frequency of 0.38777 in gnomAD v2.1.1. Note that initial reports of variation at this nucleotide position referred to the current reference allele as the variant at this position (c.1143C>A; PMID: 8878424, PMID: 20020534, and PMID: 25728920), however this reported "variant" is now considered the reference allele. In summary, this variant meets criteria to be classified as benign for GT. GT-specific criteria applied: BA1.

Variant detected

rsID	Gene	Variant
rs4634	ITGB3	c.1545G>A (p.Arg515=)

Detailed interpretation

After a comprehensive literature search of the synonymous variant NM_000212.3(ITGB3):c.1545G>A (p.Arg515=), no individuals with Glanzmann thrombasthenia were reported with the variant. Moreover, the variant has a minor allele frequency of 0.3455 (6891/19946 alleles) in gnomAD, found in the East Asian population, which is considerably higher than the expected frequency of the disease(BA1). In silico predictor spliceAI revealed that the synonymous mutation is not expected to impact splicing and a PhyloP score of 0.285 shows that the nucleotide position is not highly conserved (BP4, BP7). In summary, this variant meets the criteria to be classified as Benign for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: BA1, BP4, BP7 (PD VCEP specifications version 2.1).

Variant detected

rsID	Gene	Variant
rs1800300	GAA	c.324T>C (p.Cys108=)

Detailed interpretation

The highest continental population minor allele frequency for c.324T>C (p.Cys108=) in gnomAD v2.1.1 is 0.81776 in the South Asian population. This is higher than the ClinGen LSD VCEPâ€™s BA1 threshold (>0.01), meeting this criterion. There is a ClinVar entry for this variant (Variation ID: 92484, two star review status), with 10 submitters classifying the variant as benign. In summary, this variant meets the criteria to be classified as benign for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: BA1.

Variant detected

rsID	Gene	Variant
rs3816256	GAA	c.547-4C>G ()

Detailed interpretation

The highest continental population minor allele frequency for c.547-4C>G in gnomAD v2.1.1 is 0.7403 in the European non-Finnish population. Note that the minor allele frequency is even higher in the Ashkenazi Jewish (0.77927) and European Finnish (0.75914) populations. These allele frequencies are higher than the ClinGen LSD VCEPâ€™s BA1 threshold (>0.01), meeting this criterion. There is a ClinVar entry for this variant (Variation ID: 92485, two star review status), with 6 submitters classifying the variant as benign. In summary, this variant meets the criteria to be classified as benign for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: BA1.

Variant detected

rsID	Gene	Variant
rs1042395	GAA	c.668G>A (p.Arg223His)

Detailed interpretation

The highest continental population minor allele frequency for c.668G>A (p.Arg223His) in gnomAD v2.1.1 is 0.74034 in the European non-Finnish population. This is higher than the ClinGen LSD VCEPâ€™s BA1 threshold (>0.01), therefore meeting the BA1 criterion. There is a ClinVar entry for this variant (Variation ID: 92488; 2 star review status) with six submitters classifying the variant as benign, and one as likely benign. In summary, this variant meets the criteria to be classified as benign for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: BA1.

Variant detected

rsID	Gene	Variant
rs1800304	GAA	c.1203G>A (p.Gln401=)

Detailed interpretation

The highest continental population minor allele frequency for c.1203G>A (p.Gln401=) in gnomAD v2.1.1 is 0.74003 in the European non-Finnish population. Note that the minor allele frequency is even higher in the Ashkenazi Jewish (0.77901) and European Finnish (0.76403) populations. These allele frequencies are higher than the ClinGen LSD VCEPâ€™s BA1 threshold (>0.01), meeting this criterion. There is a ClinVar entry for this variant (Variation ID: 92461, two star review status), with 7 submitters classifying the variant as benign. In summary, this variant meets the criteria to be classified as benign for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: BA1.

Variant detected

rsID	Gene	Variant
rs1126690	GAA	c.2338G>A (p.Val780Ile)

Detailed interpretation

The highest continental population minor allele frequency for c.2338G>A (p.Val780Ile) in gnomAD v2.1.1 is 0.8129 in the South Asian population. This is higher than the ClinGen LSD VCEPâ€™s BA1 threshold (>0.01), therefore meeting the BA1 criterion. There is a ClinVar entry for this variant (Variation ID: 92476; 2 star review status) with six submitters classifying the variant as benign. In summary, this variant meets the criteria to be classified as benign for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: BA1.

Variant detected

rsID	Gene	Variant
rs1042397	GAA	c.2553G>A (p.Gly851=)

Detailed interpretation

The highest continental population minor allele frequency for c.2553G>A (p.Gly851=) in gnomAD v2.1.1 is 0.63818 in the European non-Finnish population. Note that the minor allele frequency is even higher in the Ashkenazi Jewish (0.70216) and European Finnish (0.64436) populations. These allele frequencies are higher than the ClinGen LSD VCEPâ€™s BA1 threshold (>0.01), meeting this criterion. There is a ClinVar entry for this variant (Variation ID: 92481, two star review status), with 6 submitters classifying the variant as benign. In summary, this variant meets the criteria to be classified as benign for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: BA1.

Variant detected

rsID	Gene	Variant
rs10250	MAP2K2	c.660C>A (p.Ile220=)

Detailed interpretation

The filtering allele frequency of the c.660C>A (p.Ile220=) variant in the MAP2K2 gene is 65.271% (3631/5412) of Latino chromosomes by the Exome Aggregation Consortium, which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen RASopathy Expert Panel (BA1; PMID:29493581)

Variant detected

rsID	Gene	Variant
rs3810381	ETHE1	c.6G>A (p.Ala2=)

Detailed interpretation

The allele frequency of the c.6G>A variant in the ETHE1 gene is reported as >16% in gnomAD, including >2,000 homozygotes, which is high enough to be classified as benign based on thresholds defined by the ClinGen ETHE1 Variant Curation Expert Panel (>0.1% in gnomAD- BA1 and BS2). In silico splicing predictors (Splice AI) do not predict a deleterious effect (BP7). In summary, this variant meets criteria to be classified as benign for ETHE1-related ethylmalonic encephalopathy. ETHE1-specific ACMG/AMP criteria applied: (BA1, BS2, BP7).

Variant detected

rsID	Gene	Variant
rs73900787	RUNX1	c.58+265G>A ()

Detailed interpretation

Intronic variant with a MAF of 0.06181 (6.2%, 538/8704 alleles) in the African/African-American subpopulation of the gnomAD v2.1.1 cohort (â‰¥ 0.0015 (0.15%)) (BA1). In addition, this variant is reported in 44 homozygotes in gnomAD v2.1.1 (BP2). Splice AI predicts no impact on splicing â‰¤ 0.20 (score: 0.00-0.06) (BP4). Intronic variants which SpliceAI â‰¤ 0.20 AND evolutionary conservation prediction algorithms predict the site as not conserved (phyloP100 way (GRCh38/hg38) â‰¤2.0). In summary, this variant meets criteria to be classified as benign. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: BA1, BP2, BP4 and BP7.

Variant detected

rsID	Gene	Variant
rs2229137	PDHA1	c.844A>C (p.Met282Leu)

Detailed interpretation

The allele frequency of the c.844A>C; p. M282L variant in the PDHA1 gene is 0.207% in gnomAD, including 1,436 hemizygotes. This allele frequency, and the frequency with which it is seen in hemizygotes in the general population are high enough to be classified as benign based on thresholds defined by the ClinGen PDHA1 Variant Curation Expert Panel (>0.092%; gnomAD >16 hemizygotes). In summary, this variant meets criteria to be classified as benign for PDHA1- related pyruvate dehydrogenase deficiency in an X-linked manner. PDHA1-specific ACMG/AMP criteria applied: (BA1, BS2). This was reviewed with the PDHA1 expert panel on 2/16/2021 and approved on 2/16/2021.

Section 2: Pharmacogenomic Findings

Unnamed: 0	REPORTING SCOPE	YOUR RISK
Total genes assessed	12	YOUR PHARMACOGENOMIC RESULTS
Total drugs assessed	96	14 Drugs Potentially Impacted

The way you respond to therapeutic drugs depends on your genes as well as other factors. This analysis found all your genetic alterations (genotypes) that may have a impact on how your body processing or metabolizing drugs (phenotypes). It helps your doctor better understand your personal situation, and your doctor will take these factors into account when deciding which drug or what drug dose is the best for you. Do not stop taking or alter the dosage of any prescribed medications without consulting with your doctor beforehand.

Subsection 2.1: Gene and Phenotype Findings

Gene	Genotype	Phenotype	Drugs
CYP2B6	*9/*9	Poor Metabolizer	Efavirenz
CYP2C19	*38/*38	Normal Metabolizer	Abrocitinib, Brivaracetam, Citalopram, Clobazam, Clopidogrel, Flibanserin, Pantoprazole, Mavacamten, Voriconazole, Carisoprodol, Dexlansoprazole, Diazepam, Doxepin, Escitalopram, Esomeprazole, Lansoprazole, Omeprazole, Rabeprazole
CYP2C9	*3/*3	Poor Metabolizer	Celecoxib, Dronabinol, Erdafitinib, Flurbiprofen, Meloxicam, Nateglinide, Piroxicam, Siponimod, Warfarin, Avatrombopag, Ibuprofen
CYP2D6	*1/*1	Normal Metabolizer	Amphetamine, Aripiprazole, Aripiprazole Lauroxil, Atomoxetine, Brexpiprazole, Clozapine, Codeine, Deutetrabenazine, Eliglustat, Gefitinib, Iloperidone, Lofexidine, Meclizine, Metoclopramide, Oliceridine, Pimozide, Pitolisant, Propafenone, Tetrabenazine, Thioridazine, Tramadol, Valbenazine, Venlafaxine, Vortioxetine, Carvedilol, Cevimeline, Codeine, Perphenazine, Tolterodine, Tramadol, Amitriptyline, Amoxapine, Clomipramine, Darifenacin, Desipramine, Donepezil, Doxepin, Fesoterodine, Fluvoxamine, Galantamine, Imipramine, Metoprolol, Mirabegron, Nebivolol, Nortriptyline, Paroxetine, Propranolol, Protriptyline, Risperidone, Tamoxifen, Tamsulosin, Trimipramine, Viloxazine
CYP3A5	*3/*3	Poor Metabolizer	Tacrolimus
CYP4F2	*1/*4	V433M variant carriers	Warfarin
DPYD	c.1627A>G (*5)/c. 1627A>G (*5)	Normal Function	Capecitabine, Fluorouracil
NUDT15	*1/*1	Normal Metabolizer	Azathioprine, Mercaptopurine, Thioguanine
SLCO1B1	*37/*37	Normal Function	Simvastatin, Atorvastatin, Elagolix, Rosuvastatin
TPMT	*1/*1	Normal Metabolizer	Azathioprine, Mercaptopurine, Thioguanine

UGT1A1	*1/*6	Intermediate Metabolizer	Belinostat, Irinotecan, Sacituzumab Govitecan-hziy, Nilotinib, Pazopanib, Dolutegravir, Raltegravir
VKORC1	rs9923231 variant (T)/ rs9923231 variant (T)	1639G>A variant carriers	Warfarin

Subsection 2.2: Drugs Potentially Impacted

Drug	USP.Category	USP.Class	Indication	Gene	Genotype	Phenotype	Recommendation
Avatrombopag	Blood Products and Modifiers	Platelet Modifying Agents	Thrombocytopenia in Chronic Liver Disease;	CYP2C9	*3/*3	Poor Metabolizer	Results in higher systemic concentrations.
Celecoxib	Cardiovascular Agents	Cardiovascular Agents	Osteoarthritis; Rheumatoid Arthritis; Ankylosing Spondylitis; Acute Pain; Dysmenorrhea	CYP2C9	*3/*3	Poor Metabolizer	Results in higher systemic concentrations. Reduce starting dose to half of the lowest recommended dose in poor metabolizers. Consider alternative therapy in poor metabolizers with juvenile rheumatoid arthritis.
Dronabinol	Antiemetics	Emetogenic Therapy Adjuncts	Antiemetic for Chemotherapy-Induced Nausea and Vomiting (CINV); Appetite Stimulation in AIDS-Related Anorexia; Synthetic Cannabinoid;	CYP2C9	*3/*3	Poor Metabolizer	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Efavirenz	Antivirals	Anti-HIV Agents, Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)	HIV Treatment; Prevention of Mother-to-Child Transmission (PMTCT);	CYP2B6	*9/*9	Poor Metabolizer	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation).
Eliglustat	Genetic, Enzyme, or Protein Disorder: Replacement, Modifiers, Treatment	nan	Gaucher Disease Type 1;	CYP2D6	*1/*1	Normal Metabolizer	Alters systemic concentrations, effectiveness, and adverse reaction risk (QT prolongation). Indicated for normal, intermediate, and poor metabolizer patients. Ultrarapid metabolizers may not achieve adequate concentrations to achieve a therapeutic effect. The recommended dosages are based on CYP2D6 metabolizer status. Coadministration with strong CYP3A inhibitors is contraindicated in intermediate and poor CYP2D6 metabolizers. Refer to FDA labeling for specific dosing recommendations.
Erdafitinib	Antineoplastics	Molecular Target Inhibitors	Bladder Cancer Treatment; FGFR Alterations;	CYP2C9	*3/*3	Poor Metabolizer	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Flurbiprofen	Analgesics	Nonsteroidal Anti-inflammatory Drugs	Pain Relief; Inflammation; Postoperative Pain;	CYP2C9	*3/*3	Poor Metabolizer	Results in higher systemic concentrations. Use a reduced dosage in poor metabolizers.

Ibuprofen	Analgesics	Nonsteroidal Anti-inflammatory Drugs	Pain Relief; Anti-inflammatory; Fever Reduction;	CYP2C9	*3/*3	Poor Metabolizer	May result in higher systemic concentrations.
Irinotecan	Antineoplastics	Molecular Target Inhibitors	Colorectal Cancer; Gastrointestinal Cancers; Small Cell Lung Cancer;	UGT1A1	*1/*6	Intermediate Metabolizer	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (severe or life-threatening neutropenia, severe diarrhea). Closely monitor for neutropenia during and after treatment. Consider reducing the starting dosage by at least one level in poor metabolizers and modify the dosage based on individual patient tolerance. Refer to FDA labeling for specific dosing recommendations.
Meloxicam	Analgesics	Nonsteroidal Anti-inflammatory Drugs	Osteoarthritis; Rheumatoid Arthritis; Ankylosing Spondylitis; Other Painful Inflammatory Conditions;	CYP2C9	*3/*3	Poor Metabolizer	Results in higher systemic concentrations. Consider dose reductions in poor metabolizers. Monitor patients for adverse reactions.
Nateglinide	Blood Glucose Regulators	Antidiabetic Agents	Type 2 Diabetes;	CYP2C9	*3/*3	Poor Metabolizer	Results in higher systemic concentrations and may result in higher adverse reaction risk (hypoglycemia). Dosage reduction is recommended. Increase monitoring frequency for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Piroxicam	Analgesics	Nonsteroidal Anti-inflammatory Drugs	Pain and Inflammation; Acute Gout; Post-Surgical Pain;	CYP2C9	*3/*3	Poor Metabolizer	Results in higher systemic concentrations. Consider reducing dosage in poor metabolizers.
Siponimod	Central Nervous System Agents	Multiple Sclerosis Agents	Relapsing Forms of Multiple Sclerosis; Active Secondary Progressive Multiple Sclerosis (SPMS) with Relapses;	CYP2C9	*3/*3	Poor Metabolizer	Results in higher systemic concentrations. Adjust dosage based on genotype. Do not use in patients with CYP2C9 *3/*3 genotype. Refer to FDA labeling for specific dosing recommendations.
Warfarin	Blood Products and Modifiers	Anticoagulants	Prevention and Treatment of Thrombosis; Stroke Prevention; Prosthetic Heart Valves; Hypercoagulable Conditions;	CYP2C9	*3/*3	Poor Metabolizer	Alters systemic concentrations and dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.
Warfarin	Blood Products and Modifiers	Anticoagulants	Prevention and Treatment of Thrombosis; Stroke Prevention; Prosthetic Heart Valves; Hypercoagulable Conditions;	CYP4F2	*1/*4	V433M variant carriers	May affect dosage requirements. Monitor and adjust doses based on INR.

Warfarin	Blood Products and Modifiers	Anticoagulants	Prevention and Treatment of Thrombosis; Stroke Prevention; Prosthetic Heart Valves; Hypercoagulable Conditions;	VKORC1	rs9923231 variant (T)/ rs9923231 variant (T)	1639G>A variant carriers	Alters dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.