



## Albinism Panel (Dermatology) Plus

### REFERRING HEALTHCARE PROFESSIONAL

NAME	HOSPITAL
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### PATIENT

NAME	DOB	AGE	GENDER	ORDER ID
		36		

PRIMARY SAMPLE TYPE	SAMPLE COLLECTION DATE	CUSTOMER SAMPLE ID
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### SUMMARY OF RESULTS

#### TEST RESULTS

The patient is heterozygous for **TYR c.613C>A, p.(Pro205Thr)**, which is pathogenic. The patient is heterozygous for a deletion, which encompasses exon 5 of **TYR, c.(1366+1\_1367-1)(\*1\_?)del**. This alteration is classified as pathogenic.

#### PRIMARY VARIANT TABLE: SEQUENCE ALTERATIONS

GENE	TRANSCRIPT	NOMENCLATURE	GENOTYPE	CONSEQUENCE	INHERITANCE	CLASSIFICATION
<b>TYR</b>	NM_000372.4	c.613C>A, p.(Pro205Thr)	HET	missense_variant	AR	<b>Pathogenic</b>
	<b>ID</b>	<b>ASSEMBLY</b>	<b>POS</b>	<b>REF/ALT</b>		
		GRCh37/hg19	11:88911734	C/A		
	<b>gnomAD AC/AN</b>	<b>POLYPHEN</b>	<b>SIFT</b>	<b>MUTTASTER</b>	<b>PHENOTYPE</b>	
	7/277186	probably damaging	deleterious	disease-causing	Albinism oculocutaneous	

#### PRIMARY VARIANT TABLE: COPY NUMBER ABERRATIONS

GENE	EVENT	COPY NUMBER	GENOTYPE	IMPACT	LINKS	CLASSIFICATION
<b>TYR</b>	DELETION	1	HET	partial gene	<a href="#">UCSC</a>	<b>Pathogenic</b>
	<b>OMIM</b>	<b>PHENOTYPE</b>			<b>COMMENT</b>	
		Albinism oculocutaneous			-	

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## SEQUENCING PERFORMANCE METRICS

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Albinism Panel (Dermatology)	26	351	71350	71350	296	100

## TARGET REGION AND GENE LIST

The Blueprint Genetics Albinism Panel Plus Analysis includes sequence analysis and copy number variation analysis of the following genes: *AP3B1, BLOC1S3, BLOC1S6, C10ORF11, DTNBP1, EDN3, EDNRB, GPR143, HPS1\**, *HPS3, HPS4, HPS5, HPS6, LYST, MC1R, MITF, MLPH, MYO5A, OCA2, PAX3, RAB27A, SLC24A5, SLC38A8, SLC45A2, TYR\** and *TYRP1*. This panel targets protein coding exons, exon-intron boundaries ( $\pm 20$  bps) and selected non-coding, deep intronic variants (listed in Appendix 5). This panel should be used to detect single nucleotide variants and small insertions and deletions (INDELs) and copy number variations defined as single exon or larger deletions and duplications. This panel should not be used for the detection of repeat expansion disorders or diseases caused by mitochondrial DNA (mtDNA) mutations. The test does not recognize balanced translocations or complex inversions, and it may not detect low-level mosaicism.

\*Some, or all, of the gene is duplicated in the genome. Read more: <https://blueprintgenetics.com/pseudogene/>  
The sensitivity to detect variants may be limited in genes marked with an asterisk (\*).

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## STATEMENT

### CLINICAL HISTORY

Patient is a 36-year-old individual with a history of oculocutaneous albinism and lichen planus. There is no family history of similar disease.

### CLINICAL REPORT

Sequence analysis using the Blueprint Genetics (BpG) Albinism Panel identified a heterozygous missense variant *TYR* c.613C>A, p.(Pro205Thr). Del/Dup (CNV) analysis using the Blueprint Genetics (BpG) Albinism Panel identified a heterozygous deletion encompassing exon 5 of *TYR*, c.(1366+1\_1367-1)(\*1\_?)del. Due to the large genomic distance between these variants, NGS-based methods cannot determine whether they occur on the same (in *cis*) or different (in *trans*) parental alleles.

#### ***TYR* c.613C>A, p.(Pro205Thr)**

There are 7 individuals heterozygous for this variant in the Genome Aggregation Database ([gnomAD](#), n>120,000 exomes and >15,000 genomes). No homozygotes were observed in the dataset. Database curators have made every effort to exclude individuals with severe pediatric diseases from these cohorts. The variant is predicted damaging by all *in silico* tools used.

The *TYR* c.613C>A, p.(Pro205Thr) variant is a previously reported pathogenic variant. It was described as a recurrent variant by King et al. who studied 120 individuals with albinism; the p.(Pro205Thr) variant was identified as compound heterozygous together with another *TYR* variant in 7 individuals with oculocutaneous albinism (PMID: [13680365](#)). Hutton and Spritz identified the variant as compound heterozygous together with another *TYR* variant in one additional patient with oculocutaneous albinism (PMID: [18463683](#)). In addition, the variant has been identified in clinical testing (ClinVar ID [99572](#)).

#### ***TYR* c.(1366+1\_1367-1)(\*1\_?)del**

Del/Dup (CNV) analysis using the Blueprint Genetics (BpG) Albinism Panel identified a heterozygous deletion encompassing exon 5 of *TYR*. This deletion is estimated to cover the genomic region chr11:89028250-89028594 and is approximately 344 base pairs in size. However, the exact breakpoints of the deletion cannot be determined using the present method, and therefore its exact size and genomic position are unknown.

Deletion of *TYR* exon 5 has previously been reported in the literature as disease-causing. In a large cohort of albino patients Mauri et al. identified 4 patients with a deletion of exon 5. One patient was reported homozygous for the *TYR* exon 5 deletion, while three patients were heterozygous for the deletion and also carried a heterozygous sequence variant in *TYR*. (PMID: [27734839](#))

### ***TYR***

Oculocutaneous albinism (OCA) is characterized by reduction or absence of melanin in the skin, hair, and eyes (PMID: [17980020](#)). OCA patients show symptoms such as reduced skin and hair pigmentation and consequent photosensitivity, a high risk of skin cancer, and reduced visual acuity and nystagmus. The non-syndromic OCA is inherited in an autosomal recessive manner, and is mainly due to mutations in four genes: *TYR* (OCA1), *OCA2* (OCA2), *TYRP1* (OCA3) and *SLC45A2* (OCA4). (GeneReviews [NBK1510](#))

The *TYR* (MIM [\\*606933](#)) gene encodes Tyrosinase, which participates in the catalysis of the conversion of tyrosine to melanin. Mutations in *TYR* cause autosomal recessive oculocutaneous albinism, types 1A (OCA1A) and 1B (OCA1B) (MIMs [#203100](#) and [#606952](#)). Oculocutaneous albinism is a genetically heterogeneous congenital disorder characterized by decreased or absent pigmentation in the hair, skin, and eyes and consequent photosensitivity, high risk of skin cancer, and reduced visual acuity and nystagmus. Oculocutaneous albinism caused by mutations in the *TYR* gene, is divided clinically into two types: type 1A is characterized by complete lack of tyrosinase activity due to production of an inactive enzyme, and type 1B is characterized by reduced activity of tyrosinase. In a study on a cohort of 321 albino patients, the frequencies of mutations in the major causative oculocutaneous albinism genes were: *TYR* (44%), *OCA2* (17%), *TYRP1* (1%), *SLC45A2* (7%), and *SLC24A5* (<0.5%) (PMID

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27734839). An additional 5% of patients had *GPR143* mutations, which are causative of an X-linked ocular albinism type I (MIM #300500). A second reliable mutation was not detected for 19% of cases. In 7% of the patients no mutation was detected. OCA1 is the most common subtype found in Caucasians and accounts for about 50% of albinism cases worldwide (PMID: 18463683, 18821858). Prevalence of OCA1 is 1:40,000 (ORPHA79431). Most individuals with OCA1 are compound heterozygotes with different paternal and maternal *TYR* mutations (GeneReviews: NBK1166). ClinVar reports > 50 pathogenic or likely pathogenic variants detected in clinical testing in the *TYR* gene, including missense (70%), and truncating (frameshift, nonsense and splice site variants) (30%). The HGMD professional mutation database lists over 400 variants in *TYR* in association with OCA (mainly OCA1), of which the majority are missense variants (70%) and the remaining 30% are truncating variants.

Mutation nomenclature is based on GenBank accession NM\_000372.4 (*TYR*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

## CONCLUSION

*TYR* c.613C>A, p.(Pro205Thr) and *TYR* c.(1366+1\_1367-1)\_(\*1\_?)del are classified as pathogenic, based on currently available evidence supporting their disease-causing role. Disease caused by *TYR* variants is inherited in an autosomal recessive manner. Testing of parental/offspring samples is needed to determine whether the variants occur *in cis* (on the same allele) or *in trans* (on different alleles). Compound heterozygosity of the variants (*in trans*) would explain the patient's clinical presentation. If both of these variants are parentally inherited, any siblings of the patient will have a 25% chance of being compound heterozygous and thus affected, a 50% chance of being an unaffected carrier, and a 25% chance of being an unaffected non-carrier. Genetic counseling and family member testing are recommended.

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STEP	DATE
Order date	
Sample received	
Sample in analysis	
Reported	

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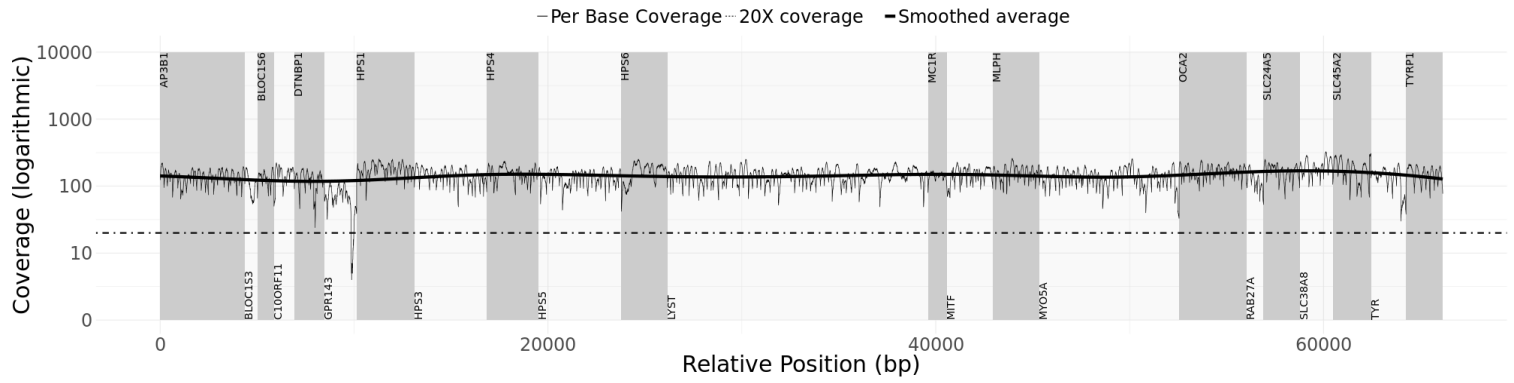
(This statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results.)

*Signature*

Name

Title

Readability of the coverage plot may be hindered by faxing. A high quality coverage plot can be found with the full report on [nucleus.blueprintgenetics.com](http://nucleus.blueprintgenetics.com).



## APPENDIX 5: SUMMARY OF THE TEST

### PLUS ANALYSIS

**Laboratory process:** When required, the total genomic DNA was extracted from the biological sample using bead-based method. DNA quality and quantity were assessed using electrophoretic methods. After assessment of DNA quality, qualified genomic DNA sample was randomly fragmented using non-contact, isothermal sonochemistry processing. Sequencing library was prepared by ligating sequencing adapters to both ends of DNA fragments. Sequencing libraries were size-selected with bead-based method to ensure optimal template size and amplified by polymerase chain reaction (PCR). Regions of interest (exons and intronic targets) were targeted using hybridization-based target capture method. The quality of the completed sequencing library was controlled by ensuring the correct template size and quantity and to eliminate the presence of leftover primers and adapter-adapter dimers. Ready sequencing libraries that passed the quality control were sequenced using the Illumina's sequencing-by-synthesis method using paired-end sequencing (150 by 150 bases). Primary data analysis converting images into base calls and associated quality scores was carried out by the sequencing instrument using Illumina's proprietary software, generating CBCL files as the final output.

**Bioinformatics and quality control:** Base called raw sequencing data was transformed into FASTQ format using Illumina's software (bcl2fastq). Sequence reads of each sample were mapped to the human reference genome (GRCh37/hg19). Burrows-Wheeler Aligner (BWA-MEM) software was used for read alignment. Duplicate read marking, local realignment around indels, base quality score recalibration and variant calling were performed using GATK algorithms (Sentieon) for nDNA. Variant data for was annotated using a collection of tools (VcfAnno and VEP) with a variety of public variant databases including but not limited to gnomAD, ClinVar and HGMD. The median sequencing depth and coverage across the target regions for the tested sample were calculated based on MQ0 aligned reads. The sequencing run included in-process reference sample(s) for quality control, which passed our thresholds for sensitivity and specificity. The patient's sample was subjected to thorough quality control measures including assessments for contamination and sample mix-up. Copy number variations (CNVs), defined as single exon or larger deletions or duplications (Del/Dups), were detected from the sequence analysis data using a proprietary bioinformatics pipeline. The difference between observed and expected sequencing depth at the targeted genomic regions was calculated and regions were divided into segments with variable DNA copy number. The expected sequencing depth was obtained by using other samples processed in the same sequence analysis as a guiding reference. The sequence data was adjusted to account for the effects of varying guanine and cytosine content.

**Interpretation:** The clinical interpretation team assessed the pathogenicity of the identified variants by evaluating the information in the patient requisition, reviewing the relevant scientific literature and manually inspecting the sequencing data if needed. All available evidence of the identified variants was compared to classification criteria. Reporting was carried out using HGNC-approved gene nomenclature and mutation nomenclature following the HGVS guidelines. Likely benign and benign variants were not reported.

**Variant classification:** Our variant classification follows the Blueprint Genetics [Blueprint Genetics Variant Classification Schemes](#) modified from the [ACMG guideline 2015](#). Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report.

**Databases:** The pathogenicity potential of the identified variants were assessed by considering the predicted consequence of the change, the degree of evolutionary conservation as well as the number of reference population databases and mutation databases such as, but not limited to, the [gnomAD](#), [ClinVar](#), HGMD Professional and Alamut Visual. In addition, the clinical relevance of any identified CNVs was evaluated by reviewing the relevant literature and databases such as [Database of Genomic Variants](#) and [DECIPHER](#). For interpretation of mtDNA variants specific databases including e.g. Mitomap, HmtVar and 1000G were used.

**Confirmation of sequence alterations:** Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) were confirmed using bi-directional Sanger sequencing when they did not meet our stringent NGS quality metrics for a true positive call. In addition, prenatal case with diagnostic findings were confirmed.

**Confirmation of copy number variants:** CNVs (Deletions/Duplications) were confirmed using a digital PCR assay if they covered less than 10 exons (heterozygous), less than 3 exons (homo/hemizygous) or were not confirmed at least three times previously at our laboratory. Furthermore, CNVs of any size were not confirmed when the breakpoints of the call could be

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determined.

**Analytic validation:** The detection performance of this panel is expected to be in the same range as our high-quality, clinical grade NGS sequencing assay used to generate the panel data (nuclear DNA: sensitivity for SNVs 99.89%, indels 1-50 bps 99.2%, one-exon deletion 100% and five exons CNV 98.7%, and specificity >99.9% for most variant types). It does not detect very low level mosaicism as a variant with minor allele fraction of 14.6% can be detected in 90% of the cases. Detection performance for mtDNA variants (analytic and clinical validation): sensitivity for SNVs and INDELS 100.0% (10-100% heteroplasmy level), 94.7% (5-10% heteroplasmy level), 87.3% (<5% heteroplasmy level) and for gross deletions 100.0%. Specificity is >99.9% for all.

**Test restrictions:** A normal result does not rule out the diagnosis of a genetic disorder since some DNA abnormalities may be undetectable by the applied technology. Test results should always be interpreted in the context of clinical findings, family history, and other relevant data. Inaccurate, or incomplete information may lead to misinterpretation of the results.

**Technical limitations:** This test does not detect the following: complex inversions, gene conversions, balanced translocations, repeat expansion disorders unless specifically mentioned, non-coding variants deeper than  $\pm 20$  base pairs from exon-intron boundary unless otherwise indicated (please see the list of non-coding variants covered by the test). Additionally, this test may not reliably detect the following: low level mosaicism, stretches of mononucleotide repeats, indels larger than 50bp, single exon deletions or duplications, and variants within pseudogene regions/duplicated segments. The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics. Laboratory error is also possible. Please see the Analytic validation above.

**Regulation and accreditations:** This test was developed and its performance characteristics determined by Blueprint Genetics (see Analytic validation). It has not been cleared or approved by the US Food and Drug Administration. This analysis has been performed in a CLIA-certified laboratory (#99D2092375), accredited by the College of American Pathologists (CAP #9257331) and by FINAS Finnish Accreditation Service, (laboratory no. T292), accreditation requirement SFS-EN ISO 15189:2013. All the tests are under the scope of the ISO 15189 accreditation (excluding mtDNA testing and digital PCR confirmation).

#### **NON-CODING VARIANTS COVERED BY THE PANEL:**

NM\_000273.2(GPR143):c.885+748G>A  
NM\_000273.2(GPR143):c.659-131T>G  
NM\_032383.3(HPS3):c.2888-1612G>A  
NM\_000275.2(OCA2):c.1117-11T>A  
NM\_000275.2(OCA2):c.1117-17T>C  
NM\_000275.2(OCA2):c.1045-15T>G  
NM\_000275.2(OCA2):c.574-19A>G  
chr5:g.33985176-33985176  
chr5:g.33985764-33985764  
NM\_000372.4(TYR):c.1037-18T>G

#### **GLOSSARY OF USED ABBREVIATIONS:**

**AD** = autosomal dominant

**AF** = allele fraction (proportion of reads with mutated DNA / all reads)

**AR** = autosomal recessive

**CNV** = Copy Number Variation eg, one exon or multiexon deletion or duplication

**gnomAD** = genome Aggregation Database (reference population database; >138,600 individuals)

**gnomAD AC/AN** = allele count/allele number in the genome Aggregation Database (gnomAD)

**HEM** = hemizygous

**HET** = heterozygous

**HOM** = homozygous

**ID** = rsID in dbSNP

**MT** = Mitochondria

**MutationTaster** = *in silico* prediction tools used to evaluate the significance of identified amino acid changes.

**Nomenclature** = HGVS nomenclature for a variant in the nucleotide and the predicted effect of a variant in the protein level

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**OMIM** = Online Mendelian Inheritance in Man®

**PolyPhen** = *in silico* prediction tool used to evaluate the significance of amino acid changes.

**POS** = genomic position of the variant in the format of chromosome:position

**SIFT** = *in silico* prediction tool used to evaluate the significance of amino acid changes.

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