THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Albinism

Albinism is a group of inherited disorders in which melanin biosynthesis is reduced or absent [1]. The lack or reduction in pigment can affect the eyes, skin and hair, or only the eyes. In addition, there are several syndromic forms of albinism in which the hypopigmented and visual phenotypes are seen in addition to other systems involvement [2].

Our Albinism Panel includes analysis of all 21 genes listed below.

Albinism Panel							
Oculocutaneous Albinism		**Ocular Albinism**	**Hermansky Pudlak syndrome**			**Chediak-Higashi syndrome**	**Griscelli syndrome**
TYR	SLC45A2	GPR143	HPS1	HPS4	BLOC1S3	LYST	MYO5A
OCA2	SLC24A5		AP3B1	HPS5	BLOC1S6		RAB27A
TYRP1	C10ORF11		AP3D1	HPS6			MLPH
			HPS3	DTNBP1			

Oculocutaneous Albinism

Oculocutaneous albinism (OCA) is a genetically heterogeneous congenital disorder characterized by decreased or absent pigmentation in the hair, skin, and eyes. Clinical features can include varying degrees of congenital nystagmus, hypopigmentation and translucency, reduced pigmentation of the retinal pigment epithelium and foveal hypoplasia. Vision acuity is typically reduced and refractive errors, color vision impairment and photophobia also occur [3].

Gene	Clinical Features	Details
TYR	Albinism, oculocutaneous, type I	OCA1 is caused by mutations in the tyrosinase gene, *TYR*. Mutations completely abolishing tyrosinase activity result in OCA1A, while mutations rendering some enzyme activity result in OCA1B allowing some accumulation of melanin pigment production throughout life. TYR is a copper-containing enzyme that catalyzes the first two steps in the melanin biosynthesis pathway.
OCA2	Albinism, oculocutaneous, type II	Mutations in the *OCA2* gene cause the OCA2 phenotype. OCA2 is the most common type of albinism in African American OCA patients. The overall prevalence is about 1:10,000 among African Americans. OCA2 protein is important for normal biogenesis of melanosomes and for normal processing and transport of melanosomal proteins
TYRP1	Albinism, oculocutaneous, type III	OCA3 is caused by mutations in tyrosinase-related protein 1,*TYRP1*. OCA3 results in Rufous or red OCA in African individuals, who have red hair and reddish brown skin. Mutations in *TRYP1* have also been described in individuals of non-African descent. TYRP1 is an enzyme in the melanin biosynthesis pathway.
SLC45A2	Albinism, oculocutaneous, type IV	OCA4 is caused by mutations in the membrane-associated transporter protein gene, *SLC45A2*. Mutations in *SLC45A2* were first identified in a Turkish patient with OCA, but have since been identified in individuals of other ethnic backgrounds including 24% of Japanese individuals with OCA according to one study [4].
SLC24A5	Albinism, oculocutaneous, type VI	Exome sequencing identified a nonsense and frameshift mutation in *SLC24A5* in a Chinese patient with nonsyndromic OCA [5]. The *SLC24A5* gene is involved in skin pigmentation although its exact role is still be elucidated.
c10orf11	Albinism, oculocutaneous, type VII	A homozygous nonsense mutation in the *c10orf11* gene was identified in 6 probands with OCA from the Faroe Islands[6]. C10orf11 is involved in melanocyte differentiation and function.

Ocular Albinism

Ocular albinism (OA) is characterized by nystagmus, impaired visual acuity, iris hypopigmentation with translucency, albinotic fundus, macular hypoplasia, and normally pigmented skin and hair

Gene	Clinical Features	Details
GPR143	Ocular albinism, type I	OA1 is caused by mutations in the G protein-coupled receptor 143 gene, *GPR143*. A wide range of mutations have been described including missense, nonsense, indels and splice-site. One study identified mutations in *GPR143* in one third of patients with OA [7]. GPR143 is exclusively expressed by melanocytes and retinal pigment epithelium.

Hermansky-Pudlak syndrome

Hermansky-Pudlak syndrome (HPS) is characterized by oculocutaneous albinism, bleeding tendency, and ceroid deposition, which likely leads to deleterious lesions in lungs, heart, and other organs. Early detection and involvement of appropriate management may mitigate the risks of life-threatening complications and provide prognostic information [8].

Gene	Clinical Features	Details
HPS1	Hermansky Pudlak syndrome I	HPSI, the most common form of HPS, is caused by mutations in the *HPS1* gene. Up to 4% of individuals of northwestern Puerto Rican descent are carriers of a mutation in *HPS1*. Affected patients generally appear classically albinotic. Lung disease in the fourth and fifth decades of life is a common cause of mortality in affected patients.
AP3B1	Hermansky-Pudlak syndrome II	HPSII is caused by mutations in the *AP3B1* gene. Only a handful of patients with HPSII have been reported. Affected individuals may present with frequent infections due to defects in innate immunity, in addition to other features of HPS. The *AP3B1* gene encodes a protein that helps to form intracellular vesicles.
HPS3	Hermansky-Pudlak syndrome III	HPSIII is caused by mutations in the *HPS3* gene. Individuals with HPSIII are typically more mildly affected and is associated with minimal bleeding tendencies and less hypopigmentation than in patients with HPSI. Pulmonary features are typically absent. The *HPS3* gene encodes a protein of unknown function that interacts with other HPS proteins.
HPS4	Hermansky-Pudlak syndrome IV	HPSIV is caused by mutations in the *HPS4* gene. HPSIV is similar in clinical features to HPSI.
HPS5	Hermansky-Pudlak syndrome V	HPSV is caused by mutations in the *HPS5* gene. HPSV is similar in clinical features to HPS3. Patients have variable hypopigmentation and bleeding tendancies. Other systemic involvement has not been reported to date.
HPS6	Hermansky-Pudlak syndrome VI	HPSVI is caused by mutations in the *HPS6* gene. Like patients with HPSIII and HPSV, patients with HPSVI typically have milder features. The *HPS6* gene encodes a protein of unknown function that interacts with HP3 and HPS5.
DTNBP1	Hermansky-Pudlak syndrome VII	A homozygous nonsense mutation in *DTNBP1* was identified in a Portuguese patient with HPS7. This patient had OCA and bleeding tendency, but normal pulmonary function [9]
BLOC1S3	Hermansky-Pudlak syndrome VIII	A homozygous frameshift mutation in *BLOC1S3* was identified in a consanguineous family with HPS8. Affected individuals displayed features of incomplete oculocutaneous albinism and platelet dysfunction[10].
BLOC1S6	Hermansky-Pudlak syndrome IX	Truncating mutations in *BLOC1S6* have been identified in a few individuals with HPS9[11]
AP3D1	Hermansky-Pudlak syndrome X	A homozygous truncating mutation in *AP3D1* has been reported in a patient with Hermansky-Pudlak syndrome [12].

Chediak-Higashi syndrome

Chediak-Higashi syndrome is characterized by decreased pigmentation of hair and eyes (partial albinism), photophobia, nystagmus, large eosinophilic, peroxidase-positive inclusion bodies in the myeloblasts and promyelocytes of the bone marrow, neutropenia, abnormal susceptibility to infection, and peculiar malignant lymphoma.

Gene	Clinical Features	Details
LYST	Chediak-Higashi syndrome	CHS is caused by mutations in the lysosomal trafficking regulator gene, *LYST.* While a variety of different mutation types have been reported, generally speaking individuals with the severe childhood form of the disease have mutations that lead to premature truncation, while missense mutations have only been reported in individuals with clinically mild forms of the disorder.

Griscelli syndrome

Griscelli syndrome is characterized by pigmentary dilution of the skin and hair, the presence of large clumps of pigment in hair shafts, and an accumulation of melanosomes in melanocytes.

Gene	Clinical Features	Details
MYO5A	Griscelli syndrome, type I	GS1 is caused by mutations in the *MYO5A* gene. Patients exhibit severe developmental delay and intellectual disability occurring early in life however they do not have immunologic impairment or manifestations of hemophagocytic syndrome.
RAB27A	Griscelli syndrome, type II	GSII is caused by mutations in the *RAB27A* gene. GSII is characterized by the same hypopigmentation associated with an immune defect, leading to episodes of a life-threatening uncontrolled T lymphocyte and macrophage activation syndrome known as accelerated phase or hemophagocytic syndrome. Bone marrow transplantation is the only curative treatment for this condition
MLPH	Griscelli syndrome, type III	A homozygous missense mutation in *MLPH* was identified in a patient with GSIII, characterized by hypopigmentation without any immunologic or neurologic manifestations[13]

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Albinism Panel (21 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2500
	81406
CPT codes:	81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

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