DOI: 10.53469/jcmp.2024.06(08).59

New Progress in Molecular Genetics Research of Albinism

Ruoyue Cui[1,2], Danli Zhang[1,2], Jianlei Li[1,3], Lifei Zhou[1,4], Pingping Zhang[1], Yali Li[1,*]

[1]Department of Reproductive and Genetic Medicine, Hebei General Hospital, Shijiazhuang 050051, Hebei, China
[2]Hebei North University, Zhangjiakou 075132, Hebei, China
[3]Hebei Medical University, Shijiazhuang 050011, Hebei, China
[4]North China University of Science and Technology, Tangshan 063210, Hebei, China
Correspondence Author, li_y_li@sina.com

Abstract: ***Albinism is a clinical and genetic heterogeneity disease associated with reduced melanin biosynthesis, characterized by visual system defects, manifested as poor vision, accompanied by varying degrees of pigment deficiency. The pigment deficiency can affect the eyes, skin, and hair in Oculocutaneous Albinism (OCA) or Oculocutaneous Albinosis (OA) that only affects the eyes. Currently, 21 genes related to albinism have been identified, including 7 OCA related genes (TYR, OCA2, TYRP1, SLC45A2, SLC24A5, LRMDA, and DCT), 1 OA related gene (GPR143), 1 FHONDA (SLC38A8), 1 CHS related gene (LYST), and 11 PHS related genes (HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3, BLOC1S6, AP3D1, and BLOC1S5). This article reviews the progress of molecular genetics research on albinism, with the aim of providing new ideas for prenatal or early diagnosis of albinism patients.***

Keywords: Albinism, Genes, Prenatal Diagnosis, Skin albinism, Ophthalmic albinism**.**

1. Introduction

Albinism is a group of single-gene inherited disorders caused by mutations in genes associated with melanin synthesis or transport. It is classified as oculocutaneousalbinism (OCA) and ocularalbinism (OA) according to clinical manifestations. The prevalence of OCA varies according to ethnicity, and epidemiological data are mostly from Western populations (mainly in North America and Europe). The global prevalence of OCA is about 1/17,000, and the mutation carrier rate is about 1/65, while the Chinese Han population has a prevalence of OCA of about 1/18,000, and the mutation carrier rate is about 1/70 [1]. In some African countries, the incidence can be as high as 1 in 1400, possibly due to inbreeding and the founder effect [2]. People with albinism often have damage to the visual system, and there is no effective way to repair or reverse it, which is the main cause of disability. Defects of the visual system in albinism include foveal dysplasia, loss of cytochrome in the retinal pigment epithelium, abnormal optic cross-projection, loss of iris pigment, photophobia, and nystagmus. Albinism has high genetic heterogeneity. This article reviews the progress in molecular genetics of albinism.

2. Overview of the Molecular Genetics of Albinism

Prior to 2019, six genes were identified as being associated with OCA, and seven types of OCA were named accordingly: TYR (OCA1), OCA2 (OCA2), TYRP1 (OCA3), SLC45A2 (OCA4), unidentified pathogenic gene (OCA5), SLC24A5 (OCA6), and LRMDA (OCA7); One gene was associated with OA: GPR143(OA1). In addition to the non-syndromes mentioned above, there are syndromes such as Hermansky-Pudlak syndrome (HPS) and Chedlak-Higashi syndrome (CHS), which involves cells other than pigment cells, has a more severe clinical phenotype. There are 10 known species of HPS and 1 species of CHS, The pathogenic genes were HPS1 (HPS1), AP3B1 (HPS2), HPS3 (HPS3), HPS4 (HPS4), HPS5 (HPS5), HPS6 (HPS6), DTNBP1 (HPS7), BLOC1S3 (HPS8), BLOC1S6 (HSP9), AP3D 1 (HPS10) and LYST (CHS1), shown in Table 1.

Table 1: Albinism-related genes and chromosome localization

Types of albinism	Gene	Chromosome localizatio
OCA1	*TYR*	11q14.3
OCA2	*OCA2*	15q122-q13.1
OCA3	*TYRP1*	9p23
OCA4	*SLC45A2*	5p13.2
OCA5	*ND*	4q24
OCA6	*SLC24A5*	15q21.1
OCA7	*LRMDA*	10q22.2-q22.3
OCA8	*DCT*	13q32.1
OA1	*GPR143*	Xp22.2
FHONDA	*SLC38A8*	16q23.3
CHS1	*LYST*	1q42.3
HPS1	*HPS1*	10q24.2
HPS2	*AP3B1*	5q14.1
HPS3	*HPS3*	3q24
HPS4	*HPS4*	22q12.1
HPS5	*HPS5*	11p15.1
HPS6	*HPS6*	10q24.32
HPS7	*DTNBP1*	6p22.3
HPS8	*BLOC1S3*	19q13.32
HPS9	*BLOC1S6*	15q21.1
HPS10	*AP3D1*	19p13.3
HPS11	*BLOC1S5*	6p24.3

After 2019, it was found that mutations in BLOC1S5 gene can also cause HPS, in addition to a new pathogenic gene DCT that causes OCA was also reported. Since then, the number of pathogenic genes of OCA has increased from 6 to 7, the number of types has increased from 7 to 8, the number of pathogenic genes/types of HPS syndrome has increased from 10 to 11, the number of albinism-related genes has increased from 19 to 21, and the number of albinism types has increased from 20 to 22[3-5].

3. New Gene Associated with Albinism

3.1 OCA8-related Gene: DCT

In 2021, Pennamen et al. [3] studied two unrelated OCA patients, reported a pathogenic variant of the DCT gene, and

provided three loci of the gene variant, respectively: Exon 1c.118T > a (p.Cys40Ser), exon 9c.1406_1419del (p.CYS469 *), and exon 1c.183C > G (p.Cys61Trp). According to the American college of medical genetics and genomics (ACMG) standards, the three variants are classified as possible pathogenesis: c.118T > A (p.Cys40Ser) (PS3, PM2, PP3, PP4), c.1406_1419del (p.CYS469 *) (PM2, PM4, PP3, PP4), C.183C > G (p.Cys61Trp) (PS3, PM2, PP3, PP4). Two unrelated individuals were found in undiagnosed patients who carried a distinct mutation in the DCT gene and exhibited mild pigmentation and moderate eye development features of albinism, thus suggesting that mutations in this site may also cause mild albinism. In addition, they tested the effects of the same mutation at DCT sites in mice using the CRISPR-Cas9 genome editing tool, showing that the animals also had reduced pigmentation. Similarly, the inactivation of the DCT gene in zebrafish also leads to reduced skin and retinal pigmentation. These findings showed that the three DCT variants identified were causative and were identified as the cause of the disease in two albino patients. Therefore, they concluded that the DCT mutation is the genetic cause of a new type of OCA, with the pseudo-name OCA8.

3.2 HPS Related Gene: BLOC1S5

In 2020, Pennamen and his team [4] reported on two unrelated individuals in a cohort of 230 undiagnosed patients who had lighter hair color than their parents, typical changes in the retina, various signs of bleeding, and other HPS-related phenotypes. The two patients carried different homozygous deletions in the BLOC1S5 gene, about 19 KB and only 1bp, both of which resulted in a nonfunctional BLOC1S5 protein, To damage the biogenesis of lysosomerelated organelles complex-1(BLOC-1) stability. All mutations result in different subunits of any known type of HPS or CHS that are genetically encoded by multiprotein complexes involved in the maturation, transport, and functioning of lysosomal associated organelles. ACMG criteria supported the pathogenicity of patient 1 and 2 variants (Patient 1: PVS1, PS3, PM2, PM3; Patient 2: PVS1, PM2, PM3). It is worth noting that in GnomAD public database (https://gnomad.broadinstitute.org/) not found in the homozygous or heterozygous state of these variations. Human and mouse comparisons with HPS-related gene mutations have helped to understand the presence of additional protein subunits formed by lysosomes or melanosomes. The light hair color and catchy color of the mouse mutants were associated with mutations in the BLOC1S5 and BLOC1S4 genes, respectively, two additional BLOC-1 subunits that had not been previously reported, and these findings indicate that the BLOC1S5 variant was identified as causative and was identified as the cause of the disease in two albino patients. It is proposed that the new syndrome albinism HPS be named HPS11. It is also predicted that mutations in BLOC1S4 may be the basis of another HPS.

4. New Loci Associated with Albinism

4.1 New Loci Associated with OCA-2

In 2019, Wang and his team [6] discovered an overall deletion of the OCA2 gene (exon 17-21) and C.1865t > C (p.Leu622Pro) not previously reported. The proband was an 11-month-old male from a non-close family of Han Chinese descent who presented with milky skin, yellow-white hair, nystagmus, astigmatism, and farsightedness. Targeted Next-generation sequencing (NGS) of the progenitor and identification of two new complex heterogenic variants C.1865T > C (p.Leu622Pro) and exon 17-21 deletions in the OCA2 gene. The variant C.1865T > C predicted by the online tools SIFT, PolyPhen-2 and MutationTaster may be pathogenic. Deletion of exon 17-21 in the OCA2 gene, which spans 7 to 10 transmembrane alpha-helix domains, has not been previously reported. It causes a partial loss of the domain and is expected to produce a non-functional truncated protein. Taken together, these two mutations may be responsible for the clinical manifestations of OCA2.

In 2024, the newly discovered c.1258G > A (p.G420R) mutation by Wang and his team [1] could renew and expand the gene mutation spectrum of OCA2 albinism. The patient's clinical manifestations are white skin, yellow hair, a few freckles on the cheeks and bridge of the nose, decreased vision, and blue irises. Retinal examination revealed orange-red reflection in both eyes, less pigmentation, blurred optic disc boundaries, extensive atrophy of the peripheral retinal pigment epithelium, and obvious exposure of the reticulochorioidal vascular system. WES tests revealed three mutations in the OCA2 gene: C.1441G > A (p.A481T) on CHR15:28228553, C.2267-2A > C on CHR15:28090200, and chr15: c.1258G > A (p.G420R) on 28230316. The c.1258G > A (p.G420R) mutation is located at the +19 position of exon 13, the base of c.1258 is changed from G to A, and the amino acid glycine at amino acid 420 is changed to arginine, which is a new mutation that is not reported and not included in the database. This is a highly conserved residue, and the function of the human P protein may be affected by mutations in this residue, which may ultimately lead to disease. According to the ACMG gene mutation interpretation guidelines, the mutation site meets two evidence: PM2_sup transplantation +PP3, the rating does not meet the criteria of potential pathogenicity/pathogenicity, and clinical diagnosis cannot be based on this gene test. However, the newly discovered mutation (c.1258G > A) will also enrich the mutation spectrum of OCA2-related genes, providing a good basis for doctors to diagnose the disease.

4.2 New Loci Associated with OCA6

In 2019, Zhang and his team [7] discovered new mutations of OCA6, c.500dupT (p.S168Ifs*15) and c.498_499delAC (p.L167Ifs*15). Two patients were clinically diagnosed with non-syndromic OCA and their parents were not married to close relatives. Molecular tests of patients 1 and 2 revealed two homozygous frameshaft alleles: c.500dupT (p.S168Ifs*15) and c.498_499delAC (p.L167Ifs*15). According to the criteria of the American Society of Medical Genetics, both are predicted to be pathogenic alleles. SLC24A5 is located on chromosome 15q21.1 and encodes the NCKX5 protein, which is a potassium-dependent exchange agent necessary for the maturation of melanosomes and the production of pigments in mature melanosomes. The mutant protein found in some OCA6 patients does not alleviate pigment reduction when transfected into melanocytes that knock down NCKX5. In addition, the authors also found that NCKX5 in mitochondria transfers calcium to melanosomes

for maturation and pigment production, revealing the potential mechanism of OCA6, and enriching the mutation spectrum of OCA2-related genes, providing a good basis for doctors to diagnose the disease.

4.3 New Loci Associated with OA

In 2021, Mao and his team [8] discovered A new mutation site for OA, c.939G > A (p.W313X). To date, more than 100 GPR143 gene mutations have been identified in OA globally, but GPR143 variants without nystagmus are rarely reported. Mao et al. reported and described a large Chinese family in which all affected individuals suffered from poor vision and foveal hypoplasia as primary manifestations without detectable signs of nystagmus. Genetic sequencing revealed that the pathogenic gene of GPR143 has A new point mutation c.939G > A (p.W313X) in exon 8, and no cases of this mutation have been found in the human gene mutation database, which is a meaningless mutation, which causes the tryptophan substitution of the stop codon at the codon 313, resulting in the loss of the C-terminal. Subsequently, the motifs that retain the location signal of the melanosome membrane are destroyed. The mutation has foveal hypoplasia without nystagmus, which further expands the gene mutation spectrum. Further study of the function of GPR143 in foveal development may help elucidate the mechanism and molecular targets of the disease.

4.4 New Loci Associated with CHS Syndrome

In 2021, Boluda-Navarro et al. [9] described a case of a CHS patient carrying a homozygous mutation in the LYST gene. The patient, a 3-year-old girl born to non-close parents following a normal pregnancy and cesarean section, was hospitalized after 2 days of high fever, expectoration, nasal discharge, and loss of appetite. A week earlier, she had suffered a non-febrile respiratory infection and was treated with azithromycin. She presents with incomplete ocular albinism, which is characterized by no pigmentation of the peripheral retina, but no history of severe recurrent infections or excessive bleeding. There is no family history of albinism or hypopigmentation, immunological or hematological changes, or early death. The mutation is inherited due to a partial uniparental homodisomy of maternal origin. The insertion mutation c.8380dupT in exon 32 of LYST gene was detected by Sanger sequencing, resulting in premature occurrence of the stop codon and loss of all conserved domains at the C-terminal of LYST protein. This case highlights the relevance of uniparental disomy as a potential mechanism for CHS expression in non-closely related families.

In 2020, Meng and his team [10] used whole exome sequencing and Sanger sequencing to detect two CHS patients from close family and found that a new homozygous nonsense mutation c.8782C > T (p.Gln2928*) was identified in exon 34 of the LYST gene. The progenitor presented with partial ocular skin albinism, immune deficiency, and eosinophilic inclusions in bone marrow and blood smear. And the same variant was found in a heterozygous state in six unaffected individuals from the same lineage. These results enrich the mutant spectrum of CHS and provide a basis for genetic counseling and prenatal diagnosis.

In 2020, Song and his team [11] described a complex heterozygote in the LYST gene, which was found in a 4-year-old female patient. Clinical examination showed hypopigmentation of the skin, sensitivity to light, mild splenomeglia, and thrombocytopenia. The bone marrow examination revealed a large intracytoplasmic inclusion body, suggesting the diagnosis of CHS. A LYST gene complex heterozygote consisting of missense mutation c.5719A > G and intron mutation c.4863-4G > A was identified from the patient by Sanger sequencing. The missense mutation c.5719A > G (p.Ile1907Val) was first reported. The findings expand the spectrum of causative mutations in the LYST gene and demonstrate that Sanger sequencing is an effective and accurate diagnostic method for genetic diseases.

In 2019, Wang et al. [12] identified an unreported homozygous mutation in LYST gene c.7645C > T (p.Q2549X) from a child through whole exon sequencing, and diagnosed CHS. c.796G > T variation was predicted as harmful by online SIFT and Polyphen2 software.

In 2019, Fukuchi et al. [13] found in LYST found heterozygous mutations, c. 6676 c > T (2226 * p.R) and c. 338 _339delgtinsagatctttgagtgga KFS (p. 113), The genetic mutation in this case does not match those previously reported. In this study, complex heterozygous frame-shifting mutations and nonsense mutations were detected. Because these mutations can lead to the development of fatal hemophagocytic lymphohistiocytosis in early childhood, hematopoietic cell transplantation was performed in this patient.

In 2019, Gomaa et al. [14] identified three previously unreported LYST gene mutations through Sanger sequencing. The nonsense mutation of exon 30 in patient 1 was homozygous c.8080C > T (p.Gln2693*), while patient 2 was homozygous. There is a single nonsense mutation c.6712C > T on exon 23 (p.Arg2238*) and patient 3 has a single base shift deletion on exon 9, resulting in a premature termination codon c.3726delG (p.Lys1242fs*25).

4.5 New Loci Associated with HPS1 Syndrome

In 2021, Wang and his team [15] identified two mutations in a new site on HPS1 in three patients: c.1279_1280insGGAG (p.Asp427Glyfs*27) and c.875_878delACAG (p.Asp292Alafs*38). Mutation screening was performed by NGS technique. The results showed that Two patients carried C. 956delA (P.Lu319GLYfs *12), C. 1279_1280insGGAG (p.Asp427Glyfs*27), and c c.875_878delACAG (P.SP292ALAFS *38), c.1932delC (p.Tyr645Thrfs*80) complex heterozygous variant. c.1279_1280insGGAG (p.Asp427Glyfs*27) and c.875_878delACAG (p.Asp292Alafs*38) have not been reported in HPS1 before.

In 2019, Doubkova et al. [16] identified the complex heterozygous genotype of the prover HPS1 gene (NM_000197.3) by exome sequencing: Pathogenic frameshift variant c.1189delC (p.Gln397Serfs*2), resulting in premature termination codons, associated with HPS; The nonsense variant, c.1507C > T (p.G 503*), which had never been described before, resulted in a premature stop codon, implying a loss of 197 amino acids or more likely a nonsense

mutation-mediated mRNA degradation decay.

4.6 New Loci Associated with HPS2 Syndrome

In 2020, Nishikawa and his team [17] found that molecular genetic analysis revealed new heterozygous mutations c.188T > A (p.M63K) and c.2546 > A (p.L849X) in AP3B1. It is suggested that when examining OCA patients, blood tests should be performed to confirm neutrophil counts, bleeding time, and platelet agglutination. When HPS2 is suspected, a detailed immunological examination should be considered, and phagocytic lymphohistiocytic hyperplasia and lung lesions should be given immediate and long-term attention.

In 2020, Alizadeh et al. [18] identified two new mutations in patients, including two large deletions of exon 14 and exon 10-25, respectively. Consider the possibility that patient 1 had HPS syndrome type 2. Genetic analysis of AP3B1 revealed a new homozygous complete deletion of exon 14 in the patient. To assess AP3P1 expression in patient 1, RNA was extracted from fresh peripheral blood of patients and their parents. No expression of AP3B1 was detected by RT-PCR. Exon analysis of the genomic DNA of the patient 2 revealed that exons 10 to 25 were missing. The deletion of AP3B1mRNA expression in patients confirmed this result. This study can provide more information to find out the impact and relative contribution of different mutations to the clinical phenotype and severity of the disease.

4.7 New Loci Associated with HPS3 Syndrome

In 2019, Lecchi et al. [19] used Sanger sequencing to reveal a novel pathogenic homozygous variant c.7 > T (p.G 3*) that causes premature termination codons at amino acid 3. In addition, the importance of assessing platelet function in children with OCA without bleeding diathesis and early identification of HPS and prevention of bleeding complications is emphasized.

In 2020, Saito et al. [20] used NGS technology to discover new frameshift variants of HPS3, c.87dupG and c.1426dupA, and at the same time, suggested the importance of genetic detection and electron microscopy studies in the differential diagnosis of HPS and X-linked eye albinism.

In 2021, Wang et al. [21] recruited a family of close relatives with typical HPS phenotypes, such as albinism, visual impairment, nystagmus, and bleeding diathesis. A new homozygous frameset mutation c.1231dupG (p.Aps411GlyfsTer32) of HPS3 was identified and co-isolated in a family member by whole exon sequencing and Sanger sequencing. In addition, real-time PCR confirmed that the mutation reduced the expression of HPS3, which has been identified as a pathogenic gene for the HPS3 type. According to ACMG guidelines, the new mutation causes an early stop codon at amino acid 442 and is a pathogenic variant. The study expanded the spectrum of HPS3 gene variants, contributing to genetic counseling and prenatal genetic diagnosis in families.

4.8 New Loci Associated with HPS6 Syndrome

In 2021, Wang et al. [15] identified three new HPS6 mutation sites in two patients by NGS technology: c.1999C > T (p.Arg667*), c.335G > A (p.W112*) and c.1732C > T (p.R578*). The results are a valuable addition to the few HPS variants reported to date.

4.9 New Loci Associated with HPS8 Syndrome

In 2021, Pennamen et al. [22] used NGS technology to find homozygous 19bp frameshift deletion of c.385_403del (p.Ser129Glnfs*90) on BLOC1S3 gene. In the GnomAD (https://gnomad.broadinstitute.org/) and EVS (https://evs.gs.washington.edu/EVS/) in the database is not reported, ACMG classification: Pathogenic variants (PVS1, PM2, PP1, PP4). Due to the small number of patients currently described, it is difficult to draw formal conclusions about the phenotype associated with HPS8. But this adds to the molecular knowledge of HPS8.

4.10 New Loci Associated with HPS9 Syndrome

In 2021, Liu et al. [23] identified the first case in a Chinese population with two novel pathogenic variants of BLOC1S6 gene, c.148G > T (P.Lu50 *) and c.351dupT (P.LE118tyrfs *10), by whole exon sequencing. The diagnosis is confirmed by electronmicroscopy (EM). No pathogenic variation of platelet dense granule BLOC1S5 is found. Westernblotting showed that the patient was deficient in pallin protein and decreased in abnormal binding protein compared with the parent. Based on the above functional analysis (Westernblotting) evidence, these two variants can be classified as pathogenic variants.

5. Outlook and Summary

There are many reports of albinism at home and abroad, but there are still a few individuals with albinism whose cause has not been found. In addition, for the currently known types of albinism, whether the pathogenic genes have regulatory regions in other locations other than exons remains to be studied. In addition, the existence of unknown types of albinism still needs to be further explored. The logical investigation of epidemiology shows that OCA1 is the main type of albinism in China, accounting for about 64.3%. OCA2, OCA4 and HPS1 accounted for 11.7%, 15.6% and 2.2% respectively. Genes carrying unknown mutations accounted for 6.2%, indicating that there may be some disease-causing genes that have not yet been discovered [1].

In China, there are relatively few reports of HPS, and an accurate correlation between specific HPS gene variants and clinical symptoms has not been established. Recent studies have identified a variety of new variants in HPS patients, which helps to expand the understanding of the HPS variant spectrum and genetic background, and to support the genetic counseling of patients. At the same time, the discovery of these new variants enriches the known variation spectrum and is expected to deepen the understanding of the relationship between phenotype and genotype of HPS, which is of great significance for studying the phenotypic relationship and helping genetic counseling of HPS patients.

Albinism does not necessarily show pigment alterations, and visual alterations should constitute a common and defining

feature of this group of disorders. Importantly, information that people with albinism may not have pigment alterations must be widely available to medical students and practitioners. Two patients reported by the team met only the ophthalmic criteria for OCA diagnosis [24]. Albinism is a disease that is easily overlooked, and in order to avoid the serious consequences of patients not being properly diagnosed, especially in the form of syndromes, more reporting of cases may contribute to a better diagnosis of albinism.

In summary, albinism has evolved from a rare genetic disorder originally known as a single gene (TYR) mutation to one of the most genetically heterogeneous phenotypes, with at least 21 gene mutations and at least 22 different types of albinism identified, and further exploration is needed considering that there may still be unknown types of albinism. The study of albinism is still a very promising area.

Acknowledgement

This paper is supported by the fund project: Medical Science Research Project of Hebei Province in 2024 (20240038).

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