Discovery of Two New Albinism Genes

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This past June, a team of French researchers from Bordeaux University Hospital published two major articles about the discovery of two new albinism genes. The first gene is responsible for a new type of oculocutaneous albinism–OCA8–while the other corresponds to a new form of Hermansky-Pudlak Syndrome–HPS11. In just a week's time, the list of human albinism genes went up from 19 to 21, thus expanding our knowledge about the complexity of albinism genetics.

The two first human albinism genes–TYR and P–were discovered in the late 1980s and early 1990s. Since then, many research studies have shown that the corresponding types of albinism–OCA1 and OCA2–happen to be the most common in the worldwide population. In France, they account for about 50% of all cases of albinism.

When performing the molecular diagnosis of a person with albinism, a geneticist aims to identify the specific DNA that causes the person to have albinism. This is the only way to determine the exact type of albinism of a given person with albinism (PWA). Despite the enormous knowledge on the genetics of albinism that has accumulated over the past three decades and the dramatic improvement of DNA sequencing technologies, today about 25-30% of people with albinism are still left without an answer about their specific genetic sequence. The main explanation for this situation is that more albinism genes might remain to be discovered. This is precisely what the team of Professor Benoît Arveiler of Bordeaux University Hospital has been working on for the past fifteen years, with the financial support of Genespoir, the French association of persons with albinism.

Over the past decade, since genetic testing has been fully covered by public health insurance, more and more people with albinism in France have gotten tested. An increasing number of French healthcare providers are becoming aware of the importance of genetic testing. Professor Arveiler's cohort of patients has dramatically grown as well, being today one of the biggest in the world with over 1,500 PWAs tested. For a researcher, a big cohort of patients usually means more opportunities for studies. This certainly explains how Professor Arveiler's team identified these two new types of albinism, which appear to be exceedingly rare.

Discovery of OCA8

Going through the files of about 250 of their patients whose test had remained unsuccessful, Professor Arveiler's team identified two unrelated persons harboring pathogenic DNA changes in the DCT gene (formerly known as TYRP2). These two women (one of French origin, the other from North Africa) both displayed the typical characteristics of oculocutaneous albinism, but at a milder degree compared to the average albinism population. They both had congenital nystagmus, photophobia, hypopigmentation of the retina, iris transillumination, and a reduced visual acuity (ranging from 20/40-50). Both also have a creamy skin complexion and light-brown hair, thus illustrating a slight oculocutaneous hypopigmentation compared to their respective parents.

The link between these clinical observations and the identified DNA changes was established through experiments performed on animal models, thanks to a close collaboration with the Scottish research team of Professor Ian

Jackson. This latter used the recently developed CRISPR-Cas9 gene editing technology to create mice harboring the exact same DNA changes as the ones of the two women mentioned above. This being done, they then observed an obvious oculocutaneous phenotype in the mice. Additional experiments performed on zebra fish in Bordeaux led to similar conclusions, thus confirming that the gene identified was indeed an albinism gene.

Discovery of HPS11

In the same group of about 250 people with albinism left without a conclusive genetic designation, two other unrelated persons were found to harbor pathogenic DNA changes on a potential new HPS gene: BLOC1S5.

The first one, a 20-year-old woman living in the north of France, had been clinically diagnosed at the age of 2 with a mild form of oculocutaneous albinism. As an adult, after an unsuccessful genetic test, she mentioned to her doctor that she had mild problems of coagulation: tendency to bruise easily in infancy as well as episodes of nose and gingival bleeding occurring once or twice a year and lasting for about a week.

The second person was a 39-year-old woman whose parents come from the same Slovenian village and, although not related, happen to be carriers of the same mutation on the BLOC1S5 gene. The woman's skin and hair pigmentation and her relatively mild visual impairment could easily lead a medical practitioner to a diagnosis of ocular albinism (or mild oculocutaneous albinism). However, many additional clinical features led to suspecting a syndromic form of albinism (namely Hermansky-Pudlak Syndrome): heavy nose bleeding (especially during infancy), easy or unexplained bruising, menorrhagia, excessive blood loss after deliveries, surgery, and dental extraction, as well as abdominal pain, dyspnea, and recurrent infections (pneumonia, herpes, conjunctivitis).

Here again, different experiments were necessary to confirm that the DNA changes found in the BLOC1S5 gene were indeed what caused HPS in these two individuals. Most of these experiments were performed in Professor Michael Marks's lab at the University of Pennsylvania, Philadelphia. It is worth noting that this collaboration between Professors Arveiler and Marks started after they met in Milan, Italy, at the European Days of Albinism, a scientific conference series initiated in 2012 by Genespoir, and now co-organized every two years by Albinism Europe, the network of European albinism support groups.

Discussion

Although OCA8 and HPS11 are very rare types of albinism, their discovery will allow a few more people to get an answer from their genetic test and, through that, to know for sure what causes their health issues. By knowing what exact health condition they have, these people may get access to the most appropriate healthcare available, which is particularly important in the case of HPS, whose specific symptoms can sometimes be extremely serious. While lack of money and convoluted insurance policies may bar some from treatment, especially in the United States, new information will at least provide some clarity.

Conclusions

Promoting research has been one of the main missions of Genespoir since it was founded in France in 1995, and although the association's financial capacities have always remained very limited, the discovery of these two albinism genes confirm today the relevance of the work that has been done so far.

These discoveries would never have been possible without the many donations of private citizens to Genespoir and, above all, without the PWAs asking for genetic testing. Molecular diagnoses might not change anything in the daily life of most PWAs (who already know that they have albinism, thanks to basic clinical examinations), but by getting tested, every PWA contributes to improving our knowledge on the condition, thus making possible the development of future therapies.

List of all known genes responsible for the different types of albinism in 2020

Gene	Classification	Type of albinism
TYR	OCA1	Oculocutaneous Albinism Type 1
OCA2	OCA2	Oculocutaneous Albinism Type 2
TYRP1	OCA3	Oculocutaneous Albinism Type 3
SLC45A2	OCA4	Oculocutaneous Albinism Type 4
n.d.	OCA5	Oculocutaneous Albinism Type 5
SLC24A5	OCA6	Oculocutaneous Albinism Type 6
C10orf11	OCA7	Oculocutaneous Albinism Type 7
DCT	OCA8	Oculocutaneous Albinism Type 8
GPR143	OA1	Ocular Albinism Type 1
SLC38A8	FHONDA	FHONDA Syndrome
LYST	CHS1	Chediak–Higashi Syndrome Type 1
HPS1	HPS1	Hermansky–Pudlak Syndrome Type 1
AP3B1	HPS2	Hermansky–Pudlak Syndrome Type 2
HPS3	HPS3	Hermansky–Pudlak Syndrome Type 3
HPS4	HPS4	Hermansky–Pudlak Syndrome Type 4
HPS5	HPS5	Hermansky–Pudlak Syndrome Type 5
HPS6	HPS6	Hermansky–Pudlak Syndrome Type 6
DTNBP1	HPS7	Hermansky–Pudlak Syndrome Type 7
BLOC1S3	HPS8	Hermansky–Pudlak Syndrome Type 8
BLOC1S6	HPS9	Hermansky–Pudlak Syndrome Type 9
AP3D1	HPS10	Hermansky–Pudlak Syndrome Type 10
BLOC1S5	HPS11	Hermansky–Pudlak Syndrome Type 11