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Implementation of an optimized strategy for genetic testing of the Chinese patients with oculocutaneous albinism

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ABSTRACT

Background: Oculocutaneous albinism (OCA) is a relatively common inherited disorder in all populations worldwide. The mutational spectra of OCA are population-specific.
Objective: Based on our previous molecular epidemiological studies, we have implemented an optimized strategy for the genetic testing of Chinese OCA patients.
Methods: Genomic DNA was extracted from the blood samples of 52 clinically diagnosed OCA patients and 100 unaffected subjects. The amplified DNA segments were screened for mutations of *TYR*, *OCA2*, *TYRP1*, *SLC45A2* and *HPS1* by direct sequencing. To exclude the previously unidentified alleles (PUAs) from polymorphisms, samples from 100 unaffected controls were sequenced for the same regions of variations.
Results: Among the 52 OCA patients, 26 (50.0%) were found mutations on *TYR* gene, 8 (15.4%) on *OCA2*, 12 (23.1%) on *SLC45A2*, 2 (3.8%) on *HPS1*, and 4 (7.7%) patients uncharacterized. We identified 18 PUAs in these patients, 2 in *TYR*, 7 in *OCA2*, 8 in *SLC45A2*, and 1 in *HPS1*.
Conclusion: The optimized method to screen the OCA mutations is efficiently implemented in the routine genetic testing of Chinese OCA patients accompanied with genetic counseling.

1. Introduction

Oculocutaneous albinism (OCA) is an autosomal recessive disorder with a relatively high incidence in Chinese Han population as estimated as 1:18,000 [1]. It manifests as a reduction or complete loss of melanin in the skin, hair, and eyes, often accompanied with eye symptoms such as photophobia, strabismus, moderate to severe visual impairment, and nystagmus. OCA could be caused by mutations in non-syndromic OCA genes (*TYR*, *OCA2*, *TYRP1* and *SLC45A2*) or syndromic OCA genes (*HPS1*, *HPS2*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *HPS7*, *HPS8*, *LYST*, *MYO5A*, *RAB27A* and *MLPH*) [2]. OCA1 is the predominant form which accounts for about 70% of the Chinese OCA patients, while OCA2, OCA4 and HPS1 are less common, reflecting a population-specific distribution of different subtypes of OCA [3].

OCA is clinically characterized as OCA1A, OCA1B or OCA2. OCA1A presents a complete lack of tyrosinase activity and produces a totally depigmented phenotype with affected individuals exhibiting white hair, white skin, and blue, brown or pink iris throughout life. OCA1B is characterized by reduction of tyrosinase activity. Individuals with OCA1B are born with white hair and then change to blond or yellow with age [4]. OCA2 is characterized by yellow, brown or golden hair at birth with or without darkening of hair color at later age. However, the clinically diagnosed subtypes of OCA could be mixed forms of molecularly diagnosed OCA subtypes, such as clinical OCA1 could be molecularly identified as OCA1, OCA2, OCA4 or HPS1, whereas clinical OCA2 could be OCA1, OCA2, OCA4, or HPS1 [3]. Hermansky-Pudlak syndrome (HPS) is a more severe form of OCA. Patients with HPS often die in their middle ages [5]. Therefore, the genetic testing of OCA is needed for routine diagnosis of OCA to better characterize the prognosis of OCA. Based on our previous genetic epidemiological studies of OCA in Chinese Han population, we have implemented an optimized strategy to molecularly screen the mutations on the known OCA genes.

2. Materials and methods

2.1. Study subjects

We recruited 52 unrelated OCA patients (Table 1) and 100 unaffected subjects from the Chinese Han population. The patients

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Table 1
Genotypes of 52 Chinese OCA patients.

Patient ID	Sex	Age	Clinical diagnosis	Molecular diagnosis	Mutational allele 1	Mutational allele 2
TYR						
1	F	8y	OCA1A	OCA1A	c.896G>A (p.R299H)	c.929insC
2	M	31y	OCA	OCA1A	c.929insC	c.929insC
3	M	1m	OCA1	OCA1A	c.346C>T (p.R116X)	c.896G>A (p.R299H)
4	M	3m	OCA1A	OCA1A	c.896G>A (p.R299H)	c.929insC
5	F	25y	OCA1A	OCA1A	c.758G>A (p.G253E)	c.896G>A (p.R299H)
6	F	5y	OCA1A	OCA1A	c.832C>T (p.R278X)	c.896G>A (p.R299H)
7	F	5y	OCA1A	OCA1A	c.832C>T (p.R278X)	c.832C>T (p.R278X)
8	M	21y	OCA1A	OCA1A	c.230G>A (p.R77Q)	c.896G>A (p.R299H)
9	M	22y	OCA2	OCA1B	c.832C>T (p.R278X)	c.IVS2-7T->A and IVS2 10delTT
10	F	2y	OCA1A	OCA1A	c.714G>A (p.W238X)*	c.929insC
11	F	3y	OCA1A	OCA1A	c.832C>T (p.R278X)	c.896G>A (p.R299H)
12	F	1m	OCA1	OCA1A	c.71G>A (p.C24Y)	c.832C>T (p.R278X)
13	F	1m	OCA1	OCA1A	c.929insC	c.896G>A (p.R299H)
14	M	30y	OCA1A	OCA1A	c.1168C>G (p.H390D)	c.1255G>A (p.G419R)
15	M	29y	OCA1A	OCA1A	c.832C>T (p.R278X)	c.896G>A (p.R299H)
16	M	32y	OCA1A	OCA1A	c.896G>A (p.R299H)	c.929insC
17	M	2m	OCA1	OCA1A	c.895C>A (p.R299S)	c.896G>A (p.R299H)
18	F	57y	OCA1A	OCA1A	c.632A>G (p.H211R)	c.232insGGG
19	F	2y	OCA2	OCA1A	c.230G>A (p.R77Q)	c.1265T>A (p.M426 K)
20	M	28y	OCA1A	OCA1A	c.896G>A (p.R299H)	c.1196delA*
21	F	5y	OCA1B	OCA1B	c.896G>A (p.R299H)	c.1265G>A (p.R422Q)
22	F	4m	OCA1B	OCA1A	c.896G>A (p.R299H)	c.929insC
23	F	32	OCA1B	OCA1	c.164G>A (p.C55Y)	–
24	M	11	OCA2	OCA1B	c.1204C>G (p.R402G)	–
25	M	1m	OCA2	OCA1	c.575C>A (p.S192Y) # rs1042602	–
26	M	20y	OCA1	OCA1A	c.929insC	–
OCA2						
27	F	2y	OCA1B	OCA2	c.1560-1562delCCT*	c.1610A>T (p.Y537F)*
28	F	3y	OCA2	OCA2	c.1255C>T (p.R419W)	c.2491G>C (p.A831P)*
29	F	3m	OCA2	OCA2	c.1349C>T (p.T450M)	c.1001C>T (p.A334V)
30	M	25y	OCA2	OCA2	c.1423A>G (p.T475A)*	–
31	M	8m	OCA2	OCA2	c.1182+1G>A*	–
32	F	3m	OCA2	OCA2	C.1327G>A (p.V443I)	–
33	M	7m	OCA1B	OCA2	c.1193T>C (p.V398A)*	–
34	M	3m	OCA2	OCA2	c.406C>T (p.R136X)	–
SLC45A2						
35	F	7y	OCA2	OCA4	c.478G>C (p.D160H)	c.478G>C (p.D160H)
36	M	13d	OCA1B	OCA4	c.663-665delCTC*	c.663-665delCTC
37	F	24y	OCA2	OCA4	c.478G>C (p.D160H)	c.478G>C (p.D160H)
38	F	8d	OCA	OCA4	c.328G>A (p.G110R)	c.1210G>A (p.G404R)*
39	M	6m	OCA2	OCA4	c.143-145delGCT*	c.478G>C (p.D160H)
40	F	1m	OCA2	OCA4	c.478G>C (p.D160H)	c.1304C>A (p.S435Y)*
41	F	7m	OCA1	OCA4	c.168-173delGACCCC*	–
42	M	6y	OCA2	OCA4	c.551C>T (p.A184V)*	–
43	F	1m	OCA1B	OCA4	c.152-153delTG*	–
44	M	7m	OCA1	OCA4	c.1033-2A>T (IVS4-2A>T)*	–
45	M	2m	OCA1	OCA4	c.1519G>C (p.V507L) # rs3733808	–
46	M	28y	OCA2	OCA4	c.152-153delTG	–
HPS1						
47	F	1m	OCA1B	HPS1	c.391C>T (p.R131X)	c.965insC
48	F	6m	OCA2	HPS1	c.1885delC*	c.1885delC
Uncharacterized						
49	M	4y	OCA2	OCA2?	c.1441G>A (p.A481T)# rs74653330	–
50	F	4m	OCA2	?	–	–
51	M	11m	OCA2	?	–	–
52	M	13	OCA1A	?	–	–

The descriptions in the parentheses denote mutations at protein level. A novel allele appeared the first time in this table is marked with a star (*) symbol. A dash in the mutation column denotes uncharacterized allelic mutation. A question mark represents unconfirmed genotype. A symbol (#) indicates a very rare SNP in this population. In the column of "Age", 'y' = year; 'm' = month; 'd' = day.

were from 19 different provinces of China in the Chinese Albinism Registry [6]. None of these patients have a family history of consanguinity. We followed the criteria for the differentiation of OCA1A, OCA1B and OCA2 as described [3]. Among the 52 OCA patients, thirty were clinically diagnosed as OCA1A or OCA1B, twenty were diagnosed as OCA2 and two OCA patients were not differentially diagnosed due to unclear onset history (Table 1). In all the 52 OCA patients, white skin, blue or brown iris and mild to severe nystagmus were observed. This study was approved by the Internal Review Board of the Bioethics Committee of the Institute of Genetics and Development Biology, Chinese Academy of Sciences. The study was conducted according to Declaration of Helsinki Principles. Written informed consents were obtained and 8 ml peripheral blood samples were collected from all subjects participating in this study.

2.2. DNA amplifications

The optimized strategy for the DNA amplifications of the five OCA genes, *TYR*, *OCA2*, *TYRP1*, *SLC45A2* and *HPS1*, was followed as described [3]. Total genomic DNA was extracted from blood samples by the routine proteinase K/SDS method. Standard PCR amplification procedures were conducted with an annealing temperature of 57–59 °C for all primers. The primer sequences