Original Article

Differential Diagnosis of Two Chinese Families with Dyschromatoses by Targeted Gene Sequencing

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Abstract

Background: The dyschromatoses are a group of disorders characterized by simultaneous hyperpigmented macules together with hypopigmented macules. Dyschromatosis universalis hereditaria (DUH) and dyschromatosis symmetrica hereditaria are two major types. While clinical and histological presentations are similar in these two diseases, genetic diagnosis is critical in the differential diagnosis of these entities.
Methods: Three patients initially diagnosed with DUH were included. The gene test was carried out by targeted gene sequencing. All mutations detected on *ADAR1* and *ABCB6* genes were analyzed according to the frequency in control database, the mutation types, and the published evidence to determine the pathogenicity.
Results: Family pedigree and clinical presentations were reported in 3 patients from two Chinese families. All patients have prominent cutaneous dyschromatoses involving the whole body without systemic complications. Different pathogenic genes in these patients with similar phenotype were identified: One novel mutation on *ADAR1* (c. 1325C>G) and one recurrent mutation in *ABCB6* (c. 1270T>C), which successfully distinguished two diseases with the similar phenotype.
Conclusion: Targeted gene sequencing is an effective tool for genetic diagnosis in pigmentary skin diseases.

Key words: Dyschromatoses; Dyschromatosis Symmetrica Hereditaria; Dyschromatosis Universalis Hereditaria; Targeted Gene Sequencing

Introduction

Dyschromatoses are a group of disorders clinically characterized by hyperpigmented macules together with hypopigmented macules of various sizes.[1] Dyschromatosis universalis hereditaria (DUH; Online Mendelian Inheritance in Man [OMIM] 127500, 615402 and 612715) and dyschromatosis symmetrica hereditaria (DSH; OMIM 127400) are two classic forms of dyschromatoses.[2] DSH is characterized by a symmetrical distribution of hyperpigmented and hypopigmented macules over the dorsa of the hands and feet, while DUH shares similar skin lesion but occurs in a more generalized distribution – presenting as a generalized leukomelanoderma with sparing of the palms, and soles. But for DSH patient, the skin lesion can also be extensive, involving face, upper trunk, forearm, and shank. Histology or electron microscope examination is not completely capable to distinguish two diseases. Differentiation can be challenging in clinical practice. In fact, they were considered to be phonotypical variation of the same entity, until recently it was demonstrated that these diseases were genetically distinct disorders. DUH is caused by heterozygous mutations in *ABCB6* gene, while DSH is caused by mutations in *ADAR1* gene. Genetic evaluation can help clinicians determine the precise diagnosis, and provide etiotropic treatment and

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prognosis. Recently, targeted gene sequencing is proved to be an efficient method for the clinical genetic test.

Here, we reported three cases of dyschromatoses from two Chinese families initially diagnosed with DUH, until targeted gene sequencing revealed a novel *ADAR1* gene mutation in one family and a recurrent *ABCB6* gene mutation in another family.

Methods

Patient recruitment, blood sampling, and DNA extraction

Careful physical examinations and hospital medical record reviews were performed for each affected member to confirm the clinical diagnosis. Digital photographs were taken, and peripheral blood samples were collected from 3 patients. Genomic DNA was isolated from peripheral blood leukocytes according to the standard instructions of the manufacturer using a QIAamp DNA Blood MiNi Kit (Qiagen, Germany). The study was approved by Ethics Committee of Beijing Genomic Institute (BGI), and all patients provided written informed consents.

Targeted capture and next generation sequencing

The exons, splicing sites and 10 bp flanking intron sequences of *ADAR1* and *ABCB6* genes were captured by a gene chip commercially ordered from NimbleGen (Roche NimbleGen, Madison, WI, USA). A previously described pipeline was used to capture targeted sequences and prepare sequencing library.[3] The capture library was sequenced on Hiseq2500 platform (Illumina, San Dieago, CA, USA) for a 100-bp paired-end run by BGI (Shenzhen, China).

Data analysis

Image acquisition, image processing, error estimation, and base calling were processed by Illumina Pipeline (version 1.3.4) during the run. Low-quality reads and adaptor contamination were removed from primary data as described previously.[4] Clean reads (in FASTQ format) were aligned to the reference human genomic sequence (NCBI37/gh19) of *ADAR1* and *ABCB6* genes by using BWA software package (Burrows Wheeler Aligner, http://www.sourceforge.net/projects/bio-bwa/).[5] Variants (single nucleotide variants and small insertion) were identified using the GATK Genotyper (http://www.broadinstitute.org/gsa/wiki/index.php/).[6] Variant call format files including variants basic information were annotated using a BGI in-house developed annotation pipeline, which generate a file contain mutation name, frequency of control database, disease information, and software prediction result. The control database used in the pipeline are 1000 genome database (http://www. 1000genomes.org), dbSNP database, and a BGI in-house database, which included 2087 normal subjects. Phylop (phyloP46wayPlacental) was used to calculate the conservation for each missense mutation.

Sanger sequencing

Identified mutations were confirmed by Sanger sequencing. Primers used for amplification of *ADAR1* gene are 5'-AAACCCCATCCCTCTGACTG-3' (forward) and 5'-AGGAGAGAGAGGCTTGGAGA-3' (reverse), and primers used for amplification of *ABCB6* gene are 5'-AAGATCTCTCTCTGGGCAGC-3' (forward) and 5'-AGGGAGAGGAGGTAAGAGGG-3' (reverse). Purified PCR products from the same primers and PCR conditions was performed in both directions on an ABI 3730XL Genetic Analyzer (PE Applied Biosystems, Forest City, CA, USA) and analyzed with the sequencer software (Sequencing Analysis 5.2) from ABI (PE Applied Biosystems).

Results

Clinical features

The proband (patient 1) in family 1 was a 17-year-old male who had a history of progressive and asymptomatic mottled hyperpigmentation spreading over almost the entire body. The lesions appeared when he was 2 years old and initiated from his abdomen. The hyperpigmentation had extended progressively to his face, neck, and limbs over the years. Spotty hypopigmentation amongst the hyperpigmented macules were also noticed in this patient [Figure 1b and 1c]. He did not have a history of photosensitivity or a significant history of drug intake. He was born of nonconsanguineous parents by normal pregnancy and spontaneous vaginal delivery. Mental and physical development appeared normal. His father, uncle, and grandfather had a history of similar skin lesions [Figure 1a], which indicated a possibly autosomal dominant inheritance pattern.

On physical examination, hypopigmented and hyperpigmented macules and patches with various shapes and sizes were observed all over the body in a symmetrical pattern in this patient. The lesion was more obvious on the face, trunk, and the dorsum of both hands and both feet. The palms and soles, mucous membranes, teeth, nails, and hair appeared normal. No obviously telangiectasia, erythema, or atrophy was observed.

The patient 2 was a 9-year-old girl who was born to nonconsanguineous parents with a normal pregnancy and delivery. The lesion appeared initially from her dorsal hands since 1-year-old and progressively extended to her face, neck, trunk, and limbs over years. Similar lesions also appeared in her father (patient 3) since infancy. Physical examination revealed mixed hypopigmented and hyperpigmented macules, 3–11 mm in diameter on her limbs and hyper-/hypo-pigmented macules 1–2 mm in diameter on her trunk [Figure 2]. There was also no palm, sole or mucus membranes involvement.

Targeted sequencing of *ADAR1* and *ABCB6* genes

The exons and adjacent intronic sequences of *ADAR1* and *ABCB6* genes were captured and sequenced for the DNA samples of 3 patients. The *ADAR1* gene consists of 15 exons and 40 kbp, and *ABCB6* gene consists of 19 exons and 9 kbp. The 10X coverage rate of both genes is more than 99% for each sample. Sequencing depth and coverage statistics for each exon of two genes are listed in Supplementary

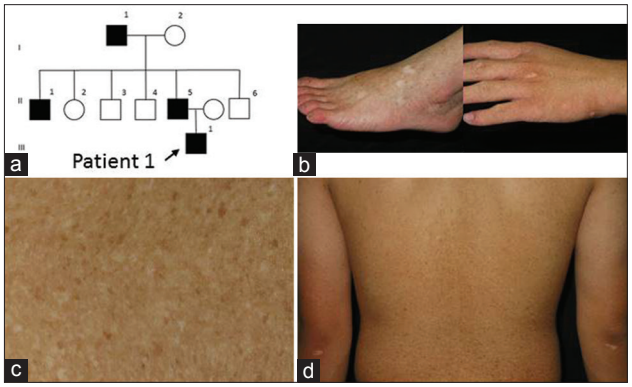

Figure 1: Pedigree and clinical features in patient 1. (a) Pedigree of family 1. The proband presented with mottled hyperpigmented (c) and hypopigmented macules on his trunk (d), dorsum of hands and feet in a symmetrical pattern (b).

Material 1. Eighteen variants in total were identified on *ADAR1* and *ABCB6* genes after reads alignment and variants calling. Six variants were identified on each gene for each sample [Table 1]. The identified pathogenic mutations were confirmed by Sanger sequencing for 3 patients.

Identification of pathogenesis mutations by targeted gene sequencing

Of all identified variants, those with frequency more than 1% in control databases or not functionally affecting the protein were considered as benign and filtered out. After the filtration, one heterozygous mutation on *ADAR1* (c. 1325C>G) in patient 2 and patient 3, and one heterozygous mutation on *ABCB6* (c. 1270T>C) in patient 1 were left as candidate disease-causing mutations.

The c. 1325C>G of *ADAR1* shared by patient 2 and patient 3 from a family is a novel nonsense mutation and has not been reported in any previously publication, which introduced a premature stop codon on amino acid 442 (Ser442Ter, full size of protein is 1227). This variant was not detected in any control database and was predicted to be null function mutation. Nonsense mutations in *ADAR1* gene have been reported to be pathogenic for DSH patients (such as c. 1969A>T [p.Lys657Ter] behind the Ser442Ter). Thus, the variant was highly likely pathogenic.

The c. 1270T>C of *ABCB6* gene, leading to a change of Tyr to His at an evolutionary conserved 424 amino acid in protein sequence, is absent in all control databases and has been reported in two DUH patients from a Chinese family.

The result from Sanger sequencing validation was consistent with next generation sequencing result [Figure 3], but the other family members of patients refused to accept the genetic test. The two mutations showed strong evidence of the pathogenesis though no family segregation data were available.

Discussion

DUH was described firstly by Ichikawa *et al*. in 1933. It is usually an autosomal dominant disorder, but autosomal

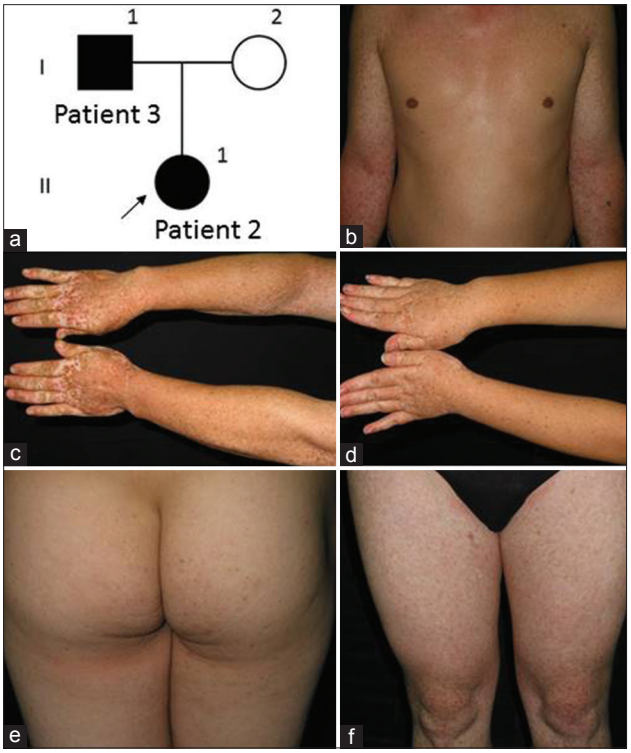

Figure 2: Pedigree and clinical features in family 2. (a) Pedigree of family 2. Both patient 2 and patient 3 presented with extensive mixed hypopigmented and hyperpigmented macules involving trunk, thigh, button and dorsal limbs. Patient 2 presented with similar lesion (d and e) and distribution with patient 3 (b-f), but with lighter pigmentation.

recessive inheritance has also been reported.[7] Clinically, it is characterized by generalized distributed hyper- and hypo-pigmented macules in a reticulate pattern, involving the trunk and limbs. The lesions usually appear in infancy or early childhood, develop after puberty and persist throughout life without a significant change in color or distribution. Systemic abnormalities are not frequent in DUH patients. A few DUH cases have been reported to have abnormalities of hair and nails, dermal connective tissue, and nerve tissue.[8] Mutations in the *ABCB6* gene (ATP-binding cassette transporter) have been reported to be the pathogenesis mutation in DUH patients in 2013 by Zhang *et al*.[9] Only 9 mutations have been reported in DUH (p.S170G, p.S322K, p.S322R, p.L356P, p.Y424H, p.A453V, p.Q555K, p.G579E, and c. 459delC) until now.[9-12]

DSH is an autosomal dominant disorder first described in 1929 by Kondo *et al*.[13] It is characterized by freckle-like macules on the face, and a mixture of hyperpigmented and hypopigmented macules of various sizes on the dorsum of the hands and feet.[2] DSH patients are more associated with neurologic abnormalities such as mental deterioration, dystonia, and seizure.[14] Pathogenic mutations of the *ADAR1* gene, which encodes for a double-stranded RNA-specific adenosine deaminase, were identified to cause DSH by Miyamura *et al*.[15] Until now, more than 130 of various mutations have been reported.[14]

Although both diseases have similar skin lesions that appear from early life, DSH meanly affects face and dorsum of

Table 1: Summary of all variants identified in *ABCB6* and *ADAR1* genes

Patient number	Genes	Transcripts	Exons	Function	cHGVS	pHGVS	rsID	Zygosity	Fr. 1	Fr. 2	Fr. 3	PhyloP
1	*ABCB6*	NM_005689.2	EX6	Missense	c. 1270T>C	p.Tyr424His	Not available	Het	0	0	0	2.288
	ABCB6	NM_005689.2	EX1	Coding-synon	c. 117G>A	p.(=)	rs1109866	Hom	·	·	·	·
	ABCB6	NM_005689.2	EX1	Utr-5	c.−58C>A	–	rs1109867	Hom	·	·	0.02	·
	ABCB6	NM_005689.2	EX1	Utr-5	c.−260G>A	–	rs4674369	Hom	·	·	0.03	·
	ADAR1	NM_001111.4	EX2	Missense	c. 1151A>G	p.Lys384Arg	rs2229857	Hom	0.61	0.62	0.67	0.459
	ADAR1	NM_001111.4	EX2	Coding-synon	c. 78G>A	p.(=)	rs1802645	Hom	0.99	0.99	0.37	−0.361
2	*ABCB6*	NM_005689.2	EX1	Coding-synon	c. 117G>A	p.(=)	rs1109866	Hom	·	·	·	·
	ABCB6	NM_005689.2	EX1	Utr-5	c.−58C>A	–	rs1109867	Hom	·	·	0.02	·
	ADAR1	NM_001111.4	EX9	Coding-synon	c. 2682G>A	p.(=)	rs1127309	Het	0.3	0.31	0.29	0.655
	ADAR1	NM_001111.4	EX2	Nonsense	c. 1325C>G	p.Ser442	Not available	Het	·	·	·	0.561
	ADAR1	NM_001111.4	EX2	Missense	c. 1151A>G	p.Lys384Arg	rs2229857	Het	0.6	0.62	0.67	0.459
	ADAR1	NM_001111.4	EX2	Coding-synon	c. 78G>A	p.(=)	rs1802645	Hom	0.99	0.99	0.37	−0.361
3	*ABCB6*	NM_005689.2	EX1	Coding-synon	c. 117G>A	p.(=)	rs1109866	Het	0.25	0.23	0.19	·
	ABCB6	NM_005689.2	EX1	Utr-5	c.−58C>A	–	rs1109867	Het	0.24	0.23	0.02	·
	ADAR1	NM_001111.4	EX9	Coding-synon	c. 2682G>A	p.(=)	rs1127309	Het	0.29	0.31	0.29	0.655
	ADAR1	NM_001111.4	EX2	Nonsense	c. 1325C>G	p.Ser442	Not available	Het	·	·	·	0.561
	ADAR1	NM_001111.4	EX2	Missense	c. 1151A>G	p.Lys384Arg	rs2229857	Het	0.61	0.62	0.67	0.459
	ADAR1	NM_001111.4	EX2	Coding-synon	c. 78G>A	p.(=)	rs1802645	Hom	0.99	0.99	0.37	−0.361

When two alleles are different, it is defined as Het; otherwise, it is defined as Hom. Fr. 1 represents frequency in dbSNP database; Fr. 2 represents frequency in 1000 genome database; Fr. 3 represents frequency in BGI in-house database. HGVS: Human Genome Variation Society; −: Not applicable; ·: Frequency not recorded; rsID: dbSNP database ID.

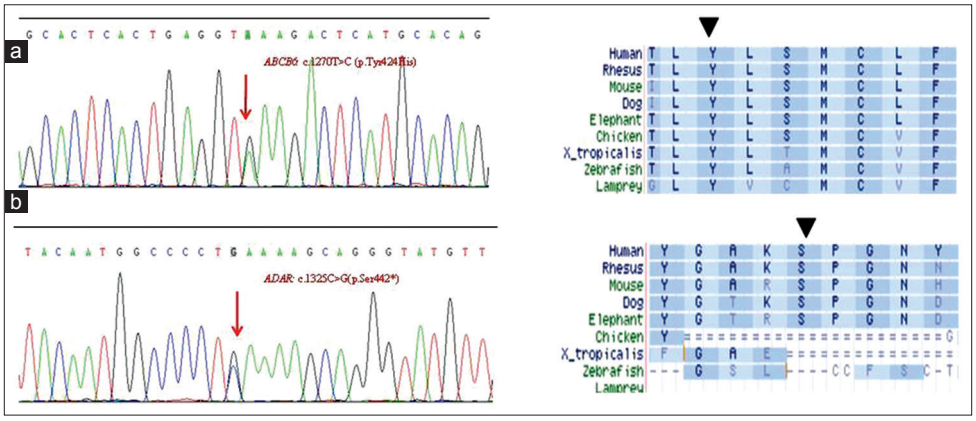

Figure 3: Sanger sequencing validation of mutated genes. (a) Heterozygous mutation of c. 1270T>C in *ABCB6* gene in patient 1. (b) Heterozygous mutation of c. 1325C>G in family 2. Partial sequence of *ABCB6* and *ADAR* genes was compared with other species orthologs (directly cut from the University of California Santa Cruz [UCSC] website). Both areas were highly conservative. Arrows indicate the location of the two mutations.

the extremities, while DUH presents with more widespread lesion, involving both trunk and extremities, with facial lesions presenting in about 50% of affected individuals.[1] Some reports also described that DSH affects the neck and upper chest.[16] In early stage of the disease, the lesion can be localized and with a light color. Differentiation with clinical experience in these two diseases can be challenging.

Histological or ultrastructural skin investigation provides limited evidence in the differentiation of DUH and DSH. Histological studies have showed a focal increase or decrease melanin pigmentation in the basal layer in both diseases, depending on the type of lesion biopsied[13] and occasionally pigmentary incontinence in DUH.[8] A normal amount of morphologically intact melanocytes was present in the basal layer in hypopigmented skin areas in DUH patient. While in DSH, the number of the melanocytes in the hypopigmented areas was significantly lower than that of normal skin. Electron microscopic examination revealed degenerative vacuolation in melanocytes in depigmented lesions in both diseases.[8,13] In DSH, small and immature melanosomes sparsely distribute in the melanocytes in the hyperpigmented region, while there were many small melanosomes singly disperse or aggregate in the adjacent keratinocytes.[13] In DUH, the hyperchromic macules contain a lot of fully melanized melanosomes forming melanosome complexes. Within the hypopigmented macules, melanocytes and keratinocytes also contain considerable amounts of melanosomes, but the content in melanosomes is less than normal.[10,17,18] As the difference is very delicate, and the process for histology and electron microscope examination is complex, genetic analysis is

key to differential diagnosis of these two diseases under certain circumstances.

In our cases, patients had extensive skin lesions with simultaneously occurring hyper- and hypo-pigmentation, fully developed after puberty, with no tendency of spontaneous remissions, and no poikiloderma, alopecia or signs of malignancy. The initial clinical diagnosis was DUH. As both patients had prominent acral involvement, DSH was considered to be an important differential diagnosis. Gene detection is applicable in our case and is promising in clarifying the clinical diagnosis.

Gene detection was carried out on both of the pathogenic genes. As *ABCB6* contains 19 exons and spans 9 kbp, and *ADAR1* contains 15 exons and spans up to 40 kbp. Due to the large sizes of these regions, traditional technologies may be time and cost prohibitive. We chose targeted gene capture to test these two genes and identified pathogenic mutations of different genes in these patients with similar phenotype: c. 1270T>C in *ABCB6* gene and c. 1325C>G in *ADAR1*gene, and both mutations showed strong evidence of pathogenicity. These results proved that patient 1 was DUH and patient 2 was DSH, despite their highly resembled clinical presentation. Skin lesions in patient 2 were different from the classic distribution in DSH and mimicked the distribution of DUH lesion, involving the flexural areas of extremities and trunk. By genetic approach, we achieved accurate clinical diagnosis and provided genetic evidence for the prenatal test in descendants.

Targeted gene sequencing provides us with a new prospective in genetic diagnosis of highly heterogeneous genodermatosis as its low costing and high accurate level, especially in pigmentary dermatosis. There are more than 10 genes which can lead to cutaneous dyschromias and more than 60 in pigmentary dermatosis.[18] Different diseases, such as xeroderma pigmentosum[19] and dermatopathia pigmentosa reticularis,[20] need to be distinguished in clinical practice.[21] Timely and accurate genetic diagnosis will save patients from unnecessary laboratory tests and provide etiotropic suggestions.

In conclusion, we present the clinical features of 3 patients with dyschromatoses, who were initially diagnosed as DUH. A novel mutation in the *ADAR1* gene and a recurrent mutation in *ABCB6* gene were identified in two pedigrees. This allows us to successfully distinguish two diseases with similar phenotype, indicating that targeted gene sequencing could be an effective tool for molecular diagnosis in pigmentary skin diseases.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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