

INVESTIGATIVE REPORT

Platelet-derived Growth Factor Receptor Alpha Gene Mutations in Vitiligo Vulgaris

Shengxin XU^{1,2}, Youwen ZHOU^{1–3}, Sen YANG^{1,2}, Yunqing REN^{1,2}, Chi ZHANG^{1,2}, Cheng QUAN^{1,2}, Min GAO^{1,2}, Caifeng HE^{1,2}, Hui CHEN^{1,2}, Jianwen HHAN^{1,2}, Jianjun CHEN^{1,2}, Yanhua LIANG^{1,2}, Jianqiang YANG^{1,2}, Liangdan SUN^{1,2}, Xianrong YIN^{1,2}, Jianjun LIU^{1,2} and Xuejun ZHANG^{1,2}

¹Institute of Dermatology & Department of Dermatology, The First Affiliated Hospital, Anhui Medical University, ²The Key Laboratory of Gene Resource Utilization for Severe Genetic Diseases, Ministry of Education and Anhui Province, Hefei, Anhui, China, and ³Cheng Genomics Center and Laboratory of Predictive Medicine and Therapeutics, Vancouver Coastal Health Research Institute, and Department of Dermatology and Skin Science, University of British Columbia, Vancouver, Canada

Vitiligo vulgaris is an acquired depigmenting disorder resulting from the loss of melanocytes in the skin. Though several putative susceptibility loci of vitiligo have been identified in different populations, the pathogenesis of the disease remains poorly understood. Through genetic linkage analysis of a large Chinese family cohort of vitiligo, we identified a vitiligo linkage locus AIS4 within chromosome 4q12-q21, a region containing several possible candidate genes, including the platelet-derived growth factor receptor alpha (*PDGFRA*) gene. We postulated that PDGFR mutations may be linked with vitiligo. To test this hypothesis, we performed DNA sequencing on this gene in 143 multiplex families with familial vitiligo vulgaris, 480 patients with sporadic vitiligo vulgaris, and 480 healthy subjects. Mutations were found in 3.5% of familial vitiligo cases, which is significantly higher than for the general population (0.42%, $p=0.008$, Fisher's exact test), and possibly higher than in sporadic vitiligo patients (1.0%, $p=0.053$). To our knowledge, this is the first observation that *PDGFRA* mutations are linked with familial vitiligo vulgaris. **Key words: *PDGFRA*; gene; mutation; vitiligo.**

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Xuejun Zhang, Institute of Dermatology, Anhui Medical University, 69 Meishan Road, Hefei, Anhui 230032, China. E-mail: ayxj@vip.sina.com

Vitiligo vulgaris (MIM193200) is an acquired, non-contagious disorder in which progressive loss of viable melanocytes results in patchy pigmentation of the skin, hair and oral mucosa (1). It affects all populations worldwide, with diverse prevalence rates ranging from 0.1% to 2% among different geographical regions and ethnic groups (1). In some cases the disorder is associated with other syndromes, such as autoimmune diseases (2, 3). At present, it is generally accepted that the pathogenesis of the disease is multifactorial and genetically heterogeneous (4). Mutations or polymorphisms in several genes have been associated with development of vitiligo

(5–8). However, together they account for only a small proportion of the genetic susceptibility for vitiligo. Recent gene mapping studies have identified several major susceptibility loci for vitiligo (9), including evidence for a major vitiligo susceptibility locus on chromosome 4q12-q21 (*AIS4*) in the Chinese population (10). However, the genes responsible have not been identified.

The platelet-derived growth factor receptor alpha (*PDGFRA*) gene is a proto-oncogene that maps to 4q12. It belongs to the human type III family of transmembrane receptors, with an intrinsic tyrosine kinase component. The *PDGFRA* protein has been shown to be important for several cellular and tissue processes, such as proliferation, apoptosis, chemotaxis, melanogenesis, hematopoiesis and gametogenesis (11). Several reports have documented *PDGFRA* in regulation of pigmentation. First, a deletion encompassing the *PDGFRA* gene, found in Patch (Ph) mutant mice, initially studied by Gruneberg & Truslove (12), is associated with defective melanocyte migration in heterozygotes leading to the development of white patches on the trunk. Secondly, several reports have documented that vitiligo is severely exacerbated by protein tyrosine kinase inhibitor therapy (13). Thirdly, platelet-derived growth factor (PDGF) has been shown to be important for the differentiation and survival of melanocytes during embryonic development (14). These reports lead us to speculate that the *PDGFRA* gene may be a candidate susceptibility gene of vitiligo mapped to the region of 4q12, and prompted us to sequence the coding region of this gene in a large number of familial and sporadic vitiligo cases using healthy individuals as the controls. Our results show that a small, but not insignificant, number of patients with familial vitiligo carry mutations in the *PDGFRA* gene, significantly more than the general population, supporting a role for this gene in the development of at least some cases of vitiligo.

MATERIALS AND METHODS

Subjects

The subjects studied were recruited from three different populations: the vitiligo families, sporadic cases, and controls. A total

of 143 multiplex vitiligo Chinese Han families, including the 106 pedigrees used in our previous genome-wide linkage study (10), were recruited from the Dermatology Department of the Anhui Medical University and the Vitiligo Clinic of the Railway Hospital, Xiangfan, Hubei, China. Each family had at least two siblings with vitiligo. We first sequenced one case in each family (the family proband). We then determined the mutation status at the mutation site for the rest of the members (both affected and unaffected) of the probands carrying the mutations. Furthermore, the sites of the *PDGFRA* gene carrying the mutations were sequenced in 480 sporadic vitiligo cases and an equal number of controls, recruited from the same institutions.

The diagnosis of vitiligo was made on the basis of patient's history and typical clinical features consisting of discrete, well-circumscribed and depigmented patches. Phenotypes were determined by history, lesion maps, physical examination and/or photographs. Any individual whose phenotype was questionable was excluded from this study, in particular atypical lesion distribution and congenital depigmentation. Only patients with clear signs of acquired patches on the extremities, trunk, genitalia, central face, or other areas were classified as affected. All the participating individuals provided informed written consent. The study was approved by the ethics committee of Anhui Medical University and was conducted according to Declaration of Helsinki principles.

Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes using a standard procedure (15). We designed primers flanking the entire coding sequence, exon-intron junctions, promoter regions and 5'- and 3'-untranslated regions of *PDGFRA* using the web-based version of the Primer 3.0 program (<http://frodo.wi.mit.edu/primer3/>). Primer sequences were available on request. A polymerase chain reaction (PCR) was performed in 10 µl reaction volume containing 20 ng of genomic DNA, 0.3 mM dNTPs, 0.3 µM of each primer, 3.0 mM MgCl₂ and 0.1 units of Hotstar® Taq DNA polymerase (Qiagen, Hilden, Germany). The PCR conditions were: Hotstar® Taq activation at 95°C for 15 min, followed by 40 cycles, each having denaturation at 94°C for 40 s, annealing at 57°C for 60 s and extension at 72°C for 55 s, except that in the first 14 cycles the annealing temperature decreased

Table I. Five rare *PDGFRA* mutations in three different populations (the vitiligo families, sporadic cases, and controls)

PDGFRA mutations	Protein designations	Position	Frequency		
			Families	Sporadic	Control
c.367-3C>T ^a		Intron 4	0/143	1/480	0/480
c.418G>T	p.V140L	Exon 4	1/143	0/480	0/480
c.2986G>A	p.E996K	Exon 22	1/143	0/480	0/480
c.3098A>T	p.D1033V	Exon 22	2/143	4/480	2/480
c.3154A>T	p.T1052S	Exon 23	1/143	0/480	0/480
Total			5/143 (3.5%)	5/480 (1%)	2/480 (0.4%)

^aThis mutation is located in the acceptor splice site and could prevent proper splicing of the transcript.

from 64°C to 57°C by 0.5°C per cycle, and the final extension was 72°C for 10 min. After the amplification, products were purified using a QIAquick PCR Purification Kit (Qiagen) and directly sequenced on ABI PRISM® 3730 automated sequencer (Applied Biosystems). Sequence comparisons and analysis were performed using Phred-Phrap-Consed Version 12.0 program. The A of the ATG of the initiator Met codon is denoted as nucleotide +1. *PDGFRA* GenBank sequences used: NM_006206 (mRNA); NP_006197 (protein).

RESULTS

We first screened for sequence variants of *PDGFRA* in genomic DNA samples from one affected individual (proband) from each of 143 families affected with vitiligo. Four non-synonymous mutations (c.418G>T, p.V140L; c.2986G>A, p.E996K; c.3098A>T, p.D1033V; and c.3154A>T, p.T1052S) were identified in the *PDGFRA* gene (Table I and Fig. 1). The four mutations were found in a total of five families. None of these sequence variants have been listed in the National Center for Biotechnology Information (NCBI) or Celera single nucleotide polymorphism (SNP) databases.

To investigate whether these mutations co-segregated with vitiligo, we analyzed all available DNA samples from all members of the above five families affected with vitiligo. The pedigrees of the five families showing the mutation status and phenotypic information for each member are shown in Fig. 2. The missense mutation c.3098A>T (p.D1033V) was observed in two different families, and the remaining mutations affected single families only. In every case, the mutations co-segregated with the vitiligo phenotypes within the affected families.

We further evaluated the association between these mutations and vitiligo by screening 480

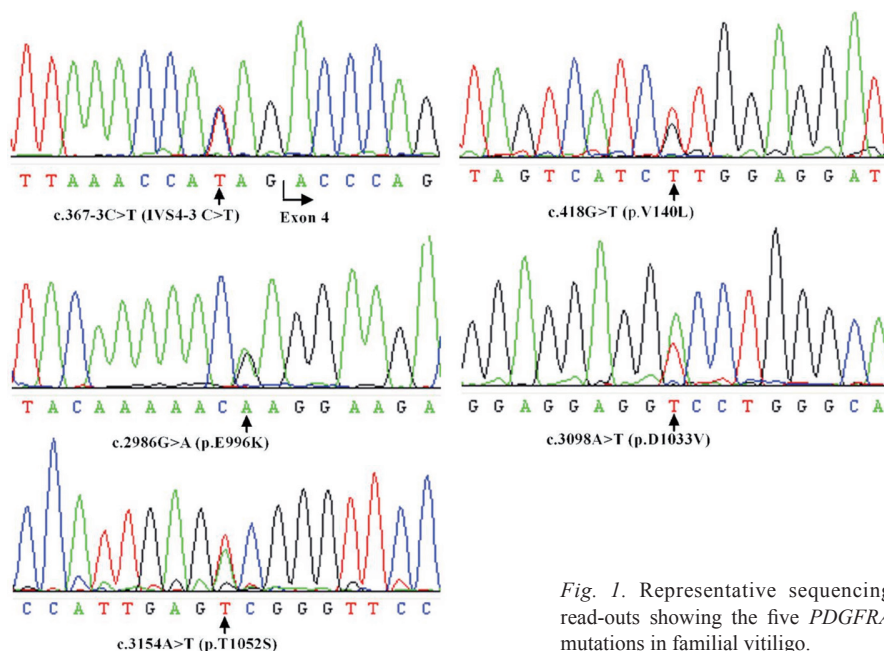


Fig. 1. Representative sequencing read-outs showing the five *PDGFRA* mutations in familial vitiligo.

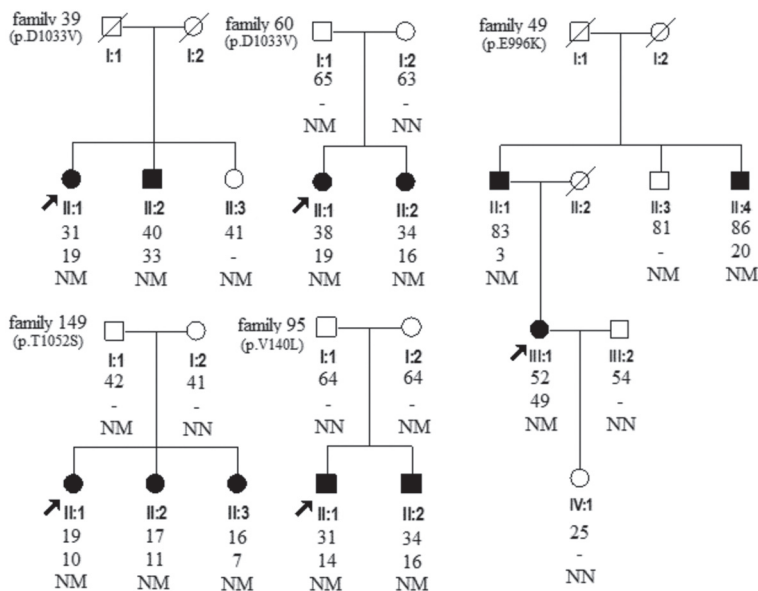


Fig. 2. Pedigrees representing the five generalized vitiligo families with *PDGFRA* mutations identified in this study. The probands are indicated by arrows. Black symbols denote affected individuals and unfilled symbols denote the unaffected individuals. Under each symbol, the first line corresponds to the current age of subjects; the second line shows the age at diagnosis of overt generalized vitiligo (when known). The third line shows the genotype at *PDGFRA* gene: N: normal allele; M: mutant allele.

sporadic cases and 480 controls. It was found that 5 of 480 (1%) sporadic vitiligo vulgaris patients carry mutations in the *PDGFRA* gene, compared with 2 of 480 (0.42%) of control unaffected subjects (Table I). Of note, *PDGFR* mutation rate in familial vitiligo cases (3.5%) is significantly higher than in the control population (0.42%, $p=0.008042$, Fisher's exact test), probably higher than in sporadic vitiligo patients (1.0%, $p=0.053306$), although the mutation rates between sporadic vitiligo and control populations were not significantly different ($p=0.225704$). More clinical details of the patients are presented in Table II.

DISCUSSION

In the present study, we have identified five novel mutations in the *PDGFRA* gene associated with vitiligo. To our knowledge, this is the first time that *PDGFRA*

has been implicated as a predisposing gene for development of vitiligo.

PDGFRA is a gene that spans 23 exons. It encodes a transmembrane protein composed of five immunoglobulin-like domains in the extracellular region, a transmembrane domain, an adenosine-triphosphate binding site, and a hydrophilic kinase insert domain in the intracellular portion (16). Upon binding to the extracellular immunoglobulin-like domains with the ligand (PDGF), *PDGFR* proteins form dimers, leading to the activation of the intrinsic tyrosine kinase activity. Four of five *PDGFRA* missense mutations described here, the p.V140L, p.E996K, p.D1033V, and p.T1052S, are linked to an autosomal-dominant form of vitiligo (Fig. 3). The p.V140L point mutation is localized to exon 4 of *PDGFRA*, which encodes parts of the extracellular domain of *PDGFRA*, which may modulate ligand-binding and dimerization, thereby indirectly influence tyrosine kinase activity.

Table II. Clinical features of patients with platelet-derived growth factor receptor alpha mutations

Patient ID		Sex/age (years)	Onset (years)	Clinical type	Course	Severity	Other autoimmune disease	Mutation
Family F-039	II1	F/31	19	Universal	Progressive	Moderate	Not observed	c.3098A>T
	II2	M/40	33	Universal	Progressive	Moderate	Not observed	
Family F-060	II1	F/38	19	Localized	Stable	Mild	Chronic urticaria	c.3098A>T
	II2	F/34	16	Localized	Stable	Mild	Not observed	
Family F-149	II1	F/19	10	Localized	Decubation	Mild	Not observed	c.3154A>T
	II2	F/17	11	Generalized	Decubation	Mild	Not observed	
	II3	F/16	7	Generalized	Decubation	Mild	Not observed	
Family F-095	II1	M/31	14	Localized	Decubation	Mild	Not observed	c. 418G>T
	II2	M/34	16	Acrofacial	Stable	Mild	Not observed	
Family F-049	III1	M/83	3	Generalized	Stable	Moderate	Not observed	c.2986G>A
	II4	M/86	20	Generalized	Stable	Moderate	Not observed	
	III2	F/52	49	Localized	Progressive	Mild	Diabetes mellitus	
Sporadic	case307	F/20	20	Localized	Stable	Mild	Not observed	c.367-3C>T
Sporadic	case156	M/11	8	Localized	Progressive	Mild	Not observed	c.3098A>T
Sporadic	case191	M/24	20	Localized	Stable	Mild	Not observed	c.3098A>T
Sporadic	case197	M/15	13	Localized	Stable	Mild	Not observed	c.3098A>T
Sporadic	case389	M/11	9	Generalized	Progressive	Mild	Not observed	c.3098A>T

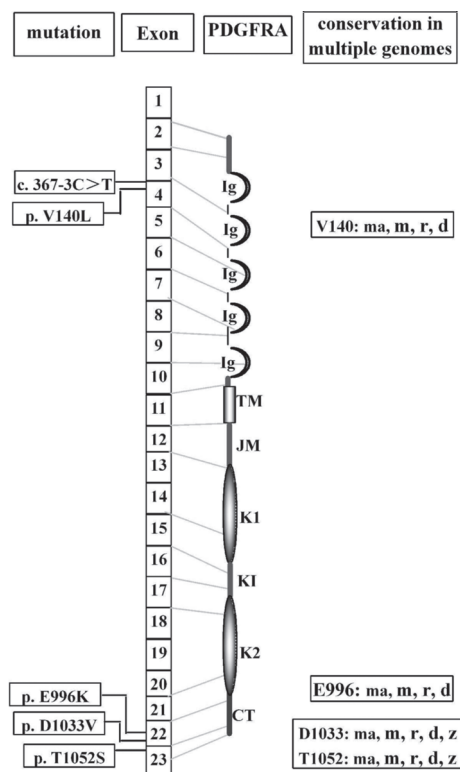


Fig. 3. Location of the mutations in the PDGFRA protein. The locations of the mutations identified in this study are shown on the left. The results from protein alignment of multiple genomes are shown on the right. Ig: immunoglobulin-like domains; TM: transmembrane domain; JM: juxtamembrane domain; K1: kinase insert; K1: kinase domain I; K2: kinase domain II; CT: C-terminal tail; Ma: *Macaca fascicularis* (crab-eating macaque); m: *Mus musculus* (mouse); r: *Rattus norvegicus* (Norway rat); d: *Canis familiaris* (dog); z: *Danio rerio* (zebrafish).

The other three missense mutations (p.E996K, p.D1033V, and p.T1052S) are localized to the C-terminal tail of PDGFRA. The exact function of these missense mutations found in this study is unknown. It is known that the C-terminal region from residue 977 to 1024 of PDGFRA is required for ligand-dependent focus formation, and that the tyrosine residues 988 and 1018 located within this domain constitute the major binding site for phospholipase C- γ (PLC- γ) (17). Therefore, the three mutations identified in this study may interfere with the catalytic actions of the PDGFRA, although more studies are needed to verify this possibility. Finally, the c.367-3 C>T mutation was identified in one sporadic patient. This mutation is located in the splice acceptor site and may result in mis-splicing of the PDGFRA transcript.

PDGFR is a receptor tyrosine kinase that is known to be required for melanocyte development. Several lines of clinical observation suggest that proper function of receptor tyrosine kinase receptor signaling pathways are required for melanocyte viability in mature adult human skin: First, Legros et al. (13) have observed a marked progression of a vitiligo after treatment with tyrosine kinase inhibitors in a patient with stable vitiligo

for many years. Secondly, several cases of vitiliginous depigmentation occurring after treatment with new tyrosine kinase inhibitors (STI-571 and SU11428) have been reported (18–21). Imatinib mesilate is a selective inhibitor of several tyrosine kinases, such as PDGFRA and KIT, another melanocyte receptor shown to be required for melanocyte survival. Previously, most of the explanations for the observed effect of tyrosine kinase inhibition on melanocyte survival focused on the role of KIT receptor. However, our results suggest that PDGFR, which also is inhibited by the same inhibitors, could also be responsible, or contribute to the death of melanocytes in patients undergoing tyrosinase kinase inhibitor therapies.

It should be pointed out that the number of pedigrees containing PDGFRA mutations is low overall, and thus cannot explain the major linkage signal observed in the initial genome-wide linkage studies (10). Therefore, additional candidate genes in the 4q12 region, such as KIT gene, may still exist in addition to the PDGFRA gene. Detailed investigation of KIT gene in the familial vitiligo cases is in progress, and will be reported elsewhere.

Vitiligo is a complex disease that is strongly influenced by both genetic and environmental factors. While the pathogenesis is unknown, multiple hypotheses have been proposed to explain the clinical observations. The most commonly referred pathogenesis mechanisms include: genetic hypothesis (9) or intrinsic hypothesis (22, 23), autoimmune hypothesis (24), autocytotoxic hypothesis (25) and neural hypothesis (26). Our results are consistent with the genetic/intrinsic hypothesis. Two general models of complex diseases have been proposed. One is the common disease–common variant model, which holds that genetic susceptibility to common diseases is conferred primarily by alleles that are common in the population and have modest phenotypic effects (27, 28). This model is supported by a number of well-validated examples (29–32). The alternative model is that susceptibility to common diseases is the result of multiple rare alleles with large phenotypic effects (common disease–rare variant model). Although individually rare, these alleles may be collectively common in the population (33–35).

In summary, we have discovered that mutations of PDGFRA gene are associated with vitiligo development in a small number of cases of familial and sporadic vitiligo in China. This observation lends support to the genetic/intrinsic hypothesis of vitiligo pathogenesis. Specifically abnormalities in the genes involved in melanocyte survival/viability may lead to melanocyte death, causing vitiligo.

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