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Original Article

Surfactant protein A1 mutation Arg219Trp: a potential cause of familial idiopathic pulmonary fibrosis

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Abstract: Increasing attention has been directed toward clarifying the relationship between genetic mutations and onset of familial idiopathic pulmonary fibrosis (FIPF). We identified one FIPF family with two patients, and sampled whole blood of all family members followed by DNA extraction and detection to identify shared gene mutation sites. The results were analyzed and summarized after reviewing related studies in the literature. A total of 52 exons from seven genes were detected in eight family members, with 16 mutation sites identified among the *SFTPA1*, *SFTPA2*, *SFTPB*, *SFTPC*, and *TERT* genes. Among these, *SFTPA1* Arg219Trp mutation, which is a missense mutation that can lead to amino acid changes, was only found in onset patients and their children. *SFTPA1* Arg219Trp mutation should be regarded as a potential cause and a target for further studies of FIPF.

Keywords: *SFTPA1*, Familial idiopathic pulmonary fibrosis, mutation, exon

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common type of interstitial pneumonia and is characterized by dyspnea, lung infiltration, and ventilation dysfunction [1]. Familial IPF (FIPF) is defined as IPF occurring in two or more members of the same primary biological family [2, 3]. The criteria used to define FIPF and sporadic cases are the same. FIPF may develop at an earlier age and seem to have different patterns of gene transcription. The proportion of FIPF among all IPF cases is reportedly 0.05%-2.2% in the UK [4] and 3.3%-3.7% in Finland [5]. Less than 5% of total patients with IPF is FIPF [6]. The familial aggregation of IPF has prompted some researchers to investigate the genetic components underlying IPF in recent years. Some of these studies have reported that, in addition to the slightly earlier onset of FIPF compared with sporadic IPF, there is no obvious difference between these two types of IPF in terms of symptoms, lung function, imaging, and other aspects [4, 7]. However, genetic studies of FIPF present a convenient and effective way to further elucidate the pathogenesis of disease onset and development. Current researches on the genetic involvement in IPF have centered on the following genes: *SFTPA1* [8], *SFTPA2* [9], *ELMOD2* [10], *SFTPB* [8], *SFTPC* [11-13], *TERT* and *TERC* [14, 15], *et al*. The results of previous studies have suggested that some mutations to these genes were associated with the development of IPF. To date, only one study by Zhang *et al*. [8] has investigated genetic mutations in FIPF among the Chinese Han population. In the current study, exons in the above genes were identified in all members of a single family with FIPF and compared with the mutations reported by Zhang *et al*. [8] to further identify FIPF-related gene mutations in the Chinese Han population.

Cases report

Informed written consent of this study was obtained from all patients and their family members.

Medical history and family information of the proband

The proband of the current study was a 64-year-old female, who was admitted to our hospital

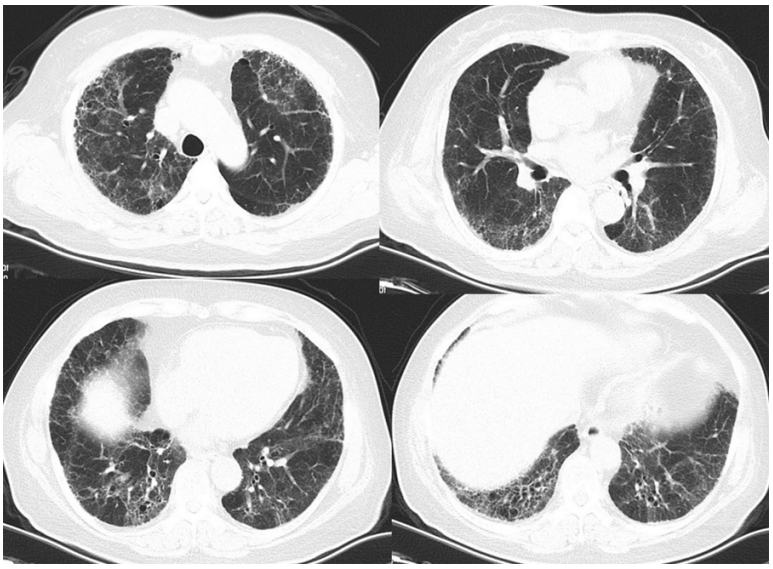

Figure 1. Computed tomography scan of the proband (II.1) before acute exacerbation shows reticulations and subpleural honeycombing in the basal lateral portions of the both lungs.

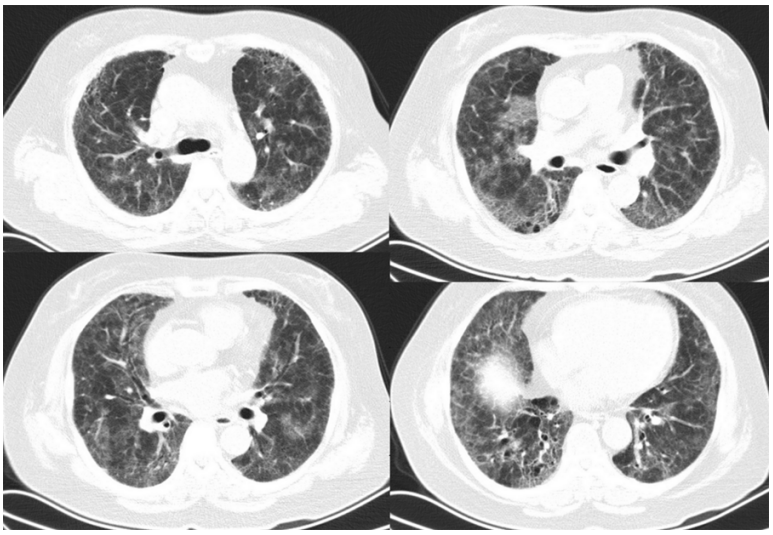

Figure 2. Computed tomography scan of the proband (II.1) at the onset of acute exacerbation shows diffuse areas of ground glass attenuations superimposed on underlying fibrotic opacities throughout both lungs.

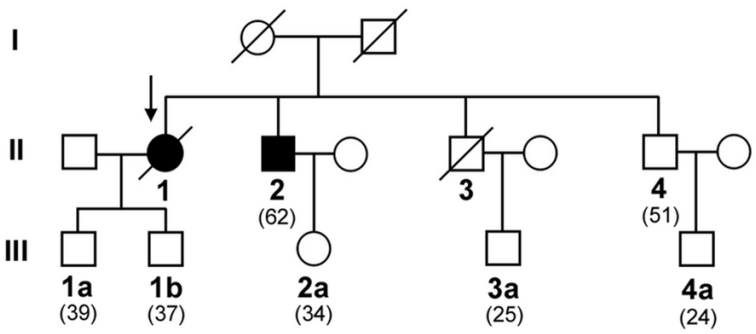

Figure 3. Pedigree of a family with familial idiopathic pulmonary fibrosis (FIPF). This pedigree represents a three generation pedigree and all encoding members participated in this study. Two individuals in generation II (II.1 and II.2) had documented idiopathic pulmonary fibrosis (IPF). II.1 was the proband and her age at diagnosis and death was 61 and 64 years. Age of II.2 at diagnosis was 62 years. II.3 died from lung cancer. (□ male, ○ female, ↓ proband, ■● patient/dead, numbers in brackets are ages of family members when drawing blood).

because of repeated coughing and a 3-year history of shortness of breath, which was aggravated for 1 month before presentation, with no apparent cause for the occurrence of cough or shortness of breath. A chest computed tomography (CT) scan revealed pulmonary interstitial fibrosis. To control the disease, the patient was treated with oral acetylcysteine and tripterygium, as well as intermittent administration of oral glucocorticoid hormones. Pirfenidone was used orally for 10 days, but no significant improvement was observed and symptoms gradually worsened 1 month prior to admission, which was combined with fever and body temperature as high as 39°C. The patient's medical history also included hypertension and hypothyroidism, which were treated with oral amlodipine, valsartan, bisoprolol, and levothyroxine. The primary symptoms of IPF observed during aphysical examination at admission were a typical audible Velcro sounds within both lungs, but no clubbing. Findings of blood gas analysis on admission were as follows: pH 7.45, $PaCO_2$ 41 mmHg, PaO_2 68 mmHg, and SaO_2

Table 1. PCR primers

Genes	Coding regions	Forward sequences (5'-3')	Reverse sequences (5'-3')	Size (bp)
ELMOD2	Exon2	TGCCATTGTTTTTAAATGCCTA	GTCAAAGCGGGACTTCAGAG	447
	Exon3	AGGTAATGAGGTTGGTGTCA	TACCTCTAAACGGGGAAAAT	400
	Exon4	TGGGTTTATTTTGCATTTTT	GATCTCAACTGCTCCTCTTG	363
	Exon5	TATTTAAGGTGGCCTTTGGT	TCTAAGGGCAAAGAAACCAT	399
	Exon6	TGCGTGTTTTAGGATAATTG	CTGCAGTTATTAAAATTCAGAGA	400
	Exon7	GAAGCATTTGTGAATCACTG	GGTTTACAATCACATTTTTCCT	398
	Exon8	GTCTATAGTCCCCCTGACCCC	GGGGACCCATCTTCCACTGT	590
	Exon9	AAGTCCCTCAGGCTTCTAAT	GGTACCTTTGGAGAACAGTG	496
SFTPA1	Exon2	CACAGCAGGGATGAGGACAG	GGCTTCCAACACAAACGTCC	561
	Exon3	CACAGCAGGGATGAGGACAG	GTCACCCACAACTGGTTGGA	925
	Exon4	CCACGGAGTGATAGAGTGAT	GCTTTCTCCCTCAAGCTTAT	392
	Exon5	CGCCTAACAGCAATGAAA	GTGCATGCCTATTTGTAATCT	298
	Exon6	TCTGAAGGGTGAATGCGGAC	CCTGCTGGAACACTACCTGG	1949
SFTPA2	Exon3	AGGTGATGCTTGGAATTTT	AGTCCCACCCAGCTTACTAT	482
	Exon4	ATAGTAAGCTGGGTGGGACT	GCTTTCTCCCTCAAATTCAT	475
	Exon5	AGAGTTCCAGGATTGCAG	ATCATTCCTTTCCCCAAC	300
	Exon6	GACTGGGGAGAATCTGGTA	CCAGCTCTAATAGCCACAAG	598
SFTPB	Exon2	CCAGGACAGGTGGTAAGG	TGTGACCTTGGATAAGCTCT	396
	Exon3	TGACGTCCACATGTTTAATG	ATTTCATCTCATCCCATTTC	380
	Exon4	GGATGAGATGGGACAAGTT	TCTCTGGCTGTGCTATTGA	400
	Exon5	CCTACATGTGCCCAACTACT	TAGTTTCCTAGGCCCTTTGT	756
	Exon6	CCCCCACATAGAGTTCTAAA	TCTCTTCCTCCCTTTCTCTC	490
	Exon7	GGGAAGGTGATAGGAAGC	CTCTCTCCCCTCCTAACTTC	353
	Exon8	GATCCCCAGTGTCCTTATTT	CCCTACAGAGGTGTTTGGT	469
	Exon9	CTCTCCTCCTCCCCCTAC	AACTTACAGTCCCACCATTG	441
	Exon10	GTTTCAACTGCAGCCAGA	TTTTTACACTGAAACAGAGAGG	394
	Exon11	GAGGGGTCTACAGAGTCACA	AAAGGGTGTTTTCCTGATG	399
SFTPC	Exon1	AGGAACAAACAGGCTTCAA	CCCATCCTGACTTATCACAG	330
	Exon2	AAGCCTTCTCTGATCTCCTC	CTCTTTCCTTCTAGCTGTGC	445
	Exon3	GGGGCACAGCTAGAAGGA	GTTGGGCACGGGAGTCAT	513
	Exon4	CACATCCATCTCTCCCTCT	ATAGGAGAGGGGCAGTCA	400
	Exon5	GGTGGCTTCTGACTCTAGC	AATGTTGAGGATGGACAGAG	500
TERC	Exon1a	GAACTTTAATTTCCCGTTCC	CTGACAGAGCCCAACTCTT	454
	Exon1b	CACCGTTCATTCTAGAGCA	CTCACTGCCCATTCATTTT	472
TERT	Exon1	GAGTTTCAGGCAGCGCTGCGTC	CAGGTGAACCAGCACGTCGTCGC	624
	Exon2a	GTGGCCCAGTGCCTGGTGT	CTATGGTTCCAGGCCCGTTC	571
	Exon2b	GCTAGTGGACCCCGAAGG	CCTGGAACCCAGAAAGATG	540
	Exon2c	CCTCCTTCCTACTCAGCTCT	ACGTGACGATGGAGACAG	653
	Exon3	GGTGGGCTGTATGTGTGT	CAGAATCCACTTGGACCAG	698
	Exon4	CTATAGGACCAGGTGTCCAG	TTCTTGTGGTCCTCAGAGC	636
	Exon5	CAAACAGGGTCTGAGGAAG	TGTGTCCTCAACAGTGACAG	475
	Exon6	GCCGGATCCACTTTCCTGACTGT	CACAGACACGACTGCATTCTAGAC	450
	Exon7	CTGTAGCTACTTTGCGTCCT	AGGCACACAGCTCATCAT	436
	Exon8	GCACTTCATCACAAACACTG	CAGAAAAGGAGACTCTGGTG	326
	Exon9	GTTCAGAGGTCTCATCTGGT	ACCTTGTCTGGTTCCTCAA	399
	Exon10	GTAGAGAGCTCGTCTGTTGG	ACTCACCACGTGTGTAACCT	494
	Exon11	GTTCTTGCATGCTCACCTAC	AGAAAGATGCATTTCTGCTC	584
	Exon12	TGGAGTCCATGGAGTGAG	CAGTCACCATCAGCCTTG	393

Exon13	GCAGATGACACAGAGTCTTGA	AGCACCACTGAAAACGTAAG	399
Exon14	TACAGATGGTGCACAGAAAC	GGTTAAACCACTTCCTGATG	489
Exon15	AACATTTCTGTCGTGACTCC	CACCAGCGTTTAATCACATA	455
Exon16	CGTCCTAGGGAGGGTTGGA	CACTCAGGCCTCAGACTCC	300

94%. After admission, the patient was diagnosed with IPF based on her medical history and imaging findings (**Figure 1**). The patient received routine treatment, but her condition gradually worsened. With acute exacerbation of IPF shown in the second chest CT scan (**Figure 2**), the patient eventually died. Since the brother of the proband was also diagnosed with IPF, these cases were suspected to be FIPF (**Figure 3**). The mother of the proband died from colon cancer and her father died from laryngeal cancer. The proband's sibling (II.3) died from lung cancer. II.1, II.2 and II.3 had a history of smoking. After obtaining informed consent, whole blood samples were collected from a total of eight family members of the proband, including the proband, her brothers, and their children.

Genetic testing

The blood samples were collected in anticoagulant tubes, centrifuged at 5000 rpm for 20 min, and the separated serum was stored at -80°C until assayed. DNA was extracted and gene sequence analysis was performed by the Beijing Genomics Institution (Beijing, China). A total of 52 exons were identified in seven genes [8] (**Table 1**).

Results

We examined 52 exons from seven genes identified in eight members of the family, including two with IPF and one of their siblings, as well as the children of these three. A total of 16 mutations were found among *SFTPA1*, *SFTPA2*, *SFTPB*, *SFTPC*, and *TERT*, five of which were found to be both homozygous and heterozygous mutations (**Table 2**). Among them, there were 10 missense mutations, five cds-synon mutations, and one UTR-5 mutation. There were five benign alleles, one untested allele, one allele of uncertain significance, and the rest were identified as non-applicable (NA).

We identified two gene mutations (His39 and Arg219Trp) present in patients II.1 and II.2 and their children (III.1a, III.1b and III.2a), but did not appear in other family members. Among these, Arg219Trp is a heterozygous missense mutation that can lead to a change in the amino acid sequence, while His39 is a synonymous mutation.

Discussion

Genetic factors play an important role in the pathogenesis of IPF, suggesting that IPF is a genetic disease [16]. Most FIPF cases show autosomal dominant heredity with mutations to *SFTPA*, *SFTPC*, or *TERT/TERC* occurring in 15%-20% of cases [17]. Santangelo *et al*. [18] summarized studies of gene mutations or polymorphisms in IPF, which included some FIPF-related genes, such as *SFTPC*, *TERT/TERC*, and *MUC5B* (Mucin 5b), but did not mention the mutations identified in the current study. Since FIPF is a multi-gene disease and the distribution of genetic polymorphisms is also related to race and region, results obtained from different populations may be completely different. There are relatively few studies of genetic mutations in IPF among the Han population, with only one report by Zhang *et al*. [8]. In the present study, genetic testing was conducted in eight family members, and Arg219Trp mutation at exon 6 of *SFTPA1* was detected for the first time in FIPF.

Mutations at site Arg219Trp were found in two IPF patients (II.1 and II.2) and their children, but not their unaffected siblings (II.4) or other family members, suggesting that this genetic mutation may be related to FIPF and might be the onset site for this family. *SFTPA1* codes for a lung surfactant protein, a member of the C-type lectin family, which binds to specific carbohydrate moieties on lipids and the cell surface of microorganisms. *SFTPA1* plays an important role in the maintenance of surfactant homeostasis and defense against respiratory tract pathogens. *SFTPA1* mutation is associated with several chronic respiratory diseases, such as lung fibrosis and cancer in adult patients [19]. The content of this protein in the alveolar lavage fluid of IPF patients was found to be increased, as compared to controls [20].

Table 2. Sequence variants in candidate genes identified in all familial members

Genes	Locations	Allele change	Residue changes	Clinical significance	Functional consequence	Patients
SFTPA1	Exon2	NA > T	NA	NA	Intron variant	1, 2, 4, 1a, 1b, 2a
	Exon3	CAC > CAT#	His39	NA	Intron variant	1, 2, 1a, 1b, 2a
	Exon3	CTC > GTC#	Leu50Val	NA	Intron variant, missense	4a
	Exon6	TAT > TAC	Tyr184	With benign allele	Synonymous codon	4, 4a
	Exon6	TAT > TAC	Tyr184	With benign allele	Synonymous codon*	3a
	Exon6	CCC > CCT#	Pro216	NA	Synonymous codon	2
	Exon6	CGG > TGG	Arg219Trp	With uncertain significance allele	Missense	1, 2, 1a, 1b, 2a
SFTPA2	Exon3	ACC > AAC#	Thr9Asn	NA	Missense	3a, 4a
	Exon4	GCT > CCT#	Ala91Pro	NA	Missense	2
	Exon6	TCC > TCT#	Ser140	NA	Synonymous codon	1, 2, 4, 2a
	Exon6	TCC > TCT#	Ser140	NA	Synonymous codon*	1a, 1b
	Exon6	CAG > AAG#	Gln223Lys	NA	Missense	1a, 1b
SFTPB	Exon2	CAC > CCC#	His2Pro	With benign allele	Missense, upstream variant	1, 4, 1a, 1b, 3a
	Exon2	CAC > CCC#	His2Pro	With benign allele	Missense, upstream variant*	2, 2a, 4a
	Exon3	GGA > AGA	Gly76Arg	NA	Missense, upstream variant	4a
	Exon5	ACT > ATT	Thr143Ile	With benign allele	Missense	4a
SFTPC	Exon4	ACT > AAT	Thr138Asn	With benign allele	Missense, upstream variant	1, 4, 1b, 4a
	Exon4	ACT > AAT	Thr138Asn	With benign allele	Missense, upstream variant*	1a, 2a
	Exon5	AGC > AAC	Ser186Asn	With benign allele	Intron variant, missense, upstream variant	1, 4, 1b, 4a
	Exon5	AGC > AAC	Ser186Asn	With benign allele	Intron variant, missense, upstream variant*	2, 1a, 2a
TERT	Exon2	GCG > GCA#	Ala305	With untested allele	Synonymous codon	1a, 1b, 3a, 4a

Note: #Also reported by Zhang *et al*. [8]. *Homozygous mutation.

Selman *et al*. [21] conducted Arg219Trp genetic studies in 54 patients with IPF and identified the Arg219Trp mutation in 22.2% (12/54) of cases, which was significantly different from the detection rate of 7.8% (8/103) observed in a normal population ($P = 0.02$). The site mutations identified in the current study resulted in structural changes to proteins, suggesting that such mutations could lead to structural or functional changes to the pulmonary surfactant protein, thereby increasing the susceptibility of patients to certain diseases under certain conditions, especially IPF. Sumita *et al*. [22] reported that this gene mutation was associated with concomitant interstitial lung disease in patients with systemic sclerosis (SSc), indirectly confirming the close relationship between this mutation and IPF. However, the above study did not treat FIPF as an independent factor and no previous study has investigated the relationship between this gene mutation and FIPF. In the current study, both patients carrying the Arg219Trp mutation passed it on to their children (III.1a, III.1b, III.2a), while the mutation was not present in other healthy family members, suggesting that the Arg219Trp mutation may have been involved in the pathogenesis of FIPF in this family. The present study is the first to report a correlation between Arg219Trp and FIPF in a Chinese Han population. However, due to the limited sample size, further studies with larger sample sizes are needed to explore the relevance of this mutation in FIPF.

Due to the characteristics of IPF itself, disease onset usually occurs in middle age. There were only two onset patients in this family, II.1 and II.2. Although their children may inherit the gene mutation that increases the risk of FIPF, we cannot prove that the gene mutation do cause illness, since the children have not yet reached the age associated with an increased incidence of IPF. Therefore, long-term follow-up observations and analysis of more FIPF family members are required to further elucidate the relationship between gene mutation and disease onset and progression. Although one of the brothers of the proband (II.4) has reached the age associated with a higher incidence of IPF, he did not develop FIPF, which might be due to the lack of inheritance of the gene mutation associated with IPF onset or necessary interactions between genes. Therefore, close follow-up is needed.

According to the detection and analysis results of the candidate genes in the family members, many genetic factors may affect the development of IPF. Understanding FIPF has important significance in allowing us to obtain an improved understanding of the pathogenesis of IPF. In the present study, a total of 16 mutations were identified in a Chinese family with FIPF. The Arg219Trp mutation of exon 6 in the *SFTPA1* may have potential susceptibility in the development of FIPF. We propose for the first time that the mutation should be used as a target for further in-depth studies of the FIPF population and the pathophysiological mechanisms need to be further elucidated.

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Disclosure of conflict of interest

None.

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