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# Advances in Molecular Genetics and Gene Diagnosis of Marfan Syndrome

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## Abstract

**Marfan syndrome (MFS) is a hereditary connective tissue disease involving multiple organ system lesions. MFS is autosomal dominant, and FBN1 is the pathogenic gene of the disease. In recent years, with the deepening research on the pathogenesis of MFS, FBN1 mutation plays a more and more important role in clinical diagnosis, which promotes the improvement of diagnostic criteria. People have also developed rapid gene detection technology for FBN1 to benefit more patients.**

## Keywords

**Marfan Syndrome; FBN1 Mutation; Gene Diagnosis; Gene Detection.**

## 1. Introduction

Marfan syndrome (MFS; OMIM: 154700) is a connective tissue disease involving multiple organ system manifestations caused by mutations in extracellular matrix protein fibrillin 1[1]. In 1896, Antoine Bernard Marfan, a professor of Pediatrics in Paris, first reported the special signs of Gabrielle, a 5-year-old girl. She had severe skeletal abnormalities, such as slender limbs and subarachnoid hemorrhage, and died early[2,3]. Therefore, people named this syndrome MFS, and it took nearly 50 years to elaborate on this syndrome. The incidence of classic MFS is about 2–3 cases per 10 000 individuals/adults. The incidence may be underestimated by various factors, for example, the early phenotype of patients is not obvious, clinicians omit signs with important diagnostic value, or lack of efficient and rapid molecular diagnosis methods[1]. In China, the incidence of classic MFS is about 1-2/10000[4], and its main clinical manifestations generally involve multiple systems and organs, such as cardiovascular system, skeletal system, ocular lesions, etc. Some cases do not show all systemic manifestations, but only some features. These cases are called atypical MFS. 75% of MFS cases are acquired by familial inheritance, with a definite family genetic history and autosomal dominant inheritance, but about 25% of MFS cases are sporadic cases caused by de novo mutations[1,5]. In 1955, Victor McKusick[6] first described the cardiovascular diseases of patients with Marfan syndrome in detail, and more than 90% of the deaths were caused by cardiovascular diseases[7]. Almost all MFS patients have life-threatening aortic aneurysm or aortic dissection, which is also the main cause of death and shortened life span. Early studies found that the life span of patients is only about two-thirds of that of normal people[7]. Patients with aortic root dilation greater than 5cm have a higher risk of death. They usually die of sudden rupture of aortic aneurysm without time to rescue[8]. The life expectancy of patients is close to normal with the progress of diagnostic technology, drugs and surgical treatment[9]. Therefore, early diagnosis and timely treatment of MFS are very important.

At present, it is known that MFS is an autosomal dominant disease. It is mainly caused by mutations of fibrillin 1 (FBN1) gene, which encodes a glycoprotein, namely FBN1. The protein is the main component of extracellular matrix. Most mutations will affect the amino acids of the protein. The decrease or abnormality of FBN1 will lead to tissue weakness, the increase of

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transforming growth factor β (TGFβ) signal and the loss of cell matrix interaction, eventually lead to various phenotypes of Marfan syndrome[10]. With in-depth understanding and research on the pathogenesis, the diagnostic criteria of MFS are constantly enriched and improved. At present, diagnosis of MFS is based on the revised "Ghent" standard in 2010, which emphasizes the diagnostic value of clinical manifestations of cardiovascular system and skeletal system. Family genetic history should also be as an important reference, but the final diagnosis must be made in combination with comprehensive clinical evaluation and genetic testing[1,10].

## 2. Clinical Manifestations of Marfan Syndrome

The clinical manifestations of Marfan syndrome are diverse, involving multiple organ systems, and there are great differences among different individuals. According to the classification of human body system, the clinical manifestations of skeletal system mainly include long bone overgrowth and unbalanced body proportion; the arm span is usually more than 1.05 times the height without severe scoliosis. The human body is divided into upper and lower segments by the line connecting the upper edge of pubic symphysis. The length of the lower segment in patients with MFS is greater than that of the upper segment, and the proportion of the upper and lower segments is reduced. The excessive growth of ribs pushes the sternum forward, resulting in pigeon chest or pectus excavatum. Overgrowth of fingers can cause spider finger deformity. Due to excessive finger length and wrist relaxation, the patient usually has a positive wrist indication that the distal thumb and the distal fifth finger overlap completely when the finger is wrapped around the opposite wrist. Steinberg thumb sign occurs when the distal thumb is folded completely beyond the ulnar border on the palm. Most patients have thoracolumbar scoliosis, but only scoliosis > 20 ° can be included in the diagnostic criteria of skeletal manifestations[11]. In addition, the dysfunction of hip joint and knee joint caused by acetabular protrusion and flat foot are also common. Overactivity caused by joint relaxation is common, but a few cases have normal or even contracture joints. Most MFS patients have several skeletal manifestations, but few MFS families lack skeletal features[12]. MFS patients present special craniofacial features, such as dolichocephaly, arched jaw, tooth crowding, retrognathic, flat zygomatic, and palpebral aperture, etc.[13,14]. These special craniofacial features are not specific to MFS, and often overlap with other diseases, so they are not included in the main diagnostic criteria.

Ocular manifestations are common, including increased axial length of eyeball, decreased corneal curvature and myopia etc. Ectopia lentis caused by lens suspension ligament defect is a typical manifestation of ocular abnormalities in MFS. In some studies, the incidence of ectopia lentis in MFS varies from 30 % to 72 %, which usually occurs between 40 and 50 years old[15]. Patients have a tendency to retinal detachment, early cataract or glaucoma, which are serious complications in ocular system. Studies have shown that the axial length of the eyeball in adult patients is longer than that in normal people, but that in children is shorter. It reminds to update the diagnostic criteria in time according to changes in clinical manifestations[16].

The cardiovascular system manifestations of MFS are mainly caused by aortic media defect, valve tip defect, atrial conduction and pectus excavatum. The manifestations are divided into two aspects : heart and blood vessels. In the heart, atrioventricular valve is most often involved, and atrioventricular valve stenosis is common. One-year follow-up of 21 children with MFS showed that 52.4 % of the patients had mitral valve prolapse. It is a high incidence. It is suggested that the early harm of MFS should not be ignored and we should intervene and manage MFS patients as soon as possible[17]. Aortic and atrioventricular valves in MFS patients are more prone to calcification, making repair complex[18]. Family inheritance causes congenital metabolic abnormalities in patients, which is the basis of abnormal aortic morphology in MFS[6]. When the maximum diameter of aorta reaches 50 mm, surgical repair

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is recommended. About 10 % of MFS patients have type B dissection after preventive aortic root replacement, which exceeds the incidence of type A dissection after operation. This finding shows the importance and unpredictability of the increasing proportion of type B dissection, and more attention should be paid to these patients[19].

The clinical manifestations of respiratory system in MFS patients are mainly caused by thoracic deformity (pigeon chest or pectus excavatum) and scoliosis, and about 60 % of patients have these deformities. These deformities can cause the change of lung parenchyma and then lead to restrictive or obstructive pulmonary disease. The decrease of chest wall compliance, rib offset, respiratory intensity and diaphragm mechanical defects lead to restrictive pulmonary disease, while obstructive pulmonary disease may be secondary to increased airway smooth muscle tension, variant asthma and intrathoracic airway compression[20]. Other clinical manifestations include skin manifestations, such as maculation and inguinal hernia. MFS patients have an increased risk of inguinal hernia and recurrent hernia. Most patients also have dural dilatation leading to lumbar pain and so on.

## 3. Pathogenic Gene and Mutation Phenotype

### 3.1. Fibrillin 1 Gene (FBN1)

In 1991, Dietz et al. [21] found two unrelated MFS patients with the same and new missense mutations. The MFS locus FBN1 was mapped to chromosome 15q15 - q21.3 through linkage analysis. FBN1 contains 65 exons forming a 235 kb genomic DNA encoding a 350 kDa glycoprotein, fibrinogen 1, which is highly conserved in different species[1].

For a long time, the recombinant expression of FBN1 in vitro is difficult to achieve due to the lack of regulatory region information. Nancy Jensen Biery et al.[22] successfully constructed artificial chromosomes expressing human FBN1 and regulated the expression of recombinant genes in mice, which proved that flanking sequences and introns are important factors for exogenous gene expression. This finding promoted the establishment of MFS animal models. Differential gene expression caused by sequence differences in the promoter region of FBN1 is likely to result in phenotypic variability of MFS. The promoter contains many potential binding sites related to mesenchymal differentiation and gene expression, and its activity change has a genetic effect on gene expression. Therefore, the polymorphic variation of FBN1 may be involved in controlling the absolute levels of mRNA and protein[23]. This finding is of great significance for evaluating the severity and variability of phenotype.

### 3.2. Fibrillin 1

FBN1 protein is a structural macromolecule that contributes to the integrity and function of all connective tissues, forms fibers visible under electron microscope[24]. Its amino acid sequence shows a modular structure, mainly composed of epidermal growth factor (EGF) -like domain (each domain has six cysteines) and new domain containing 8-cysteine. Each fibrinogen molecule has 47 EGF-like domains, including 43 calcium-chelating (cbEGF) domains, 7 8-cysteine domains (8-cys), 2 hybrid domains (both 8-cys and EGF-like domains), 1 proline-rich domain and amino-terminal and carboxyl-terminal domains[25,26].

FBN1 protein is involved in the formation of uniform microfibers with diameter of 10-12nm and exists in various forms[27]. In skin tissue, elastic fibers form a loose network structure. In tendons and periosteum, elastic fibers parallel to the long axis. In muscular arteries, elastic fibers surround the lumen[24]. The structural integrity of aortic wall (containing fibrin) and lens suspension ligament (excluding elastin) requires microfiber support in particular. In the clinical manifestations of MFS, aortic dilatation and ectopia lentis are the most typical manifestations. The electron microscopic immune localization experiment proved that FBN1 proteins were arranged along the 10 nm diameter microfibers[28], a single FBN1 protein has

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extensibility, with a length of 148nm and a diameter of 2.2nm[29]. FBN1 proteins and microfibers are in bead-like arrangement, and it is also possible to form spherical bead structure or staggered arrangement from beginning to end in bead-like arrangement[30,31,32]. There are about eight FBN1 proteins on each microfiber.

### 3.3. FBN1 Mutation and Phenotype

FBN1 mutation is the main pathogenic factor of MFS. Since FBN1 was identified as the pathogenic gene of MFS, the most widely used FBN1 mutation database (http://www.umd.be/FBN1/) reported about 1850 different mutations, including various types of mutations such as missense mutations, transcoding mutations, splicing mutations, and deletion of multiple exons of the whole gene etc. Missense mutations are the most common, accounting for about 2/3 cases. Different types of splicing errors account for 10% -15% of existing mutations. Another 10-15% of reported mutations include insertions, deletions or duplications of small fragments, most of which have premature termination codons, and a few MFS patients have large segment rearrangements including deletions and insertions, but deletion of the entire gene is very rare[5,24].

FBN1 mutation is associated with a wide range of overlapping phenotypes, but the clinical variability of MFS is very large, so it is difficult to determine the genotype-phenotype correlation. Exploring this correlation is conducive to disease screening and diagnosis. A large multicenter international study showed a strong correlation between ectopia lentis and mutations affecting cysteine residues, premature termination codons are associated with severe skeletal and skin phenotypes, while mutations in exons 24-32 lead to severe MFS phenotypes in both newborns and adults[33]. Haploinsufficiency is often associated with early aortic lesions, dural dilatation and maculation in MFS[5,34]. Patients with both mutations show early onset and are highly likely to develop severe MFS. Patients with FBN1 frameshift mutation and nonsense mutation are prone to aortic dissection, while patients with missense mutation are prone to aortic aneurysm[35]. Homozygous mutations appear to be more severe, while heterozygote mutations are usually asymptomatic or only mild[36]. FBN1 mutation can explain phenotypic variability to some extent, but there are still many problems that cannot be fully elucidated.

## 4. Pathogenesis of Marfan Syndrome

Aortic aneurysm or dissection resulting from aortic root dilatation is a typical clinical manifestation of MFS. At present, it is believed that FBN1 mutation may lead to the loose structure of aortic wall. Two mechanisms have been proposed to explain this process. One is that the abnormal FBN1 proteins synthesized under the control of mutation alleles interferes with the formation of polymers, resulting in structural abnormalities in all microfibers of extracellular matrix. Another mechanism is that haploinsufficiency determines phenotype development[10]. The study of MFS mouse model enriches our understanding of molecular pathogenesis. FBN1 proteins have high homology with transforming growth factor β (TGFβ) binding proteins (LTBPs), which promotes extracellular microfibrils to participate in the regulation of TGFβ activation[37].

Analysis of the mouse model with FBN1 protein deficiency free TGFβ and binding signaling pathways were significantly increased during alveolar septum development. The use of TGFβ neutralizing antibody was sufficient to rescue alveolar septum separation in FBN1 protein deficiency mice[38,39]. TGFβ neutralizing antibody can prevent atrioventricular valve elongation, thickening and dysfunction in MFS mice[40]. TGFβ signaling pathway is an important link in the pathogenesis of MFS. Further studies on the increase of TGFβ activity focus on typical signaling pathways (SMAD2 / 3 cascade) and atypical pathways (ERK1 / 2 and other media)[37].

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# 5. Diagnostic Criteria and Detection Techniques of Marfan Syndrome

## 5.1. MFS Diagnostic Criteria

In 1986, the International Conference on pathology of connective tissue genetic diseases was held in Berlin[1]. The conference formulated the first edition of MFS diagnostic criteria. The main diagnostic criteria of skeletal system include pigeon chest, pectus excavatum, arm span to height ratio greater than 1.05, positive wrist indication, and scoliosis greater than 20°, etc. Secondary criteria include moderate pectus excavatum, excessive joint activity, special craniofacial features, etc. The presence of at least two major or one major and two minor criteria constitutes the diagnosis of MFS skeletal system. The main criterion of ocular system is ectopia lentis, secondary criteria include abnormal flat cornea, iris hypoplasia, etc. At least two minor criteria appear in ocular system to meet MFS diagnosis. The main diagnostic criteria of cardiovascular system include ascending aortic dilatation and dissection. The secondary criteria include mitral valve prolapse and pulmonary artery dilatation, etc. In this version of the diagnostic criteria, if the patient has no family history, it requires at least two major criteria for different organ systems and clinical manifestations of another system to make a definite diagnosis. If the patient has identified mutations that cause MFS, it meets at least one of the main criteria for an organ system to make a definite diagnosis.

The revised diagnostic criteria in 1996 have the following changes[11]. First, there are more strict diagnostic requirements for the affected individuals in the relatives of patients. Second, if there are at least four typical manifestations of the skeletal system, it can be used as a main criterion. Third, pay more attention to the role of molecular genetics in the diagnosis of MFS. Fourth, clarify the differential diagnosis criteria of other genetic diseases with overlapping phenotypes.

In 2010, in order to identify this hereditary aneurysm syndrome more accurately and improve patient management, clinical experts from various countries agreed to develop a new version of Ghent diagnostic criteria[41]. This edition emphasizes the role of aortic root aneurysm and ectopia lentis in diagnosis. In the absence of other MFS manifestations, the simultaneous presence of these two main manifestations is sufficient to make a diagnosis. The criteria emphasize the role of FBN1 and other related genes, and strengthen the application of gene detection in clinical diagnosis. Gene detection also plays an important role in differential diagnosis of different genetic diseases.

## 5.2. MFS Detection Techniques

According to the phenotype, the current molecular genetic detection can be divided into target gene detection and whole genome sequencing. Whole genome sequencing is expensive, while it is easier to detect the target gene FBN1 for MFS. However, genetic factors may involve not only FBN1 but also mutations in other related genes, which require clinicians to determine the range of genes to be tested. The total mRNA is extracted from the blood or intraoperative specimens, then reversely transcribed into cDNA for sequencing. The operation method is simple and accurate. For patients who have no classic MFS phenotype and have difficulties in differential diagnosis, whole genome sequencing can more accurately identify and analyze disease-related genetic mutations. Clinical genetic counseling can improve treatment management and prognosis. Genetic counseling should be conducted throughout the family members of the proband, including the proband, the proband's parents, the proband's siblings and the proband 's descendants, and preventive advice should be given to members with mutations or phenotypes in the family.

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## 6. Summary and Prospect

So far, the clinical diagnostic criteria for MFS are still based on the 2010 Ghent criteria. With the in-depth study of the pathogenesis and the progress of gene detection technology, diagnostic criteria will be more perfect and better guide clinical treatment. According to the pathogenesis, doctors and scholars are studying the rapid molecular diagnosis method of the gene. However, due to the 65 exons of FBN1, the genetic variation types of MFS are complex and changeable, and the genotype-phenotypic correlation is difficult to identify. These are the difficulties to establish rapid genetic diagnosis methods.

Although the rapid diagnosis of MFS is faced with many problems, gene detection is still increasingly widely used in clinical practice. Detailed genetic counseling helps to prolong life expectancy for patients by using more advanced treatments, develop more effective preventive measures for their offspring, delay onset, improve quality of life and help more MFS patients.

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