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Incidence and de novo mutation rate of Marfan syndrome and risk of ectopia lentis

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Abstract

PURPOSE—To investigate the population-based incidence and de novo mutation rate of Marfan syndrome and risk of ectopia lentis.

METHODS—Patients newly diagnosed with Marfan syndrome in Olmsted County, Minnesota, from January 1, 1976, through December 31, 2005, were identified through medical records review. Outcome measures were Marfan incidence, de novo mutation rate, risk of ectopia lentis.

RESULTS—Marfan syndrome was identified in 17 patients during the 30-year period, yielding an incidence of 0.52 per 100,000 people/year (95% CI, 0.27-0.77). Mean age at diagnosis was 24.4 years (range, 1.7 year to 51.3 years). Nine patients (53%) were female. Of the 17, 5 (29%) were new mutations, with a calculated mutation rate of $3.8 \pm 1.7 \times 10^{-5}$. Four (24%) were diagnosed with ectopia lentis, including 3 at the time of their Marfan diagnosis. Of the 14 patients at risk for developing ectopia lentis after being diagnosed with Marfan syndrome, 1 (7%) developed it during a mean follow-up of 9 years (range, 0-6.4). Twelve (71%) were diagnosed with dilated ascending aorta during a mean follow-up of 13.2 years (range, 6.7 months to 28.9 years).

CONCLUSIONS—Incidence and de novo mutation rate of Marfan syndrome in this population-based cohort was higher than prior reports. Ectopia lentis, whose prevalence in North America has not been reported previously, occurred in approximately one-fourth of study patients and more commonly around the time of initial Marfan diagnosis.

Marfan syndrome is an autosomal dominant systemic disorder caused by mutations in the extracellular matrix protein fibrillin 1. The most common manifestations include proximal aortic aneurysm, dislocation of the ocular lens (ectopia lentis), and overgrowth of the long bones.[1] Very few investigators have evaluated the incidence and de novo mutation rate of Marfan syndrome. Although it is widely accepted that Marfan syndrome is one of the most common inherited disorders of connective tissue, epidemiological data related to the syndrome is sparse. The most extensive study to date was conducted using Danish patient-registries from 1977 to 2014, which found an incidence of Marfan syndrome of 0.19 in 100,000 people.[2] Additionally, a 1994 study from northeast Scotland reported

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that 27% (8/30) of patients with Marfan syndrome presented with de novo mutations.[3] No corresponding study on incidence or de novo mutation rate of Marfan syndrome has been performed in the United States. Moreover, the risk of ectopia lentis in individuals with Marfan syndrome is poorly understood. The purpose of the current study was to evaluate a large patient database to identify the incidence and de novo mutation rate of Marfan syndrome and to determine the risk of ectopia lentis in Marfan patients in a defined population from the United States using a medical record retrieval system.[4]

Subjects and Methods

The medical records of all residents of Olmsted County diagnosed with Marfan syndrome from January 1, 1976, through December 31, 2005, were retrospectively reviewed. All followup visits were reviewed until June 30, 2018. Institutional review board approval was obtained for this study from Mayo Clinic and Olmsted Medical Group. Potential cases were identified using the resources of the Rochester Epidemiology Project, a medical record linkage system designed to capture data on any patient-physician encounter in Olmsted County. The population of Olmsted County is relatively isolated from other urban areas, and almost all medical care is provided to its residents by the Mayo Clinic, Olmsted Medical Group, and their affiliated hospitals. This study conformed to the requirements of the US Health Insurance Portability and Accountability Act of 1996.

A list of potential cases from the two institutions, generated by a comprehensive diagnostic code search, identified 200 patients. The codes searched included any terms that had the word “Marfan” in it. Cases were excluded if the patient was found to have a diagnosis other than Marfan syndrome, was diagnosed clinically with Marfan syndrome using Ghent-2 nosology[5] but later reversed based on genetic review or was diagnosed outside the time period of this study or outside of Olmsted County. The medical records of the patients were reviewed for demographics (including sex, race, date of diagnosis), medical, genetic, and familial histories, and medical and ocular management. Clinical characteristics of the Marfan syndrome, including systemic medical findings and final outcome, were reviewed.

To determine the incidence of Marfan syndrome in Olmsted County, annual incidence rates were constructed using the age- and sex-specific population figures for this county from the US Census Bureau. The mutation rate was calculated based on the formula used by Gray and colleagues.[3]

Results

Seventeen new cases of Marfan syndrome were diagnosed during the 30-year study, yielding an incidence of 0.52 per 100,000 people per year. The demographic characteristics of the 17 patients are summarized in Table 1. Five (29%) of the 17 were considered new mutations with a calculated mutation rate of $3.8 \pm 1.7 \times 10^{-5}$. The mean age at diagnosis (Figure 1) for the 17 patients was 24.4 years (range, 1.7-51.3) and 8 (47%) were male. The 17 patients were observed for a mean of 11 years (range, 6.7 months to 28.9 years) after initial diagnosis.

Fourteen patients (82%) had at least two ophthalmic examinations and were observed for a mean of 12.2 years (range, 1.3 to 26.4). Four patients (24%) were diagnosed with ectopia lentis, including 3 at the time of their Marfan diagnosis (Table 2). Of the 14 patients at risk for developing ectopia lentis after being diagnosed with Marfan syndrome, 1 (7%) developed it during a mean follow-up of 9 years (range, 0 to 26.4). The mean age at diagnosis of ectopia lentis was 10.6 years (range, 1.0 to 30.2). Of the 4 patients with ectopia lentis, 3 (75%) had bilateral involvement. Final refractive error was recorded in 11 of the 17: 9 (53%) had myopia, 3 (18%) had astigmatism, and 1 (6%) had hyperopia. Myopic refractive errors ranged from −3.25 to −10.50 D. One (6%) of the 17, who also had ectopia lentis at their initial diagnosis, was diagnosed and treated for a unilateral retinal detachment at age 30. Management was documented in 3 of the 4 patients with ectopia lentis (75%): one underwent bilateral lensectomy surgery, one was observed, and the last was prescribed glasses.

Eight of the 17 patients (47%) had a reduced upper to lower segment ratio or increased arm span to height ratio. Nine (53%) had mitral valve prolapse with or without mitral valve regurgitation. Twelve patients (71%) were diagnosed with a dilated ascending aorta during a mean follow-up of 13.2 years (range, 6.7 months to 28.9 years). Three (18%) experienced dissection of the ascending aorta (Table 2). Ten (67%) of the 15 patients with either ascending aortic dilation or dissection were treated medically with a β-blocker.

Discussion

This population-based study describes the incidence, de novo mutation rate, ocular findings, and systemic conditions associated with Marfan syndrome. Marfan syndrome was diagnosed in 17 patients during the 30-year study period for an incidence of 0.52 in 100,000 people per year. Approximately 3 in 10 were new mutations. Two-thirds of patients had ocular involvement, including one-fourth with ectopia lentis and one-half with myopia. The majority of study patients had cardiovascular manifestations, including dilated ascending aorta and mitral valve prolapse, and two-thirds had significant musculoskeletal defects.

Population-based incidence rates for Marfan syndrome have only been reported in 2 Danish studies,[2,6] ranging from 0.14 per 100,000 to 0.19 per 100,000. However, these rates are a factor of threefold lower than the rate of 0.52 per 100,000 people diagnosed among Olmsted County residents. There are several possible explanations for this difference. First, incomplete capture of all patients is likely in the previous studies because they relied on national registry data or national surveys. Danish hospitals are obliged to store patient records for only 10 years after the latest entry, so many records have been destroyed over time.[2] Additionally, elderly persons who died before computerization of records were evaluated as “not MFS” due to lack of data.[2] National surveys are similarly flawed, because milder cases of Marfan syndrome may be underreported.[6] Second, diagnostic criteria may vary across time and between countries.[7] Ethnic differences may also contribute to different Marfan syndrome incidence rates in different populations.[8]

The de novo mutation rate of Marfan syndrome in this cohort is higher than the only known prior report, performed in northeast Scotland. Gray and colleagues[3] observed a mutation rate

of $15 \pm 6.7 \times 10^{-6}$, which is more than twofold lower than the de novo mutation rate of $3.8 \pm 1.7 \times 10^{-5}$ in patients of Olmsted County. The difference in mutation rate is likely due to incomplete capture of patients with de novo mutations. As noted by the authors, 10% of patients under 20 years of age had a new mutation compared to 20% of patients aged 20 years or older, implying that one new mutation under 20 years of age was undetected because of mildly expressed phenotypic features at an earlier age.[3] Despite the differences in de novo mutation rate, a similar percentage of cases in each study were reported (26.7% in Scotland and 29.4% in Olmsted County), which is consistent with widely quoted estimates of 25% to 35%.[9]

Although some risk factors, such as family history, have been associated with the development of Marfan syndrome, other factors, including race and sex, have not.[1] A positive family history of Marfan syndrome was reported in 12 patients (71%), suggesting that genetic factors are significant. Only 2 patients (12%) received genetic testing, and both were positive for the *FBN1* gene mutation.[10,11] We found no clear sex predominance for Marfan syndrome. Finally, the mean age at diagnosis for the study patients was 24.4 years, which is consistent with findings from the Danish and Taiwanese national databases.[2,12]

Two-thirds of patients in this study were diagnosed as having an ocular disorder. Although ocular morbidity is common in patients with Marfan syndrome,[13] there are few data on the prevalence of specific ocular disorders in the Marfan population, particularly in North America. In this study, 24% of patients were diagnosed as having ectopia lentis with bilateral involvement in 75%. This is consistent with more recent studies[14] and is less than early estimates of 55%-75%,[6,15] which were likely elevated due to incomplete capture of all patients, particularly those with less severe manifestations, commonly observed in national registry data. Most patients with ectopia lentis were discovered at the time of their Marfan diagnosis. Refractive error was recorded in the majority of patients, with myopia developing in 53% and hyperopia in 6%. The percentages of myopic patients are greater and hyperopic patients less than the estimated prevalence rates of myopia and hyperopia in the general population: 41.6%[16] (aged 12-54) and 10%[17] (aged 40 or greater), respectively. Most patients were noted to have high myopia, which is consistent with the literature. Retinal detachment was a rare complication in patients with Marfan syndrome in this study, affecting only 6%. This is consistent with multiple studies reporting retinal detachment in 4%-15% of Marfan patients.[14,18–20]

Musculoskeletal and cardiovascular manifestations are common in patients with Marfan syndrome.[1] Six of 10 patients in our study had skeletal defects, most commonly a reduced upper to lower segment ratio or increased arm span to height ratio in half of patients. This rate is consistent with recent studies.[5] Cardiac manifestations were seen in 89% of our patient population; most were diagnosed with a dilated ascending aorta at a rate similar to previous reports.[21] Eighteen percent also experienced dissection of the ascending aorta. Two-thirds of patients with ascending aortic dilation or dissection were treated medically with a β-blocker. Half of Marfan patients developed mitral valve prolapse, similar to prior studies.[22]

The findings of this study have several limitations. Its retrospective design is limited by nonstandardized and incomplete data collection. In addition, some patients with Marfan syndrome may be asymptomatic, thereby going unnoticed by the patient's caretaker or physician. Although most patients in Olmsted County are treated by the two medical systems within the community, some residents may have sought care outside Olmsted County, thereby further underestimating the true incidence in this population. Our ability to generalize these findings to other populations is limited by the demographics of Olmsted County, a relatively homogeneous, semiurban, White population.

This study provides population-based data on Marfan syndrome diagnosed during a 30-year period. Marfan syndrome occurred with an incidence of 0.52 in 100,000 people per year, a rate that is higher than that of all previous studies. Less than one-third of cases were derived from new mutations. Two-thirds of patients developed ocular involvement, including one-fourth with ectopia lentis. The majority of study patients were diagnosed as having cardiovascular involvement and two-thirds of the patients had significant musculoskeletal involvement.

Literature Search

PubMed (MEDLINE) was searched on November 20, 2022, for articles, without specification for language or publication dates, using combinations of the following search terms: *Marfan, epidemiology* OR *Marfan, incidence* OR *Marfan, mutation rate* OR *Marfan, ectopia lentis OR ectopia lentis* OR *lens subluxation* OR *dislocated lens*.

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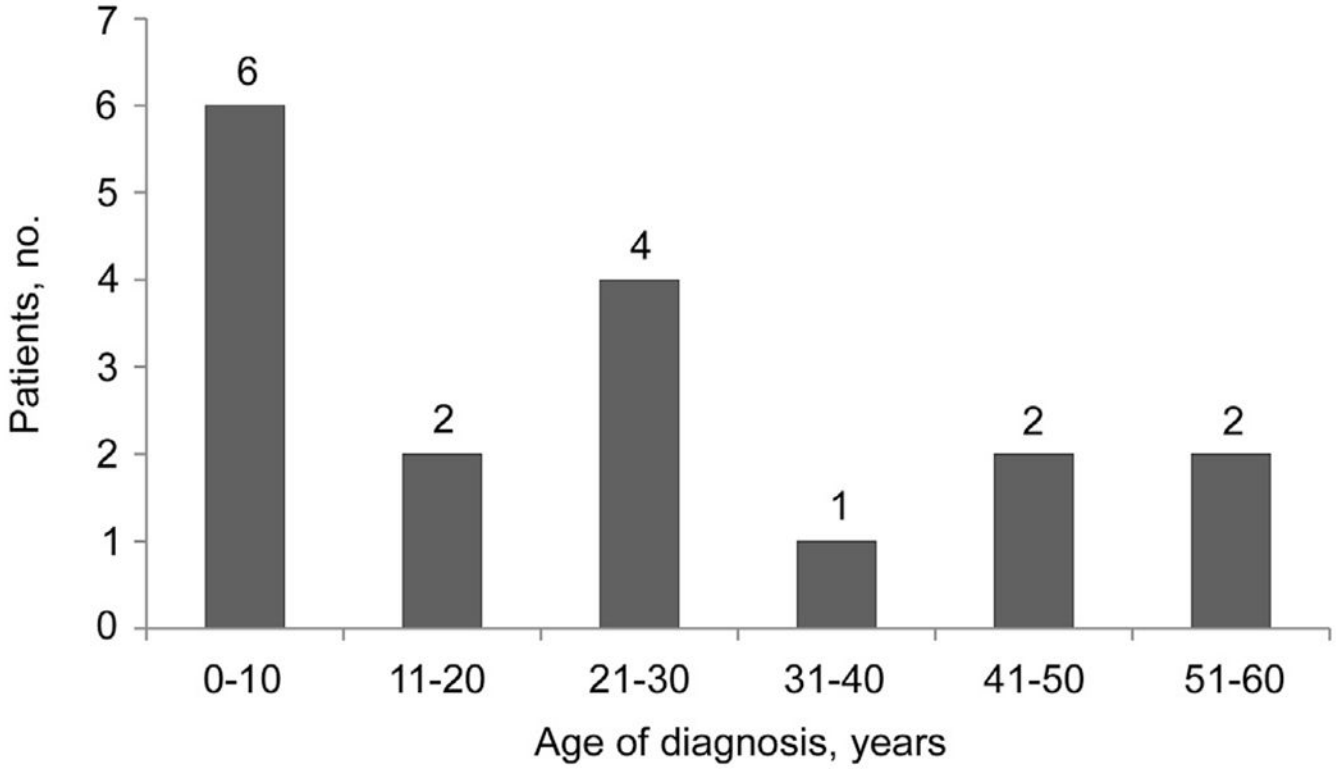

FIG 1.
Age at diagnosis of Marfan syndrome in 17 patients from Olmsted County from 1976 to 2005.

Table 1.

Demographic characteristics of 17 patients diagnosed as having Marfan syndrome in Olmsted County from 1976 to 2005

Characteristics	Findings
Sex	
Male, no. (%)	8 (47)
Race, no. (%)	
White	11 (65)
African American	2 (12)
Hispanic or Latino	2 (12)
Positive family history of Marfan syndrome, no. (%)	12 (71)
Positive family history of ectopia lentis, no. (%)	3 (18)

Table 2.

Prevalence of the individual features in 17 patients with Marfan syndrome diagnosed in Olmsted County from 1976 to 2005

Study parameter	Fulfilling Ghent (N = 17)
Skeletal system involved	10
Reduced upper to lower segment ratio (<0.85) or arm span to height ratio >1.05	8
Wrist and thumb signs	3
Scoliosis of >20° or spondylolisthesis	2
Medial displacement of the medial malleolus causing pes planus	2
Marfanoid habitus, not otherwise specified	1
Ocular system involved	11
Ectopia lentis	4
Other[a]	11
Cardiovascular system involved	15
Dilatation of ascending aorta	12
Dissection of ascending aorta	3
Mitral valve prolapse with or without mitral valve regurgitation	9
Dilatation of descending thoracic or abdominal aorta at <50 years	3
Dissection of descending thoracic or abdominal aorta at <50 years	1
Lungs involved	1
Spontaneous pneumothorax	1
Skin and integument involved	3
Recurrent or incisional hernia	1
Striae atrophica from puberty	3
Genetics	11
Having parent, child, or sibling who meets diagnostic criteria independently	11
Presence of a mutation in *FBN1* known to cause Marfan syndrome	2

[a]Non-criteria-fulfilling ocular involvement: myopia, hyperopia, astigmatism, strabismus, retinal detachment, amblyopia, and blurred vision.