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A Familial Syndrome of Pulmonary Nontuberculous Mycobacteria Infections

To the Editor:

Women over the age of 50 who lack antecedent structural lung damage have emerged as a growing population afflicted with pulmonary nontuberculous mycobacteria (PNTM) (1). A common body morphology among these women, who are often tall and lean with scoliosis, pectus excavatum (PE), and mitral valve prolapse (MVP), points to a possible genetic basis for susceptibility to PNTM (2, 3). Exploration of these traits in family members of patients with PNTM provides evidence for the hypothesis that genetic factors modify disease susceptibility. To date, a systematic analysis of a large cohort of patients with PNTM and their relatives has not been performed. We describe here a comprehensive review of families with PNTM designed to identify a familial phenotype of disease. Some of the results of this study have been previously reported in the form of an abstract (4).

Methods

Probands included in our study were adult patients who met diagnostic criteria for PNTM (5) and were enrolled in a natural history of mycobacterial disease protocol at the National Institutes of Health. Probands with other known underlying structural lung diseases or characterized immunodeficiency were excluded. Chart records for each proband were abstracted for demographic data, mycobacterial species identified, and the presence of bronchiectasis, scoliosis, MVP, and PE. Bronchiectasis was identified by chest computed tomography (CT) imaging, scoliosis by spinal X-rays, MVP by echocardiogram, and PE by computing a Haller index greater than 3.5 from chest CT imaging (6). All probands were contacted to construct family pedigrees extending to first- and second-degree relatives. Probands were asked to report the following in all members of the

TABLE 1. CHARACTERISTICS OF STUDY PROBANDS (N = 109)

Characteristic	Frequency
Female sex, n (%)	97 (89.0)
Mean ± SD age, yr	66.7 ± 11.6
Mean ± SD BMI, kg/m^2	22.1 ± 4.0
Mean ± SD FEV_1, % predicted	80.3 ± 21.8
Ethnicity, n (%)	
White	100 (91.7)
Asian	7 (6.4)
Hispanic	2 (1.8)
Mycobacterium species, n (%)	
M. avium complex	82 (75.2)
M. abscessus	39 (35.8)
M. fortuitum	8 (7.3)
M. kansasii	3 (2.8)
M. mucogenicum	4 (3.7)
Other	7 (6.4)
Radiographic presentation, n (%)	
Nodular bronchiectasis	106 (97.2)
Cavitary	23 (21.1)
Scoliosis, n (%)	63 (57.8)
Mitral valve prolapse, n (%)	15 (13.8)
Pectus excavatum, n (%)	4 (3.7)

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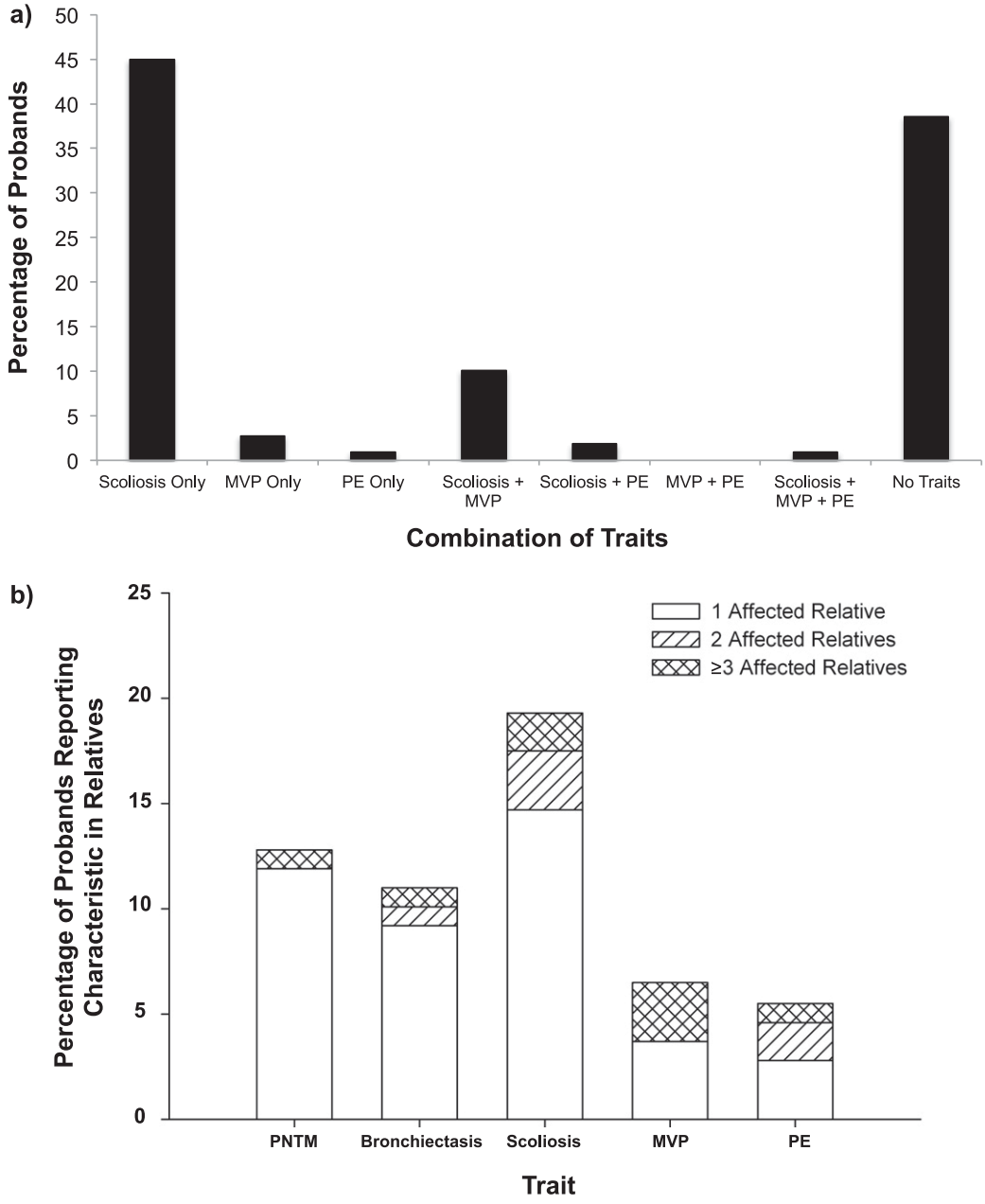

Figure 1. (*a*) The percentage of probands exhibiting different combinations of scoliosis, mitral valve prolapse (MVP), and pectus excavatum (PE) is shown. The largest proportions of probands exhibited either only scoliosis (45%) or none of the pertinent traits (39%). Combinations of traits included 11 patients (10%) with both scoliosis and MVP, 2 patients (1.8%) with both scoliosis and PE, and 1 patient (0.92%) with all three traits. (*b*) The percentage of probands reporting pertinent characteristics in one or more of their relatives is shown, with the distribution of the number of affected relatives per family shown in *white* (1 affected relative), *diagonal stripes* (2 affected relatives), and *cross-hatch* (⩾3 affected relatives). Of 109 probands, 14 (12.8%) reported at least 1 relative with PNTM, with 1 individual reporting having 3 affected relatives. Twelve (11.0%) reported at least 1 relative with bronchiectasis, with 1 individual reporting having 4 affected relatives. Twenty-one (19.2%) reported at least 1 relative with scoliosis, with 1 individual reporting having 10 affected relatives. Seven (6.4%) reported at least 1 relative with MVP, with 3 individuals reporting having 3 affected relatives each. Six (5.5%) reported at least 1 relative with PE, with 1 individual reporting having 5 affected relatives.

pedigree: current or past diagnosis of PNTM, bronchiectasis, MVP, scoliosis, and PE. When possible, consent was obtained from family members to interview them directly as well. The instrument used to ascertain these characteristics can be found in the online supplement. Summary statistics were performed in Excel (Microsoft Corporation, Redmond, WA).

Results

A total of 383 patients were enrolled in the natural history protocol, 274 of whom were excluded for the following reasons: 87 had an underlying immunodeficiency, 53 were enrolled relatives of patients, 44 had withdrawn from the study, 35 were already deceased, 24 had a known underlying structural lung disorder, 14 were unable to be contacted, 11 had tuberculosis, and 6 were pediatric patients (5 with isolated endobronchial mycobacterial lesions and 1 with pulmonary alveolar proteinosis). The remaining 109 probands included for analysis led to 2,285 first- and second-degree relatives with an average of 21 family members per proband. Seventy-two relatives consented to in-person interviews; the remainder of the relatives' medical histories were ascertained via interview of the proband.

Characteristics of the probands are listed in Table 1. The majority of probands were white females with an average age of 66.7 years. The most common mycobacterial species was *Mycobacterium avium* complex, followed by *M. abscessus* and *M. fortuitum*. Sixty-three (57.8%) patients had scoliosis, 15 (13.8%) had echocardiographic evidence of MVP, and 4 (3.7%) had radiographic evidence of PE by the Haller index. The proportion of probands featuring different combinations of these traits is shown in Figure 1a.

The proportion of probands reporting pertinent characteristics in at least one family member is displayed in Figure 1b. Of 109 probands, 14 (12.8%) reported having at least one other first- or second-degree relative diagnosed with PNTM. In addition, 13 (11.9%) probands reported bronchiectasis and 21 (19.2%) probands reported scoliosis in at least one relative.

MVP was found in 7 (6.4%) families and PE in 6 (5.5%) families. Twenty-three relatives exhibited just scoliosis, 14 exhibited just MVP, and 12 exhibited just PE. Two relatives exhibited scoliosis and MVP together, and one relative exhibited MVP and PE together. Of the 14 families with more than one member with PNTM, 8 were sibling pairs, 4 were parent–child pairs, and 2 were aunt–niece pairs.

Discussion

To date, no systematic review of a large cohort has evaluated whether conditions previously ascribed to patients with PNTM, such as scoliosis, MVP, and PE, cluster among family members. The infrequency of these traits in large population-based epidemiologic studies suggests that they are much more prevalent among relatives of patients with PNTM than in the general population. Whereas studies of general pediatric populations demonstrate rates of scoliosis of between 0.5 and 3.2% (7–10), we observe here 21 (19.2%) families with at least one member with scoliosis. Comparisons with populations similar to patients with PNTM also suggest a higher rate. For example, an estimate of scoliosis in a population of patients with cystic fibrosis, who also carry higher risk for developing PNTM, only revealed a prevalence of 2.2% (11). Similarly, our observations exceed those found in a comparable cohort of postmenopausal women, where lumbar scoliosis was found in 12.9% (12). Estimates of MVP in the general population range from 2.4 to 2.7% (13, 14) whereas we observed 7 (6.4%) families with at least one affected relative. Even rarer conditions such as PE, affecting 0.12% in one autopsy series (15) and 0.49% in one pediatric screening study (16), were found in 6 (5.5%) families. Patients with primary ciliary dyskinesia, another structural lung disease associated with PNTM, may feature similar rates of PE compared with our population, with one study finding a 9% prevalence on CT scans (17). Although inherited syndromes of these traits certainly exist, how frequently these traits are expressed in first- and second-degree relatives of comparable populations remains unknown.

The genetic underpinnings of this familial syndrome remain undetermined. The triad of scoliosis, MVP, and PE points strongly to a Marfan-like syndrome, although it should be noted that none of our probands met diagnostic criteria for Marfan syndrome. As a corollary to our findings, Marfan syndrome is known to be associated with bronchiectasis (18). Other connective tissue diseases, such as congenital contractural arachnodactyly, have been associated with PNTM infection (19). Involvement of the transforming growth factor-β pathway, alterations in which account for many connective tissue diseases, could potentially explain the marked similarities in body morphotype between the families in our cohort and the connective tissue disease population (20).

Our study has several limitations, most notably that traits identified by probands and their family members need in-person verification. These findings, based on family member report, are subject to ascertainment bias; however, this bias is likely to underestimate the prevalence, particularly for mild forms of conditions such as scoliosis and MVP, which may not be apparent to individuals without full medical examinations. Second, the fact that PNTM is a disease largely affecting postmenopausal women makes the estimation of disease difficult for younger relatives who have not yet reached the "at-risk" age for disease onset. Longitudinal follow-up over decades will be necessary to determine the true degree of risk for family members. Moreover, the identification of PNTM, bronchiectasis, and associated traits is challenging in the oldest generations of pedigrees, many of whom are already deceased or may not have undergone diagnostic testing during their lifetimes. Despite the limitations intrinsic to using generations who are presymptomatic and those who may not have had adequate testing, at least some of these families show parent–child transmission, most consistent with dominant disease. It is also possible that there are recessive families in this cohort as well. Finally, the relative rarity of exhibiting all associated traits together in both the probands and the relatives raises the possibility that although they are clustered, these traits may not necessarily be inherited together. Further explorations of larger populations of patients with PNTM in addition to clarifying the inheritance pattern of these traits would better demonstrate whether a true syndrome of traits exists, rather than mere clustering.

This study is the first to show a familial clustering of traits related to PNTM infections in otherwise unaffected relatives. The higher-than-expected prevalence of PNTM, bronchiectasis, scoliosis, MVP, and PE strongly supports a genetic basis for at least some cases of PNTM.

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Basic Research Funding by Philanthropic Organizations: A Case in Point

To the Editor:

Patient organizations play important roles in the funding of care required by their constituents. Increasingly, however, they have chosen to invest in research as national research budgets have become constrained. The dilemma facing such organizations is what type of research should be funded, as the expectations of donors, parents, and patients is that there will be quick translation of their donations into therapies. Thus, translational research is increasingly stressed with the goal of developing new therapies. However, there have been very few examples where funding of translational research by such organizations have led to tangible therapies. The best example of a private philanthropic organization substantially aiding in the development of a new therapy has been in the development of ivacaftor for the treatment of cystic fibrosis (CF). However, the foundations of this therapy lay deeply rooted in fundamental research.

Ivacaftor (VX-770) was approved in the United States and Europe in 2012 (Figure 1). Of note, only 5% of the total population with CF, those patients bearing a CF transmembrane conductance regulator (CFTR) with the specific missense mutation G551D, benefit from this agent. Ivacaftor rescues CFTR function with the consequent improvement of nasal potential difference and sweat chloride measurements, two biomarkers of CFTR function (1). Additionally, FEV_1 (a pulmonary function test) is improved by 10.5%, accompanied by a 50% reduction of pulmonary exacerbations and 3.1-kg weight gain (2) after several months of treatment.

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Would this have been possible without the contribution of basic research and the crossing of hurdles of translational research?

Although the development of this agent was a matter of screening for a compound that rescues CFTR function, the point should be made that this breakthrough was possible because of fundamental work that had at its root an understanding of the genetic basis of this disease, namely the sequence of the CFTR gene in 1989 (3–5). That this work would be relevant to pharmacologic therapy rather than gene therapy was not foreseen.

In fact, all is relative; the sequence of the CFTR gene may be considered translational research compared with the discovery of the first gene sequence (Figure 1) in 1972 (6). At that time, this work did not seem relevant to the treatment of CF patients . . . but it was!

The subsequent work that led to the discovery of ivacaftor, the description of the targeted G551D mutation (Figure 1), was also quite basic in nature (7). The authors determined the nucleotide sequences encoding the first nucleotide-binding domain and most of the second from 38 patients with CF. The clinical utility of such basic research was initially to anticipate the severity of CF given a patient's genotype. Thus, consequences of this type of mutation were rapidly analyzed, and it was claimed that patients bearing both the G551D and the ΔF508 mutations are clinically indistinguishable from ΔF508 homozygotes, except for a decreased risk of meconium ileus (8). Subsequently, more than 1,900 different mutations affecting the CFTR molecule were rapidly described.

The knowledge of the different mutations and of the biological fates of the different CFTR mutant proteins suggested the possibility for selective pharmacological targeting of CFTR malfunction. As an example, 4-phenylbutyrate was shown to increase expression of CFTR ΔF508 at the cytoplasmic membrane of cells (9), contrasting with its natural pathological fate, which is retention and degradation in the endoplasmic reticulum. This resulted in the restoration of chloride secretion. The pharmacological manipulation of the defective G551D molecule was tested in 1999 (10). Genistein added to HeLa cells expressing the CFTR G551D resulted in ~10-fold activation of Cl^- currents to a level similar to wild-type CFTR. *Another hurdle was crossed; that is, it was pharmacologically possible to compensate for a mutated CFTR.*

Taking advantage of these advances in basic science knowledge, in 2000, the Cystic Fibrosis Foundation made an agreement with Aurora Biosciences (later bought by Vertex) to screen compounds from their chemical libraries to determine whether any might correct the defective protein function. The agreement was one of the first examples of venture philanthropy and represented the largest contract ever awarded by a voluntary health organization for drug discovery. Under the agreement, Aurora used its chemical library, its secondary screening and lead optimization capabilities, and its genomic technologies for additional target and assay development. Aurora/Vertex identified selective ion channel modulators for potential application in the treatment of CF. In laboratory studies involving bronchial epithelial cells isolated from patients with CF, it was demonstrated that some compounds could improve the function of defective CFTR proteins. Among the different hits, one compound, VX-770, advanced into preclinical development, and in 2006, a patent was filed and a phase 1 clinical trial was successfully completed (Figure 1). Ivacaftor was eventually commercialized for use in patients with the G551D mutation under the brand name of Kalydeco (Figure 1). This agent is now in clinical trials for patients with two copies of the ΔF508 mutation. Additionally, in February 2013, Vertex began two international phase 3 clinical trials of ivacaftor combined with another molecule, VX-809, as an earlier phase 2 trial showed significant improvements in lung function with the latter.