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Epidemiology of the Global Fibrodysplasia Ossificans Progressiva (FOP) Community

Moira Liljesthröm[1], Robert J. Pignolo[2], Frederick S. Kaplan[3]*

[1]President of Fundación FOP, Argentina; Argentine Representative to the International President's Council of the International Fibrodysplasia Ossificans Progressiva Association (IFOPA), Buenos Aires, Argentina

[2]Department of Medicine, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN 55905, USA

[3]The Departments of Orthopaedic Surgery, Medicine and The Center for Research in FOP & Related Disorders, The Perelman School of Medicine of The University of Pennsylvania, Philadelphia, PA 19104, USA

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***Correspondence:**
Frederick S. Kaplan, Isaac & Rose Nassau Professor of Orthopaedic Molecular Medicine, Perelman School of Medicine, The University of Pennsylvania, c/o Department of Orthopaedic Surgery; Penn Musculoskeletal Center - Suite 600, 3737 Market Street, Philadelphia, PA 19104. USA; Telephone No: 215-294-9145; Fax No: 215-222-8854;
Email: frederick.kaplan@uphs.upenn.edu

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ABSTRACT

Background: Fibrodysplasia Ossificans Progressiva (FOP) is an ultra-rare disease, but the geographic distribution and regional prevalence of the condition are unknown. This study was undertaken to determine the emerging global population of FOP patients who were associated with a regional, national or international FOP organization.

Results: This study interrogated the patient registration database of the International Fibrodysplasia Ossificans Progressiva Association (IFOPA) and those of the 16 regional or national FOP organizations in order to assemble a non-redundant worldwide census of patients living with FOP in 2016 who were associated with a pre-identified FOP community. The total registered population of the global FOP community was 834 individuals [445 females (54%), 387 males (46%), 2 unassigned] distributed in 67 countries and six continents. The apparent prevalence of registered and confirmed FOP patients varied substantially from approximately 0.65 per million in North America, 0.47 per million in Western Europe, and 0.27 per million in Latin America, to 0.05 per million in Africa and nearly 0.04 per million in the Asia-Pacific region.

Conclusions: The high variability in apparent prevalence is likely associated with lack of awareness of FOP in under-represented medical communities, delay in achieving the correct FOP diagnosis, lack of supporting regional infrastructure and inability of individuals with FOP to reach a local FOP organization or the international FOP community. Emerging knowledge of the apparent prevalence of FOP can serve as a catalyst for resource allotment; physician, patient and community education and outreach; clinical trial recruitment and global networking to achieve a more globally robust and interconnected FOP community.

Abbreviation

Fibrodysplasia ossificans progressiva (FOP), International Fibrodysplasia Ossificans Progressiva Association (IFOPA), heterotopic ossification (HO), activin receptor A, type I (ACVR1), bone morphogenetic protein (BMP), International Presidents Council on FOP (IPC), International Clinical Council on FOP (ICC).

Background

Fibrodysplasia ossificans progressiva (FOP; MIM#135100) is a progressively disabling genetic disorder which leads to the formation of a second skeleton of heterotopic bone [1,2]. Individuals with FOP appear normal at birth except for characteristic malformations of the great toes that are present in all classically affected individuals [1].

During the first decade of life, episodic soft tissue swellings (or flare-ups) can arise in the neck and back and mature into heterotopic bone [3-5]. Minor trauma such as intramuscular immunizations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma, bumps, bruises, falls, or influenza-like viral illnesses can trigger new flare-ups of FOP leading to progressive heterotopic ossification (HO) [1]. Flare-ups are episodic, but disability is cumulative [4-6]. Most patients are confined to a wheelchair or immobilized in a standing position by the third decade of life, and require lifelong assistance with activities of daily living [4,5,7,8]. The estimated median lifespan is 56 years; death often results from complications of thoracic insufficiency syndrome [9].

Heterozygous missense mutations in activin receptor A, type I (ACVR1), a bone morphogenetic protein (BMP) type I receptor, were identified in all affected individuals [10,11]. Most cases of FOP are sporadic, but inheritance can occur by autosomal dominant transmission [11-13]. The mutation causes loss of autoinhibition of ACVR1 and renders it susceptible to dysregulated signaling through the BMP pathway [1,14,15].

Standard-of-care medical management is based on prevention of complications and is currently supportive [16]. Definitive treatments and cures are not yet available. There is a critical unmet need for targeted therapies many of which show promise in pre-clinical studies [17]. The discovery of the FOP gene and emerging insights into its mechanism of action has led to current and upcoming clinical trials (see [18]).

Despite the promise for the future [19] and the social connectivity of those who are known to have FOP [20], there are likely many who are yet unidentified or unconnected to a viable FOP network. The rarity of FOP, the absence of local support groups in various regions of the world, the general lack of awareness of FOP among medical professionals, the alarming rate of misdiagnosis [21] and the present lack of definitive treatments amplify the isolation of those living with this progressively disabling condition and hamper access of unidentified individuals to medical services, social support and emerging clinical trials [19].

Although there appears to be no gender, racial or ethnic bias to FOP [11], little is currently known about the regional global distribution of patients with FOP. We undertook this study to determine the worldwide distribution of patients with FOP who were associated with a pre-established FOP network to help identify regions of the world where greater efforts need to be expended to serve the needs of as yet unidentified patients.

Methods

Ascertainment of individuals with FOP

To achieve the baseline goal of accurately determining the number and geographic distribution of individuals registered or associated with FOP organizations throughout the world, the principal investigator (ML) reviewed existing databases of the International Presidents Council (IPC), the International Fibrodysplasia Ossificans Progressiva Association (IFOPA) and the respective 16 regional and national FOP associations worldwide (Argentina & Latin America, Australia, Brazil, Canada, China, Italy, Malaysia, Netherlands, Poland, Russia, Scandinavia, Serbia, South Africa, Spain, United Kingdom, United States) to assemble an anonymous and non-redundant census of expert physician-confirmed FOP patient-members who were alive in January, 2016. The anonymous data requested for each individual registrant with FOP was: year of birth, country of birth, gender and country of residence. When more than one information source existed for a country, databases were harmonized and reconciled by the principal investigator (ML) to exclude redundancy. Control population data were obtained from contemporaneous United Nations sources [22]. We refer to the "global" or "worldwide" distribution of FOP patients as those in the 67 countries and 6 continents represented by regional and national FOP associations.

The workflow of the study was composed of three iterative phases: 1) identification of individuals who were alive in 2016 and have clinically and/or molecularly confirmed FOP in the 17 databases, 2) harmonization of the databases to exclude redundancy, and 3) confirmation of FOP cases by an FOP expert from a regional medical network or from the 21 members of the International Clinical Council on FOP (ICC) [23]. All patients recorded in the regional databases were diagnosed as having FOP by expert physicians, meaning that they were seen at least once in regional, national or international FOP clinics, and they were diagnosed either by clinical-radiological hallmarks and/or by molecular testing, available since 2006. Thus patients included in the 17 databases were considered to be true FOP patients associated with a regional, national or international FOP network.

Statistical Analysis

Our analysis included an iterative method to ascertain the apparent prevalence and geographic distribution of individuals with clinically and/or molecularly confirmed FOP and who were registered or associated with pre-determined regional, national or international FOP organizations. The apparent prevalence was calculated by dividing the number of living individuals with FOP by the respective resident population(s) obtained from contemporaneous United Nations sources [22].

Results

The total known and clinically confirmed population of the worldwide FOP community associated with a regional, national or international network of individuals with FOP

Table 1: Apparent prevalence of FOP by region in the global FOP community

Region	Number of countries	Individuals with FOP	Apparent Prevalence (per 10^6 individuals)
North America	2	231	0.6465
Oceania	2	15	0.5285
Western Europe	17	198	0.4735
Eastern Europe	13	87	0.3048
Latin America	15	161	0.2758
Africa	4	10	0.0520
Asia/Pacific	14	132	0.0355
Totals	67	834	0.1494

in 2016 was 834 individuals [445 females (54%), 387 males (46%), gender not reported for two individuals] distributed in 67 of the world's 193 countries (35%). The 67 countries of the international FOP community were grouped in the following seven regions of the world: North America (Canada, United States); Latin America (Argentina, Bolivia, Brazil, Chile, Columbia, Cuba, Ecuador, Guatemala, Honduras, Mexico, Panama, Paraguay, Peru, Uruguay, Venezuela); Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Malta, Norway, Portugal, Netherlands, Spain, Switzerland, Sweden, United Kingdom); Eastern Europe (Armenia, Belorussia, Bosnia-Herzegovina, Croatia, Estonia, Georgia, Macedonia, Moldova, Poland, Romania, Russia, Serbia, Ukraine); Africa (Egypt, Libya, South Africa, Sudan); Asia-Pacific (Bangladesh, China & Taiwan, Hong Kong, India, Indonesia, Iran, Israel, Japan, Kazakhstan, Malaysia, North Korea, Pakistan, South Korea, Turkey) and Oceania (Australia, New Zealand). The greatest number of people living with FOP were located in North America (231/834; 28%), followed by Western Europe (198/834; 24%), Latin America (161/834; 19%), Asia-Pacific (132/834; 16%), Eastern Europe (87/834;10%), Oceania (15/834; 2%) and Africa (10/834; 1%).

The prevalence of FOP in each of the seven regions (expressed as the number of known individuals living with FOP in each region divided by the total population and adjusted per million individuals) varies substantially from approximately 0.65 per million in North America, 0.47 per million in Western Europe, and 0.27 per million in Latin America to 0.05 per million in Africa and nearly 0.04 per million in the Asia-Pacific region (Table 1).

The estimated prevalence often quoted for FOP is 0.5 per million individuals. However, our data reveal that 13 of the 67 countries of the FOP community have an apparent prevalence (prevalence based on currently available patients with confirmed FOP) that is higher than the estimated one. Thirteen countries (Sweden, Finland, Denmark, United Kingdom, Norway, United States, Poland, Chile, Argentina, Australia, Canada, Netherlands, and Italy) have an apparent prevalence of over 0.5 per million inhabitants (Table 2).

Table 2: Countries with the highest apparent prevalence of FOP

Country	Apparent Prevalence (per 10^6 individuals)
Sweden	1.428
Finland	1.098
Denmark	0.877
United Kingdom	0.877
Norway	0.769
United States	0.658
Poland	0.633
Chile	0.613
Argentina	0.599
Australia	0.588
Canada	0.559
Netherlands	0.532
Italy	0.526

Table 3: Decadal distribution of individuals in the global FOP community

Age range (years)	Individuals with FOP	Percentage
0-9	97	11.6
10-19	194	23.3
20-29	209	25
30-39	133	15.9
40-49	89	10.7
50-59	47	5.6
60-69	13	1.6
70-79	4	0.5
No data	48	5.8
Totals	834	100

Most individuals living with FOP (722/834; 87%) were alive in the first five decades (0-49 years of age) of their lives (Table 3). The largest percentage were individuals in the third decade of life (209/834; 25%) followed by those in the second decade of life (194/834; 23.3%).The relatively low number of individuals with FOP in the first decade of life (11.6%) is likely due to onset variability, delay in diagnosis and/or delay in reaching an established FOP organization (Table 3).

Discussion

Community was an important concept in our study.

Unlike other studies of apparent prevalence in FOP, our goal was to determine the number of true FOP patients who were associated with a regional, national or international FOP organization so that worldwide discrepancies in patient access to information, medical and social services and clinical trials could be more easily identified and remedied [24,25].

Our study documents a clinically confirmed worldwide population of 834 individuals with FOP who are associated with a regional, national or international FOP organization. This establishes a global apparent prevalence of approximately 0.15 per million individuals with enormous regional variability. The apparent global prevalence of FOP is more than three-fold lower than that previously estimated based on high ascertainment rates in circumscribed national populations [13,26-28]. This low apparent global prevalence and high regional variability is likely associated with lack of awareness of FOP in under-represented regions, delay in achieving the correct FOP diagnosis, lack of supporting regional infrastructure to patients and families and inability of individuals with FOP in remote or underserved areas to reach the international FOP community. Although these dramatic differences could be caused by lack of awareness of FOP in under-represented medical communities, it might also point out the possible effects of different genetic backgrounds or environmental factors which might affect the activity of mutated ACVR1 and thus penetrance of the phenotype.

If we hypothesize that all regions could attain the same level of ascertainment and apparent prevalence as the one estimated for Western Europe (0.47 per million) or North America (0.65 per million), we surmise the number of missing cases of FOP worldwide to be between 1800 to 2800 based on a population of around 5.5 billion for the countries included in the study (for the year 2015) and between 2600 and 4000 based on the total world population of more than seven billion people at the same time. Thus, a large proportion of those likely living with FOP are presently unaccounted for in the already-established regional, national and/or international FOP organizations. This estimation, based on regional ascertainment and apparent prevalence rates, may spearhead efforts to identify missing individuals in those regions with already established FOP organizations and promote support for the emergence of new FOP organizations in those countries and regions of the world where individuals with FOP are likely isolated, without support or information.

There are several caveats and limitations of this study worthy of note. First, the study only accounted for FOP patients who were registered with a regional, national and/or international FOP organization. Although most people from the FOP community find great benefits in being part of it, there are others with FOP who likely chose to remain isolated despite knowing the existence of FOP organizations.

Second, the data reported here are apparent prevalence rather than true prevalence since the global sources for data acquisition are still scarce and reflect bias of ascertainment. However, the apparent prevalence data reported here may provide a valuable snapshot of emerging FOP populations along with suggestions about the number of individuals with FOP that might be found in countries or regions with little or no organizational support structure. China, Italy, Poland, Russia, South Africa and Spain serve as instructive examples of countries that had no regional or national infrastructure in place prior to 2006 for reporting known FOP cases or estimating apparent prevalence data. The FOP gene discovery in 2006 focused attention on FOP and stimulated concerted efforts of committed families and physicians in each of the countries mentioned above to organize a vibrant local community to contribute to emerging representation in the global FOP community [27,29]. We anticipate that emergence of established and effective treatments will have a similar mobilization effect on identification of additional patients in the global FOP community.

Third, there are other methodologies that can be used to attain epidemiologic data on the prevalence of FOP. As an example, while this study was being conducted, an independent inquiry using an entirely different methodology and rationale was being conducted in France [26]. Unlike our study, the goal of the French study was to estimate the true prevalence of FOP in France by probabilistic record-linkage of two anonymous national databases using a well-established capture-recapture approach. Eighty-nine FOP patients were identified across France, resulting in an estimated prevalence of 1.36 per million inhabitants [26]. Thus, unlike in our study, the ultimate goal was different and screening for false positives was necessary. In contrast, all patients in our study had a confirmed clinical and/or molecular diagnosis of FOP. Thus filters to detect false positives when anonymous databases of generic rare diseases or medical insurance data are used were unnecessary [24-26].

Fourth, after we conducted this study, the IFOPA launched The FOP Connection Registry, an international, voluntary, observational study that directly captures demographic and disease information from patients with FOP. The guiding vision was to develop one unified, global registry allowing the assembly of comprehensive data on FOP that will facilitate development of therapies and tracking of their long-term treatment effectiveness and safety. Patient-reported, aggregate data from 196 enrolled patients represent participation from 42 countries and approximately 25% of the world's known FOP population and promises to add important demographic information to the emerging epidemiologic data worldwide [30].

The data from this study strongly suggest that sophisticated health systems with well-developed patient and community outreach facilitate prompt FOP diagnosis, promote active FOP community leaders who search for patients, and seem to be the major factors for achieving greater ascertainment of FOP patients while building a vibrant FOP community. In those regions where there are few patients affiliated with a patient organization, efforts are underway to promote FOP awareness and the search for undiagnosed individuals with FOP. For example, the global search for individuals with FOP, especially in developing nations, has recently been given international attention by the acclaimed documentary Tin Soldiers [31].

Conclusions

Emerging knowledge of the regional apparent prevalence of FOP can serve as a catalyst for resource allotment; physician, patient and community education and outreach; clinical trial recruitment and global networking to develop a more globally inter-connected FOP community.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ML conceived, designed and executed the study. ML & FSK wrote the manuscript. All authors interpreted the data, revised and approved the manuscript.

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