The FOP Registry: A Global Observational Study of Fibrodysplasia Ossificans Progressiva

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Introduction

Fibrodysplasia Ossificans Progressiva (FOP) is an ultra-rare, progressive genetic disorder that has an estimated prevalence of 0.5-1.3 per million. FOP is characterized by the formation of extraskeletal bone (heterotopic ossification) usually beginning in early childhood, and ultimately leading to pain, muscle destruction, joint fusion, progressive immobilization, and premature death.

The International FOP Association (IFOPA), a global patient association, developed the FOP Registry in 2015 to establish a single repository of clinical data on people living with FOP. The Registry is guided by a clinical protocol and informed consent, which have been approved by a centralized ethics committee. The FOP Registry also has a governance structure, including a Medical Board of Advisors to guide its conduct. The FOP Registry, which now includes a patient and medical portal, will advance our understanding of FOP, enhance clinical care, and facilitate clinical trial designs.

Methodology

The FOP Registry is an international, voluntary, observational study that captures demographic, socioeconomic, and disease information directly from patients with FOP via a secure web-based tool and from physicians who are caring for these patients. No experimental intervention is involved.

The FOP Registry is open to any patient with FOP across the globe, regardless of age or genotype status. To encourage global participation, the FOP Registry is currently translated into 7 languages: English, French, German, Spanish, Portuguese, Italian and Russian. Before enrolling into the registry, participants must first sign an informed consent and/or assent for minors.

The FOP Registry collects data from two portals:

Patient Portal

The Patient Portal allows FOP patients and caregivers to enter information about themselves and their experience living with FOP directly into a web-based data collection tool. Data is collected at enrollment into the Registry and then every 6 months.

Physician Portal

The Physician Portal allows physicians to enter clinical data about patients under their care, which could include information on specific marketed therapies. Patient data in the Physician Portal will be linked by key identifiers to the corresponding patient data in the Patient Portal.

Results

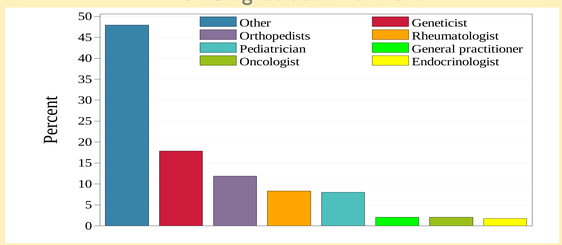
As of March 2019, the FOP Registry had 336 participants, or approximately 42% of the world's known FOP population, participating from 54 countries. Fifty-three (53%) percent of the current Registry participants are female, with a median age for all participants of 21 years (range = 0.4 - 78 years). The journey to a correct diagnosis took an average of 2 years after symptom onset at a median age of 3 years (range = 0.1 - 45 years). People with FOP are diagnosed earlier than prior generations, with a median age of diagnoses of 2 for individuals < 18 years, versus 8 for adults.

Baseline and Demographic Characteristics

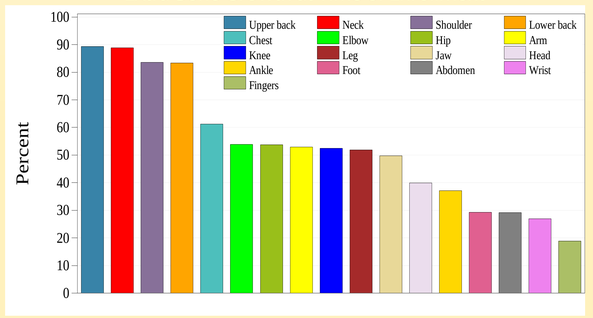
Category	Age < 18 yrs (N=140)	Age >= 18 yrs (N=196)
Age (yrs) - Median (range)	10.0 (0.4, 17.0)	31.0 (18.0, 78.0)
Age at first symptom onset (yrs) - Median (range)	1.9 (0.1, 14.0)	5.0 (0.1, 45.0)
Age at diagnosis (yrs) – Median (range)	2.0 (0.1, 15.0)	8.0 (0.1, 48.0)
Gender (%)		
Male	82 (58.6)	71 (36.2)
Female	58 (41.4)	123 (62.8)
Other	0 (0.0)	2 (1.0)
Race/Ethnicity		
Asian	11 (7.9)	8 (4.1)
White	74 (52.9)	113 (57.7)
Black or African American	3 (2.1)	3 (1.5)
American Indian or Alaska Native	1 (0.7)	1 (0.5)
Other/Unknown	7 (5.0)	10 (5.1)
Missing	44 (31.4)	61 (31.1)
Type of FOP		
FOP variant	7 (5.0)	8 (4.1)
FOP classic (R206H mutation)	59 (42.1)	61 (31.1)
FOP, type not known	31 (22.1)	65 (33.2)
Missing	43 (30.7)	62 (31.6)

Geneticists and Orthopedists are the two most common physician specialists providing a definitive diagnosis of FOP. Approximately one quarter of Registry participants first sought care from a pediatrician for their FOP symptoms, but only 8% of participants reported that a pediatrician provided their correct diagnosis. At enrollment, participants reported the most extra bone growth in the neck, upper back, lower back, shoulder, hip, jaw, and head. Heterotopic ossification resulted in a total loss of joint mobility, with the shoulder, upper back, and neck reported as the three most prevalent body regions. As FOP is a progressive disease, there are differences in total loss of mobility between adults (>= 18 years) and children (< 18 years), with the most pronounced differences in the

Specialty of Physician Who Provided Correct FOP Diagnosis at Enrollment

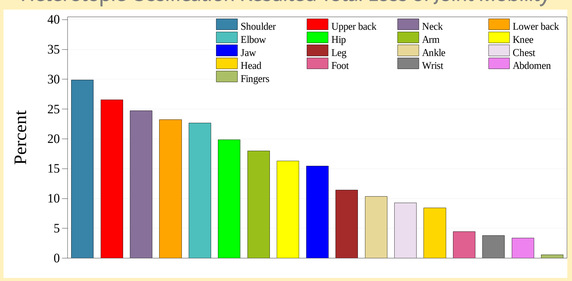


Extra Bone Growth at Time of Enrollment



shoulders, elbows, and hips. For example, 39.8% of adult participants reported a total loss of mobility due to heterotopic bone in either shoulder, while just 13.9% of children reported a total loss of mobility in this body region. Similar trends in total loss of mobility between adults and children are seen among other body locations, albeit at different magnitudes.

Heterotopic Ossification Resulted Total Loss of Joint Mobility



People living with FOP have a dramatic increase in healthcare resource utilization with 86.4% of FOP Registry participants reporting that they visited a medical doctor for any reason in the 12 months prior to registration. These participants reported a median of 10.5 visits to a medical doctor (Range: 1 – 25 visits) in the prior 12 months, and five percent (5%) reported greater than 25 visits for medical care in the same period. Further, 28.2% of the participants were admitted to the hospital in the preceding 12 months, as a result of a fall, injury, accident or fracture, which collectively instigated 25.8% of all hospital visits.

Medical Care and Clinical Research

Category	Age < 18 yrs (N=140)	Age >= 18 yrs (N=196)
Number of times visited MD for physical health n (%)		
0	8/ 92 (8.7)	22/128 (17.2)
>=1	84/ 92 (91.3)	106/128 (82.8)
Number of times visited MD for psychological/emotional health n (%)		
0	81/ 93 (87.1)	95/128 (74.2)
>=1	12/93 (12.9)	33/128 (25.8)
Number of times admitted to the hospital n (%)		
0	63/ 92 (68.5)	95/128 (74.2)
>=1	29/ 92 (31.5)	33/128 (25.8)
Reason(s) for the hospital admission(s) n (%)		
Pain management	4/ 29 (13.8)	15/ 33 (45.5)
Respiratory or pulmonary infection or illness	7/ 29 (24.1)	4/ 33 (12.1)
Fall, injury, accident or fracture	6/ 29 (20.7)	10/ 33 (30.3)
Dental procedure	2/ 29 (6.9)	4/ 33 (12.1)
Surgical procedure	3/ 29 (10.3)	5/ 33 (15.2)
Outpatient procedure	5/ 29 (17.2)	4/ 33 (12.1)
Other	21/ 29 (72.4)	17/ 33 (51.5)
Participated in past clinical trial n (%)		
No	81/ 93 (87.1)	99/128 (77.3)
Yes	10/ 93 (10.7)	24/128 (18.8)
Not sure	2/ 93 (2.2)	5/128 (3.9)
Donated a sample of blood, tissue, or biospecimen?	57/ 93 (61.3)	48/127 (37.8)
No	31/ 93 (33.3)	66/127 (52.0)
Yes	5/ 93 (5.4)	13/127 (10.2)
Not sure		
Type of biospecimen donated		
Blood	24/ 30 (80.0)	56/ 63 (88.9)
Saliva/cheek	6/ 30 (20.0)	7/ 63 (11.1)
Urine	7/ 30 (23.3)	16/ 63 (25.4)
Tissue	0 (0.0)	15/ 63 (23.8)
Teeth	16/ 30 (53.3)	8/ 63 (12.7)
Other	1/ 30 (3.3)	1/ 63 (1.6)

Conclusion

Patient registries have played a prominent role in helping to elucidate the natural history of rare diseases – knowledge that is critical in the design and conduct of clinical trials. Patient registries can empower rare disease communities to directly contribute to research. The FOP Registry is well on its way to helping the FOP community to achieve these ambitious and urgent goals.

Acknowledgements

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