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The Diagnostic Journey in Fibrodysplasia Ossificans Progressiva: Insights from the FOP Registry

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FOP Registry

INTRODUCTION

Fibrodysplasia Ossificans Progressiva (FOP) is an ultra-rare, disabling genetic disease that causes bone to form in muscle, tendons, ligaments, and other connective tissues. One of the hallmark characteristics of FOP is the malformation of the great toes, which is present in nearly all individuals with FOP. The great toe malformation, along with heterotopic ossification, are early signposts for a definitive clinical diagnosis. However, given its rarity, a diagnosis of FOP is often missed at birth and delayed for years.

The International FOP Association (IFOPA), a global patient association, developed the FOP Registry in 2015 to establish a central source of clinical data on people living with FOP. The Registry is conducted as a longitudinal observational study, approved by a centralized ethics committee. A Medical Board of Advisors was established to oversee the conduct and strategic direction of the FOP Registry. The FOP Registry, which now includes a patient and physician portal, will advance our understanding of FOP, enhance clinical care, and facilitate clinical trial designs.

METHOD

The FOP Registry is an international, voluntary, observational study that captures demographic 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 a global study available to FOP patients and their physicians worldwide. To encourage global participation, the FOP Registry has been 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 and confirm their diagnosis of FOP.

Two different data portals have been developed to capture data:

Patient Portal

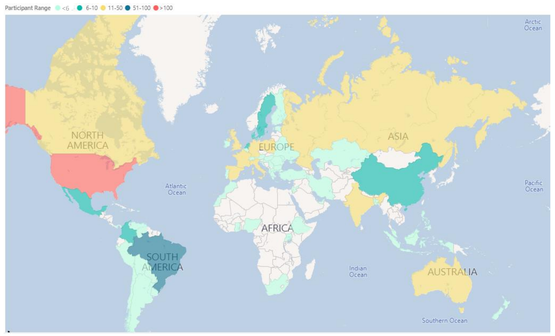
The Patient Portal allows FOP patients and caregivers to enter information about themselves and their experience living with FOP directly into a web-based data collection tool. Data is collected at enrollment into the Registry and then every 6 months.

Physician Portal

The Physician Portal allows physicians to enter clinical data about patients under their care. Patient data in the Physician Portal may be linked by key identifiers to the corresponding patient data in the Patient Portal.

RESULTS

The FOP Registry is the largest source of clinical data on people living with FOP with 415 participants – or approximately 45% of the known FOP population -- enrolled from 67 countries around the world.



Data from the FOP Registry shows the mean age of symptom onset to be 6.2 years (range, 0 – 45), whereas the age at correct diagnosis is 8.3 years (range, 0 – 48). Diagnosis takes on average longer in those patients who have the variant mutation forms of FOP versus those who have the classic FOP mutation (18.6 vs. 7.0 years).

Age of Diagnosis by FOP Mutation

	Mutation Type Unknown	FOP Variant Mutation	FOP Classic (R206H) Mutation	All FOP Mutations*
	N = 108	N = 25	N= 147	N = 299
Mean Age (Years) at Diagnosis	7.8	18.6	7.0	8.3
Range	0.0 - 38.0	0.6 - 48.0	0.0 - 33.0	0.0 - 48.0

Participants who did not know their mutation type had the option to list their mutation type as "uknown". Participants who skipped the mutation question were listed as "missing".
*Includes 19 participants with missing mutation data, in addition to 108 participants with unknown mutation type

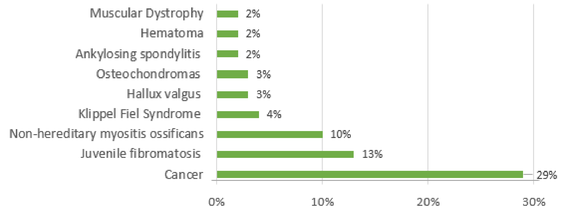
The diagnostic journey has shortened over the last four years, with patients taking on average 1.5 years to receive a correct diagnosis after their first symptom, compared to 2.2 years for participants who were diagnosed prior to 2016. This 32% decrease in age of diagnosis is likely to due to increased overall awareness of FOP due to media coverage, research and drug development activity.

Time From Symptom Onset to Diagnosis

	< 2016	≥2016	Total
	N = 238	N = 25	N = 299
Mean Time to Diagnosis	2.2 years	1.5 years	2.1 years
Range	0.0 - 22.0 years	0.0 - 13.0 years	0.0 - 22.0 years

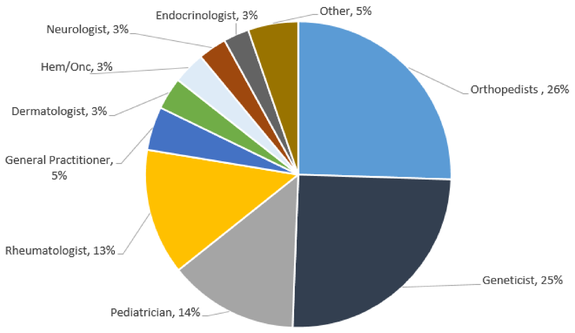
Prior to receiving a correct diagnosis, patients see on average 3.3 physician specialties (range, 1 – 10); this average has remained remarkably stable over time. Similar to many rare diseases, misdiagnoses in FOP are common. Slightly over half (52.5%) of FOP Registry participants noted receiving a misdiagnosis. For those who received an incorrect diagnosis, the three most common conditions noted are cancer (29%), juvenile fibromatosis (13%) and myositis ossificans (10%). Other erroneous diagnoses include Klippel Fiel Syndrome (4%), hallux valgus (3%), and osteochondromas (3%).

Most Common Misdiagnoses in FOP



Orthopedists (25.5%), geneticists (25.1%), and pediatricians (13.7%) are the most common physician specialists providing the definitive diagnosis for FOP. When first symptom onset occurs after the age of 12, rheumatologists (19.0%) play a larger role in providing the correct diagnosis.

Physician Specialties Correctly Diagnosing FOP Symptoms



Several physician specialties have high rates of misdiagnosis as a ratio of correct diagnoses given. General physicians are 8.9 times more likely to make an incorrect diagnosis for every correct diagnosis given, followed by pediatricians (5.5), orthopedists (2.5), rheumatologists (1.9) and geneticists (0.9). These rates provide a roadmap for further disease awareness education within these medical specialties.

CONCLUSIONS

Patient registries play a prominent role in assisting medical communities to better understand the natural history of rare diseases. Registries can also help these communities better understand the diagnostic journey taken to receive the correct diagnosis, which is critical to ensuring patients receive the proper clinical care and support services. With a misdiagnosis rate over 50%, more disease awareness is essential to increase clinicians' index of suspicion for FOP.

ACKNOWLEDGEMENTS

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CONTACT INFORMATION

To learn more about the FOP Registry, please visit fopregistry.org or ifopa.org/fopregistry, or email us at help@fopregistry.org.