**New Insights into Fibrillinopathies and Pitfalls of Variant Filtering in the Current Genomics Era**

Meienberg J1, Najafi A2, Caspar SM1, Rohrbach M1, Steinmann B2, Matyas G1,4

1Center for Cardiovascular Genetics and Gene Diagnostics, Foundation for People with Rare Diseases, Schlieren-Zurich, Switzerland; 2Cantonal Hospital Winterthur, Institute of Radiology and Nuclear Medicine, Winterthur, Switzerland; 3Division of Metabolism and Children’s Research Center, University Children’s Hospital Zurich Eleonore Foundation, Switzerland; 4Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland; These authors contributed equally to this work.

Contact: meienberg@genetikzentrum.ch, matyas@genetikzentrum.ch

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**Conclusions**

- FBN1/FBN2 dual mutations cause a mixed phenotype of MFS and CCA, thereby increasing or hiding certain clinical features of these fibrillinopathies.

- We show the presence and assess the frequency of disease-affected individuals in apparently healthy reference databases, demonstrating a pitfall in NGS variant interpretation.

- gnomAD-based prevalence estimates are 6.100 per 10,000 for MFS and 3.100 per 10,000 for CCA.

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**Introduction:** Fibrillinopathies such as FBN1-related Marfan syndrome (MFS) and FBN2-related congenital contractual arachnodactyly (CCA) are characterized by a wide and overlapping range of clinical signs with neonatal to adult onset. Although the underlying molecular etiology of MFS and CCA has been known since 1991 and 1995, respectively, their prevalence, co-occurrence, and genetic modifiers have only been estimated or are unknown. Here we address these issues by assessing the frequency of pathogenic FBN1 and FBN2 sequence variants in the largest Swiss database of MFS genomes as well as in the Genome Aggregation Database (gnomAD).

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**Results:** We detected two families harboring FBN1/FBN2 dual mutations resulting in modified MFS/CCA phenotypes (Figure 1, Table 1). In dual mutation carriers, certain clinical features of fibrillinopathies such as aortic dilation (Ab4 and Ac1) and scoliosis (Ab2 and Ac1) are exaggerated, while for other clinical features, although inconsistently, the effect of one of the mutations appears to dominate. For example, in Family 1 the dual mutation carriers (Ab2 and Ab4) show CCA-associated finger and elbow contractures (Figure 2), whereas in Family 2 the dual mutation carrier (Ac1) shows MFS-related elbow hyperextension but no CCA-specific contractures. Moreover, we show the presence of clearly pathogenic FBN1 and FBN2 sequence variants in the apparently healthy reference cohort gnomAD, allowing the calculation of gnomAD-based minimal prevalence estimates of 6.100 and 3.100 for MFS and CCA, respectively (Figure 3, Table 2).

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**Materials and Methods:** Whole genomes (60 x PCR-free WGS, PE150) of ~450 Swiss patients with MFS or rare (aortic) disorders were screened for sequence variants in FBN1, FBN2, and other related genes. Variant confirmations and segregation analyses were performed using Sanger sequencing. Moreover, we queried gnomAD for different types of a priori pathogenic sequence variants in FBN1 and in the CCA-associated exons 23-34 in FBN2 (Table 2) and thereby calculated conservative prevalence estimates for MFS and CCA.

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