Beyond FBN1: Multigene Panel Testing for Marfan syndrome

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Introduction: With clinical overlap between Marfan syndrome (MFS) and connective tissue disorders, diagnosis may not be clear without genetic testing. Multigene panel testing for (MGPT) may confirm clinical diagnosis or establish diagnosis in individuals in whom clinical features do not meet established guidelines. Identifying a genetic etiology may aid counseling and medical management, leading to improved prognosis. Herein, we sought to assess the phenotypic spectrum of individuals with clinical features of MFS who underwent MGPT for MFS. **Methods:** We performed a retrospective analysis of provided clinical records and results from a 22 gene panel test for MFS and thoracic aortic aneurysm/dissection (TAAD) (*ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2*) for 1462 sequential patients with reported MFS clinical features. **Results:** Overall, 142 patients (9.7%) had positive results. Of these 142 patients, 52 (36.6%) were positives in genes other than *FBN1*. Patients with aortic aneurysm/dilation, aneurysms in other arterial locations, aortic/vascular dissection, myopia, scoliosis and/or joint hypermobility were more likely to have findings in genes other than *FBN1* (all $p < 0.0001$) as were patients with pectus deformity and/or facial clefts ($p= 0.0013, 0.0068$, respectively). Two (3.8%) patients with a clinical diagnosis of MFS were positive in *TGFB2* and *SMAD4*. There were no differences in other reported clinical features or family history in patients with *FBN1* mutations versus other genes. **Conclusions:** Our data suggests that individuals with clinical features of Marfan syndrome may benefit from MGPT, especially when features overlap with other associated conditions. An appropriate molecular diagnosis may lead to a more successful and appropriate treatment plan. These data emphasize the importance of counseling patients with features of MFS about the likelihood of a positive result in many overlapping conditions within the clinical spectrum.