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Marfan syndrome and related disorders: A genetic panel approach

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In a recently published study spearheaded by Giovanny Fuentevilla-Álvarez and his team at the National Institute of Cardiology in Mexico, researchers have significantly advanced the diagnostic precision for

Marfan syndrome (MFS) and a spectrum of connective tissue disorders.

This comprehensive study, involving 136 Mexican patients, leverages the latest in genetic multipanel testing and next-generation sequencing to unravel the complex interplay between genotype and phenotype in these multifaceted conditions. The study not only highlights the diversity of genetic mutations present in these disorders but also sets a new standard for diagnosing and managing them with a more personalized approach.

Marfan syndrome (MFS) is a complex genetic disorder impacting connective tissue and presenting with a wide range of manifestations in the skeletal, ocular, and cardiovascular systems.

Named after Antoine Marfan, the French pediatrician who first described the condition in 1896, MFS affects connective tissue, providing essential support and elasticity to various body parts. Despite its genetic basis, the syndrome's effects are wide-ranging, leading to diverse manifestations within individuals and families.

The primary cause of MFS is mutations in the FBN1 gene, responsible for producing fibrillin-1. This condition follows an autosomal dominant inheritance pattern, meaning a single altered FBN1 gene copy can lead to the disorder. Notably, about 25% of cases arise from spontaneous mutations with no prior family history.

MFS is characterized by:

- **Cardiovascular issues:** Aortic dilation poses the greatest risk, potentially leading to life-threatening complications like dissection and rupture. Valve malfunctions, including mitral and tricuspid valve prolapse, are also prevalent.
- **Skeletal abnormalities:** Common features include a tall, slender body, long extremities, scoliosis, and chest deformities,

reflecting the syndrome's impact on the skeletal structure.
- **Ocular complications:** Lens dislocation (ectopia lentis) is a signature issue, alongside other problems such as myopia and retinal detachment.

Diagnosis relies on the Ghent nosology, which combines major and minor criteria across affected systems. Genetic testing, particularly for FBN1 mutations, plays a crucial role in confirming MFS, especially in cases where clinical presentation is ambiguous.

While no cure exists, management strategies focusing on cardiovascular risk monitoring, surgical interventions for severe complications, and comprehensive support can significantly improve outcomes. Medications like beta-blockers, regular monitoring through imaging, and targeted surgeries for aortic and valve issues are central to treatment plans.

A Novel Approach to Diagnosis: The Genetic Panel Diagnosis based on clinical characteristics vs. clinical and genetic diagnosis: In the clinical evaluation based on four clinical criteria (AHF, aortic dilatation, ectopia lentis, and systemic score), 75 cases were identified as MFS.

The research team at the National Institute of Cardiology in Mexico, led by Giovanny Fuentevilla-Álvarez et al., investigated the diagnostic potential of connective tissue disorders through a genetic multipanel that included 174 genes associated with cardiovascular diseases, cardiomyopathies, arrhythmias, and structural heart diseases.

The study cohort consisted of 136 patients who were initially evaluated and classified based on the 2010 Ghent criteria, necessitating a comprehensive diagnostic process involving extensive imaging studies and genetic testing.

Patients were selected for this prospective observational study based on their clinical presentation and family history, with a significant number undergoing comprehensive cardiovascular evaluations through echocardiography, MRI, or CT scans.

Those requiring surgical interventions for aortic dissection or dilation were closely examined to correlate genetic mutations with the severity of cardiovascular conditions, providing invaluable insights into the genetic underpinnings of disease progression and therapeutic outcomes.

The genetic multipanel revealed significant variability in mutations, leading to a reclassification of many patients' initial diagnoses. Notably, the study uncovered a prevalent frameshift mutation in the TGFBR2 gene among Loeys–Dietz syndrome patients, a finding that underscores the critical role of genetic testing in identifying specific mutations linked to severe cardiovascular conditions.

Furthermore, the high prevalence of severe mutations, such as frameshift indels and stop codons, especially among patients requiring complex surgical interventions, highlights the importance of genetic analysis in guiding clinical decision-making and personalized treatment plans.

Giovanny Fuentevilla-Álvarez, the study's lead author, remarked, "Our findings brighten the vast genetic diversity underlying Marfan syndrome and related disorders. By employing a comprehensive genetic panel, we are not just diagnosing diseases; we are unlocking the door to personalized medicine that caters to the unique genetic makeup of each patient."

Senior author Ricardo Gamboa added, "This study marks a paradigm shift in how we approach connective tissue disorders. The intricate relationship between genetic mutations and clinical manifestations challenges us to rethink our diagnostic and therapeutic strategies, making patient-specific genetic information a cornerstone of effective management."

Step forward to personalized treatment of Marfan syndrome

The study's implications extend far beyond the immediate findings. By demonstrating the utility of genetic panels in diagnosing connective tissue disorders, the research advocates for a more integrated approach that combines clinical evaluation with detailed genetic analysis. This not only enhances diagnostic accuracy but also paves the way for targeted therapies that address the genetic root of these conditions.

The innovative use of a genetic multipanel in the classification and management of Marfan syndrome and related disorders represents a significant leap forward in personalized medicine.

By illuminating the complex genotype–phenotype relationships, this study offers a blueprint for the future of diagnosis and treatment in the field of connective tissue disorders. Moving forward, the integration of comprehensive genetic testing into clinical practice promises to not only improve patient outcomes but also to enhance our understanding of these multifaceted diseases.

The work is published in the journal *Biomolecules and Biomedicine*.

More information: Giovanny Fuentevilla-Álvarez et al, The usefulness of the genetic panel in the classification and refinement of diagnostic accuracy of Mexican patients with Marfan syndrome and other connective tissue disorders, *Biomolecules and Biomedicine* (2023). DOI: 10.17305/bb.2023.9578