The role of TBX20 truncating variants in dilated and left ventricular non-compaction cardiomyopathy

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Background: The genetic cause of dilated cardiomyopathy (DCM) remains unexplained in a considerable proportion of cases. TBX20, the T-Box transcription factor 20 gene, has been linked to cardiac septal defects. Although only a few case reports have described an association between TBX20 and DCM/left ventricular non-compaction (LVNC), there are no case-control studies available, and TBX20 is still considered a gene with limited evidence for these phenotypes.

Objectives: This study sought to investigate the relationship between truncating variants in TBX20 (TBX20tv) and the development of DCM and LVNC.

Methods: TBX20 was sequenced using massive parallel sequencing in 7,463 unrelated probands with DCM/LVNC and 22,773 probands with other diagnoses (e.g., hypertrophic or arrhythmogenic cardiomyopathy, channelopathies, or aortic diseases) as internal controls. It was tested for enrichment and cosegregation of TBX20tv in DCM/LVNC, and clinical characteristics and outcomes in carriers were analyzed.

Results: Twenty-four probands with 22 TBX20tv were identified. Variant frequencies were significantly higher in patients with DCM/LVNC (24/7,463; 0.29%) than in internal controls (2/22,773; 0.008%), with an OR of 70.18 (CI95%: 9.48 to 519.8; p<0.0001) and 95.61 (CI95%: 33.06-276.55; p<0.0001), respectively. Cosegregation was studied in 21 families, identifying 57 carriers, of whom 43 (75.4%) had cardiac involvement. A combined LODs score of 4.41 was obtained, which is indicative of very strong segregation.

Regarding clinical characteristics, the mean age at diagnosis was 37 years old, and 50% of carriers were female. Forty-six percent developed left-ventricular dysfunction, which was moderate to severe in half of the cases. Three carriers received a heart transplant, and another carrier died due to heart failure.

Congenital heart defects were present in 16 patients (28.1%). Valvular involvement was the most frequent congenital abnormality (5 cases had bicuspid aortic valve, and another 5 had mitral valve defects), followed by heart septal defects (3 atrial and 3 ventricular); coronary anomalies (2) and aortic coarctation (2) were also detected. In some patients, these defects presented as complex congenital heart disease.

Conclusions: TBX20tv are associated with the development of dilated and non-compaction cardiomyopathy, and the presence of congenital heart defects is also common. Although some carriers, particularly younger ones, may not present the phenotype, nearly half of them experience ventricular dysfunction, and significant cardiac events, such as cardiac death or transplantation, are not uncommon. Therefore, the TBX20 gene should be routinely included in genetic testing panels for DCM and LVNC.