[gw22-e0960]

SYSTEMIC MUTATIONAL ANALYSIS OF THE TGF β SIGNALLING PATHWAY IN THORACIC AORTIC ANEURYSMS AND DISSECTIONS

Wen-Jing Wang,¹ Jun Zheng,² Fang-Yuan Hu,¹ Yun Zhu,¹ Jin-Sheng Xie,² Jian Guo,¹ Zhe Zhang,³ Jie Dong,¹ Gu-Yan Zheng,¹ Huiqing Cao,¹ Tian-Shu Liu,¹ Peili Han,⁴ Qinglin Fu,⁴ Lihong Sun,² Bi-Bo Yang,² Xiao-Li Tian¹ ¹*Department of Human Population Genetics, Institute of Molecular Medicine, Peking University;* ²*Department of Cardiovascular Surgery, Beijing Anzhen Hospital of the Capital University of Medical Sciences;* ³*Department of Cardiac Surgery, Peking University Third Hospital;* ⁴*Department of Cardiovascular Surgery, The First Affiliated Hospital of Xinxiang Medical University*

10.1136/heartjnl-2011-300867.665

Purpose Excessive activation of the TGF β signalling pathway caused by genetic mutations is known to be responsible for the inherited thoracic aortic aneurysms and dissections (TAAD) that is life-threatening and characterised by a broad spectrum of connective tissue disorders. This study was designed to figure out: (1) whether other components in the TGF β signalling pathway contribute to TAAD and (2) whether mutations in the TGF β signalling pathway account for the majority of TAAD sufferers.

Methods We performed mutational screening in the critical components associated with the TGF β signalling pathway and its target genes, including TGF β 1, TGF β R1, TGF β R2, SMAD2, SMAD3, SMAD4, SMAD6, SMAD7, FBN1, BGN, EFEMP2, TAGLN and ACTA2 genes in 21 sporadic TAAD participants and 8 affected families from Han Chinese. Additionally we reviewed all mutational studies of FBN1 and identified several features in the correlation between genotypes and clinical manifestations in Chinese patients compared with other ethnic groups.

Results Of 29 identified sequence variants, 23 were potential mutations in FBN1, TGF β R2, SMAD2 and SMAD3 as were not found in 500 healthy individuals, accounting for 80% of TAAD patients. Six appeared novel SNPs in FBN1, SMAD3 and SMAD7. We demonstrated that c.5917+6T>C caused skipping of exon 47, leading to the loss of the 29th cbEGF-like domain associated with Marfan syndrome without ectopia lentis.

Conclusions Our study indicates that genetic alteration of TGF β signalling pathway is a major cause for the inherited form of TAAD despite of ethnic effects.