Compound inheritance of *TBX6* gene variants in congenital scoliosis

With the support by the National Natural Science Foundation of China and National Basic Research Program of China, the multi-center study led by Professor Zhang Feng at Fudan University and Professor Qiu Guixing at Peking Union Medical College Hospital identified novel mutations of the *TBX6* gene in Chinese patients with congenital scoliosis and reported the compound inheritance of *TBX6* in congenital scoliosis. This collaborative work was published in *New England Journal of Medicine* (2015, 372: 341—50).

Congenital scoliosis (CS) is a form of vertebral malformation resulting from defects in vertebrate formation during embryogenesis. Genetic mutations have been implicated in human CS. The genome-wide analysis of copy-number variation identified twelve 16p11.2/*TBX6* deletions in 161 sporadic CS patients, whereas none in 166 Han Chinese controls. In the non-deletion patients, five novel null mutations were also identified in *TBX6*. However, the discordant intra-familial phenotypes of 16p11.2/*TBX6* deletion carriers suggest that heterozygous null *TBX6* is insufficient to cause CS. Notably, all 17 carriers of *TBX6* null mutations share a common *TBX6* haplotype as the second risk allele ($P<1.1\times10^{-6}$). Replication studies in additional patients with CS who carried a *TBX6* deletion confirmed this compound inheritance model. *In vitro* functional assays suggest that the risk haplotype is a hypomorphic allele. Compound inheritance of a rare null mutation and a hypomorphic allele of *TBX6* accounts for 7.9%—10.6% of the studied CS populations. *TBX6* mutations and variants therefore contribute substantively to the complex trait of sporadic CS. These findings will enable the molecular diagnosis of and genetic counseling for some persons with or at risk of developing the disorder.

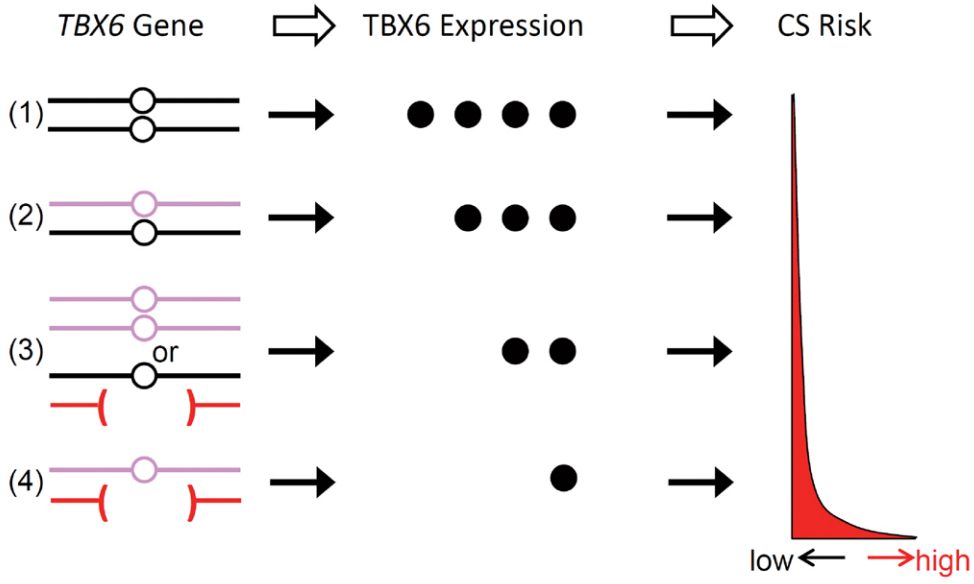

Figure A simplified model of compound inheritance for *TBX6*-associated CS. (1) *TBX6* gene expression is critical to normal vertebral formation. (2) Heterozygous hypomorphic variants (in pink) only cause moderate reduction in *TBX6* expression. (3) Even the homozygote of hypomorphic variants will not reduce *TBX6* expression dramatically. Heterozygous *TBX6* null mutations (red bracket) may only cause half reduction in gene expression. Both of these situations hardly reach the gene dosage threshold of CS. (4) Once a null allele and a hypomorphic allele of *TBX6* co-exist, the further reductions in gene expression may consequently lead to a high risk of CS.