TBX6-associated congenital scoliosis (TACS) as a clinically distinguishable subtype of congenital scoliosis: Further evidence supporting the compound inheritance and *TBX6* gene dosage model

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Qiu GuiXing (邱贵兴) and Dr. Wu Nan (吴南) at the Department of Orthopedic Surgery, Beijing Key Laboratory for Genetic Research of Skeletal Deformity, Peking Union Medical College Hospital, recently reported that *TBX6*-associated congenital scoliosis (TACS) is a clinically distinguishable subtype of congenital scoliosis as further evidence supporting the compound inheritance and *TBX6* gene dosage model, which was published in *Genetics in Medicine* (2019, Jan 14, doi: 10.1038/s41436-018-0377-x).

Congenital scoliosis (CS) is a congenital deformity of the spine accompaned by multi-organ comorbidities at a prevalence of 0.5‰—1‰. The *TBX6*-based compound inheritance model, a rare *TBX6* loss-of-function mutation *in trans* with a common hypomorphic haplotype, has recently been established as the most important genetic etiology accounting for 7.9%—10.6% of worldwide CS sporadic patients [Wu N et al., *N Engl J Med*, 2015, 372(4): 341—350]. However, the phenotypic features and clinical relevance of the TACS are still unclear. In three independent multi-center global cohorts, patients with TACS showed remarkably consistent clinical features: hemivertebrae/butterfly vertebrae involving lower part of the spine, simple rib anomaly, fewer vertebrae and intraspinal defects. These clinical findings were recapitulated in a gene-editing mouse model with $Tbx6^{-/\text{mild-hypomorphic(mh)}}$ mutations [Yang N et al., *Hum Mol Genet*, 2019, 28(4): 539—547, doi: 10.1093/hmg/ddy358]. A clinical diagnostic algorithm (TACScore) was developed to increase the efficiency for identifying TACS, which enables clinical implementation of the early intervention and genetic consultation.

This study is an extension of the Deciphering Disorders Involving Scoliosis and COmorbidities (DISCO) study (http://www.discostudy.org), which is committed to interpreting the genomic data produced from all the subjects in the study over the coming years, aiming to increase the diagnostic yield, and decipher the novel genetic etiology as well as the disease mechanisms. This publication was highlighted by the Centers for Mendelian Genomics (http://mendelian.org) and the milestone review article of genetic study of Mendelian diseases (Posey JE et al., Genet Med, 2019, Jan 18, doi: 10.1038/s41436-018-0408-7).

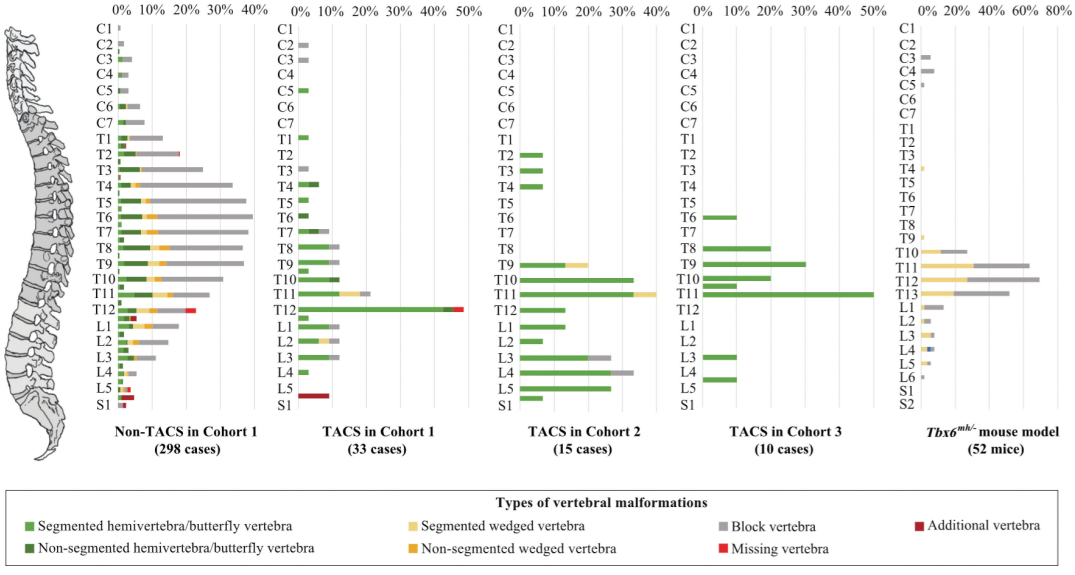

Figure Comparison of the Distribution Regarding Abnormal Vertebrae in Non-TACS and TACS Patients and in $Tbx6^{-/mh}$ Mouse Compound Inheritance and Gene Dosage Model.