0031-3998/01/5003-0307
PEDIATRIC RESEARCH
Vol. 50, No. 3, 2001
Printed in U.S.A.

RESEARCH NEWS

Wrapping Up DiGeorge Syndrome in a T-box?

A review of: Jerome AL, Papaioannou V 2001 DiGeorge syndrome phenotype in mice mutant for the T-box gene, *Tbx1*. Nature Genet 27:286–291

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DIGEORGE SYNDROME (DGS) is characterized by congenital heart disease with parathyroid and thymic hypoplasia. Patients with related velocardiofacial syndrome (VCFS) have similar conotruncal defects and abnormal facies. Most patients with DGS/VCFS have chromosome 22q deletions that commonly include 24 contiguous genes (1). However, human genetic studies have failed to identify specific gene mutations to account for individual components of this multi-organ phenotype. Therefore, investigators have now used "knockout" mice to study genes deleted in DGS/VCFS. Scientists have focused on neural crest-related genes since the pharyngeal and aortic arches which develop abnormally in DGS/VCFS are neural crest-derived.

Jerome and Papaioannou (2) studied the mouse gene encoding the Tbx1 transcription factor; this gene maps to the murine equivalent of the DGS/VCFS critical region. Because *Tbx1* is strongly expressed in the third, fourth and sixth arches during embryogenesis, they genetically engineered mice haploinsufficient (*Tbx1*−/+) or null (*Tbx1*−/−) in *Tbx1*. Tbx1−/− mice died *in utero* with abnormal facies and thymus and parathyroid aplasia along with heart failure and malformed cardiac outflow tracts and aortic arches. Although *Tbx1*−/+ mice were viable and had no noncardiovascular abnormalities, many had DGS/VCFS-like aortic arch abnormalities. Aortic arch abnormalities were also observed by Lindsay *et al*. (3) and Merscher *et al*. (4) who independently created mice hemizygous for large genomic segments including *Tbx1* and other genes. Both groups showed that specific replacement of only the *Tbx1* gene corrected aortic defects. *Tbx1*−/+ mice created by these groups also exhibited abnormal aortic arches.

Taken together, these studies show that *Tbx1* haploinsufficiency is sufficient to produce DGS/VCFS-like cardiovascular phenotypes in mice. Investigators hypothesize that human *TBX1* haploinsufficiency via chromosome 22q11 deletion plays a major role in human DGS/VCFS conotruncal defects. Mutations in the TBX5 and TBX3 transcription factors cause Holt-Oram and ulnar-mammary syndromes, respectively, and these new findings add to the body evidence that human congenital disease can be caused by alterations in gene dose of T-box transcription factors (5).

Several issues remain to be addressed. First, cardiovascular gene expression patterns in mice and humans are not always identical, and human *TBX1* expression patterns have yet to be elucidated. Second, what is the contribution of *TBX1* haploinsufficiency to noncardiovascular disease? Only mice that are completely lacking *Tbx1*, unlike haploinsufficient DGS/VCFS patients, exhibit noncardiovascular phenotypes. These discrepancies may reflect different sensitivities of human and mouse embryos to *TBX1* dosage or requirements for sequences critical to regulation of *Tbx1* expression that are physically remote from *Tbx1*'s coding sequence. Knockout mouse models of several other human chromosome 22q genes (*e.g.*, *Ufd1l, HIRA, Gsc1*) that are expressed in DGS/VCFS-affected tissues have failed to demonstrate phenotypes. However, their haploinsufficiency in humans may synergize with *TBX1* haploinsufficiency to cause DGS/VCFS. Homozygous knockout mice for the murine homolog of the human chromosome 22q11 *CRKL* gene have cardiovascular, skeletal, thymus, and parathyroid phenotypes similar to DGS/VCFS patients (6). Thus, human disease may reflect interactions between haploinsufficiencies of multiple genes.

Lastly, to definitively establish a role for TBX1 in human DGS/VCFS cardiovascular disease, it is critical to demonstrate that mutation of this gene alone causes a human phenotype. Lindsay et al. (3) note failure to detect *TBX1* missense mutations in 100 DGS patients without chromosome 22q deletions. However, disease in these patients may relate to mutations at other loci, e.g. a chromosome 10p DGS locus. Particularly important will be ongoing *TBX1* mutational analysis in patients with chromosome 22q deletions that do not encompass *TBX1*; these patients may have subtle *TBX1* sequence abnormalities to account for cardiovascular phenotypes without *TBX1* deletion. There is a high prevalence of chromosome 22q deletions in patients without DGS/VCFS but with other isolated conotruncal defects (7). Thus, patients with isolated conotruncal defects but without chromosome 22q deletions will also be an important target for *TBX1* mutational analyses.

In summary, the recent mouse studies of *Tbx1* haploinsufficiency have established *Tbx1*'s contribution to conotruncal development and provide a new scaffolding for analysis of specific gene contributions to the complex abnormalities that comprise DGS/VCFS.

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