Intervention and Treatment Affecting Brain and Behavior

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Mutation of *Tbx1* in mice recapitulates most of the core symptoms of 22q11.2 deletion syndrome, including cardiac, skeletal and immune defects. There is now compelling evidence from human and mouse studies that *Tbx1* is important for brain development. Specifically, in the mouse, *Tbx1* mutation causes premature neuronal differentiation in the embryonic brain cortex and anatomical and functional brain vascular defects that affect the entire brain. *Tbx1* mutants also have behavioral abnormalities. Thus, based on results obtained in the mouse model, it is reasonable to think that when one copy of *TBX1* is lost in humans, as occurs in 22q11.2DS, it may cause or contribute to the behavioral and psychiatric disorders that are associated with that disease.

We are testing drug therapies in the mouse model that are targetted to *Tbx1* function at the molecular level, reasoning that such drugs could potentially prevent or cure many or all of the symptoms caused by *Tbx1* mutation. Two such drugs, vitamin B12 and Tranylcypromine, were reported to reduce the severity of cardiovascular defects in *Tbx1* mutant mice (Lania, 2016).

We asked whether these drugs would also be effective in correcting the brain phenotypes in *Tbx1* mutant mice. This has important translational relevance, because the brain continues to develop after birth, thereby offering a potential therapeutic opportunity. We found that both vitamin B12 and Tranylcypromine normalized the cortical abnormalities found in the *Tbx1* mutant brain. We are now extending this promising study to test whether these drugs also correct the brain vascular and behavioral abnormalites found in these mutants.

As a potentially effective therapy to prevent or reduce the symptoms associated with 22q11.2DS, Vitamin B12 in particular is a nearly ideal drug because it has no known side effects, even at the high doses used in our mouse studies.