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CORRESPONDENCE

The evolutionarily conserved function of TBR1 in controlling the size of anterior commissure in human and mouse brains

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To the Editor:

We read with great interest the article by Nambot et al. [1], in which 25 unreported individuals with mutations in the *TBR1* gene were analyzed in great detail at molecular and anatomical levels and that also provides detailed clinical features of the patients. Since the patients carry de novo mutations, only one of their *TBR1* alleles is mutated. Among the 25 patients, seven individuals were carefully analyzed by magnetic resonance imaging (MRI). Interestingly, a specific white matter structure of the brain, the anterior commissure (AC), is either thin or absent from all seven of those individuals. Other morphological abnormalities—including dysplastic hippocampi and/or cerebral cortex, severe gyral anomalies, and microcephaly—are present in only some of the patients. Thus, reduction of the AC is the most common anatomical feature shared by patients carrying different mutations in the *TBR1* gene, although the Nambot et al. study did not quantify AC size.

These results are significant to study of TBR1. In two previous studies using *Tbr1*$^{+/-}$ mice, which mimic the condition of monoallelic mutations that result in early translational termination, small or absent ACs were identified upon hematoxylin and eosin staining, luxol fast blue/cresyl violet staining and MRI analysis [2, 3]. Note that the AC has both anterior and posterior parts. In the first of those two studies, histological methods revealed that the posterior part of the AC is the most sensitive structure to *Tbr1* haploinsufficiency [2]. Later, in the second study, more comprehensive analyses using MRI supported the findings of the first study and further demonstrated that the anterior part of the AC is also affected by *Tbr1* haploinsufficiency [3]. Apart from these two papers, another study used adeno-associated virus (AAV) for expression of YFP-tagged membrane protein to trace axonal projection via the AC. The results suggest that the two amygdalae in the two brain hemispheres do not project to each other via the AC in *Tbr1*$^{+/-}$ mice, which is in contrast to wild-type littermates [4]. Thus, the small or absent AC is the most critical phenotype of *Tbr1*$^{+/-}$ mice. The patient study contributed by Nambot and colleagues corroborates these mouse studies, further indicating that the AC defects caused by TBR1 deficiency are evolutionarily conserved between human and mice.

This evolutionary conservation suggests an interesting potential clinical therapy. In *Tbr1*$^{+/-}$ mice, autism-like behaviors—including reduced social interaction, impaired associated memory, and cognitive inflexibility—can be ameliorated by D-cycloserine treatment, which is an NMDAR co-agonist used to activate neurons [2]. Since TBR1 deficiency in both mice and human results in the same anatomical deficits, i.e. small or absent AC, it is likely that D-cycloserine could also ameliorate the behavioral defects of patients harboring mutations of their *TBR1* gene. As Nambot et al. [1] also point out in the last paragraph of their discussion, AC deficits could be a useful diagnostic feature of TBR1 deficiency. D-cycloserine might be considered for the patients with defects in the AC. However, based on results published previously [2–4], Nambot and colleagues were incorrect to claim that "Hypoplasia/absence of the AC and hippocampal dysplasia were not previously reported in mice or humans with TBR1 alterations,….". In fact, AC deficiency in mouse brains was first reported six years ago [2].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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