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Web Resources

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Response to Braun et al.

To the Editor: We note with interest the discordance between the *TUBA8* (MIM 605742) expression data obtained by Keays et al. and those we previously presented.[1] We accept that there is a possibility of cross-hybridization of the probes we used with other members of the α-tubulin family.

We suggest, however, that the tissue distribution of expression in the adult animal is of limited relevance when considering the pathogenesis of a neurodevelopmental phenotype. The high level of expression of *TUBA8* in the adult testis has been previously noted. Although this may imply a specific role of *TUBA8* in spermatogenesis, it does not imply the absence of an important role elsewhere. (We would also point out that the severe disability of the patients with homozygous *TUBA8* mutations precludes any knowledge concerning their fertility or testicular histology.)

Keays et al. also draw a contrast between low brain expression of *TUBA8* they observe and the much greater expression of *TUBA1A* (MIM 602529) and *TUBB2B* (MIM 612850), previously shown to be mutated in neurodevelopmental disorders. However, such a comparison implies very little, given that the disease-causing *TUBA1A* and *TUBB2B* mutations are de novo dominants, in contrast to the autosomal-recessive inheritance in our families.

There are many examples of apparent discordance between patterns of tissue-specific gene expression and the phenotype manifested when a gene is mutated. In some cases, these may reflect differential sensitivity of tissues to loss of gene product; neural tissues are notable in this regard. Mutations in the genes encoding the globally expressed pre-mRNA splicing factors *PRPF8* (MIM 607300) and *PRPF31* (MIM 606419), for example, result in a highly tissue-specific phenotype (retinitis pigmentosa) but no discernable phenotypic effects in other tissues in which they are highly expressed.[2] Similarly, the distinctive neurodevelopmental phenotype, Rett syndrome, results from mutation of a ubiquitously expressed DNA binding protein, *MeCP2* (MIM 300005).[3] Other highly specific phenotypes associated with mutations of widely expressed genes include motor neuron disease (*SOD1* [MIM 147450])[4] and α-thalassaemia mental retardation (*ATRX* [MIM 300032]).[5]

In the patients we described, almost all *TUBA8* transcripts are aberrantly spliced as a result of the 14 bp polypyrimidine tract mutation, in both lymphoblastoid cells and fibroblasts (unpublished data). The phenotype

of these patients had not been previously described, and this syndrome may therefore be excessively rare. Further proof of the causal effect of *TUBA8* deficiency is therefore likely to depend on the analysis of mouse mutants, presently under development in our laboratory.

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