A limitation of the approach is that it is restricted to nucleotide substitutions. However, in congenital agenesis of vas deferens, a form of male infertility, it has been shown that indels in intron 10 of *CFTR* close to the splice site influence the splicing of exon 11 (ref. 9). The restriction to intronic mutations within 300 nucleotides from splice sites is another limitation, as there are several examples of disease-associated splicing mutations located deeper in intronic regions. Finally, the method requires at least three exons to evaluate the potential effect of a nucleotide substitution on splicing. Future development of the tool to include variants other than SNVs, variants located deep in introns, and simpler exonic organizations would make it more broadly useful. The capacity to predict the levels of inclusion or exclusion of a given exon with higher precision would also be valuable, especially for the study of autosomal recessive genes, where sometimes only a small percent of functional transcript is sufficient for normal protein function.

In coupling RNA-sequencing data with whole-genome sequencing data from thousands of subjects and tissue conditions, the work of Xiong *et al.*[1] provides an important step toward defining the regulatory code of genomic regions of unknown function. The recent discovery of a large number of mini-exons that undergo alternative splicing in neurons but not in other cells[10] and the different profiles of alternative splicing in different brain cells[6] are clear indications of the many physiological and pathological scenarios that will have to be deciphered.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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