SLC6A8 is such a gene (with 13 exons, a 635-aa coding sequence, and no indication of highly recurring mutations), and thus we predict that its incidence in "nonsyndromic" MR will be in the range of 0.1%–0.3%. Indeed, even for the *ARX* (*X-linked Aristaless*) gene, which has a clear mutation hotspot that accounts for ~6.6% of families with X-linked "nonsyndromic" MR, the incidence of this *ARX* recurring mutation in cohorts of patients with MR is much lower (~0.15%) than that of *FMR1* mutations (Grønskov et al. 2004; Mandel and Chelly 2004).

I also suggest that, in reporting prevalence estimates that are based on relatively small numbers of positive cases, it would be useful to give confidence intervals (CIs). Thus, the observed prevalence, in the study by Rosenberg et al. (2004), of 2.2% may indeed be an underestimate, since some mutations may have been missed and some variants of uncertain significance at present may prove pathogenic, or it may be an overestimate of the true prevalence, since, for the reported data, the CI for the prevalence of proven mutations is 1.0%–4.4%.

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Reply to Mandel

To the Editor:

On behalf of all the authors of our recent study (Rosenberg et al. 2004), we thank Dr. Mandel for his comments (Mandel 2004 [in this issue]), to which we fully subscribe, and we apologize for the misleading statement in our article. Indeed, *SLC6A8* mutations, although probably more common than mutations in other known nonsyndromic X-linked mental retardation (MRX) genes except *ARX,* must be much less frequent than pathogenic CGG expansions in the *FMR1* gene. As pointed out by Mandel (2004 [in this issue]), this is convincingly illustrated by the relative paucity of *ARX* mutations in nonselected cohorts of males with mental retardation (MR) (Grønskov et al. 2004). Mandel's second argument, which implies that mutation rates in X-linked genes can be inferred from their lengths and must be intrinsically much lower than the rate of CGG expansions in *FMR1,* is less compelling in view of the evidence for mutational hotspots in many disease genes, including *ARX* and *PQBP1,* a recent addition to the growing list of genes involved in MRX (Kalscheuer et al. 2003). Therefore, the existence of another common but hitherto-unknown cause of nonsyndromic MR cannot be ruled out yet, even though ongoing large-scale mutation screening in regions known to carry many

mutations (Ropers et al. 2003) has so far failed to identify such a gene.

Reliable estimation of the relative importance of *SLC6A8* and other MRX genes in the etiology of MR will have to await systematic screening of large, unselected cohorts of patients with MR. So far, comprehensive studies of this kind have only been reported for a few genes, including *FMR1* and *ARX*.

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