Letter to the Editor

Although several families with X-linked mental retardation (XLMR) (Martin and Bell 1943; Allan et al. 1944; Bickers and Adams 1949; Losowsky 1961) had been reported prior to the Renpenning study (Renpenning et al. 1962), the term “Renpenning syndrome” (MIM 309500) came into general use for XLMR, encompassing both syndromic and nonsyndromic forms (Richards 1970; Gerrard and Renpenning 1974; Steele and Chorazy 1974; Jennings et al. 1980; McLaughlin and Kriegsmann 1980; Proops and Webb 1981; Archidiacono et al. 1987). Renpenning et al. (1962) described a Mennonite family in which 20 males in three generations had mental retardation (MR). Manifestations in affected males included microcephaly, short stature, and small testes; carrier females appeared normal.

Previously, we reported linkage of the family described by Renpenning and colleagues (1962) to Xp11.2–p11.4 (Stevenson et al. 1998) (fig. 1A). In addition, we identified another family exhibiting microcephaly and MR (fig. 1B). Herein, we report truncating mutations in the polyglutamine tract binding protein 1 (PQBP1) gene (MIM 300463) in both families.

Mutations in the gene that codes for the polyglutamine tract binding protein 1, located in Xp11.2–p11.4 (Stevenson et al. 1998) (fig. 1A). In addition, we identified another family exhibiting microcephaly and MR (fig. 1B). Herein, we report truncating mutations in the polyglutamine tract binding protein 1 (PQBP1) gene (MIM 300463) in both families.

Mutations in the middle of exon 4, these mutations, at either the end of exon 4 or exon 5, do not affect the PRD (fig. 2). Taking into account all mutations in the PQBP1 gene that have been described here and by Kalscheuer et al. (2003), two groups of mutations can be classified: (1) deletions or insertions of AG nucleotides affecting the DR/ER repeat in the PRD and (2) frameshift aberrations leaving the PRD undisturbed (fig. 2). However, the common clinical manifestations, MR, microcephaly, and short stature, are present in all families. Therefore, it might be of interest to determine whether the PRD in the truncated proteins from the family described by Renpenning and colleagues (1962) and the K9008 family still interacts with BRN2 or whether the loss of the last 67 or 40 amino acids disturbs this function. Alternatively, the interaction with other, yet-unknown proteins might be disrupted.

Advances in clinical delineation and in molecular un-
Figure 1  Families with novel mutations in the PQBP1 gene. A, Partial pedigree of the family described by Renpenning and colleagues (1962) (family K8110), with the c.641insC mutation. Numbering of the pedigree is consistent with that published elsewhere (Stevenson et al. 1998). The c.641insC mutation, highlighted and indicated by the arrow, is present in exon 5 and is very close to the exon/intron boundary. The shaded region shows the intronic sequence. This mutation causes a frameshift in the C2 domain, resulting in the premature truncation of the protein. B, Pedigree of family K9008, with the c.575_576delAG mutation in the NLS (nuclear localization signal) domain. This deletion is in exon 4 (highlighted in yellow) and occurs very close to the exon/intron boundary (sequence contributed from the intron is shaded). This mutation causes a frameshift and results in a premature truncation of the PQBP1 protein, which lacks the C2 domain.
Truncating mutations in the PQBP1 protein. This figure shows the structure of the PQBP1 protein with the WW domain, the PRD with DR/ER repeats, the NLS domain, and the C2 domain (modified from Waragai et al. 1999). The novel mutations reported in this study (c.575_576delAG and c.641insC) are in boldface. The three different mutations in the DR/ER domain reported by Kalscheuer et al. (2003) are in italics.

Understanding of XLMR have now identified 120 syndromic forms of XLMR and 81 families with nonsyndromic XLMR (Stevenson et al. 2003). To date, mutations in 47 genes have been linked to XLMR. Of these 47 genes, 29 have been linked exclusively to syndromic XLMR, 11 exclusively to nonsyndromic XLMR, and 7 to both (Stevenson and Schwartz 2002).

With the exception of Allan-Herndon syndrome [MIM 309600], all XLMR syndromes reported prior to the discovery of the fragile X syndrome [MIM 309550] have now been linked to mutations of a specific gene. Identification of a PQBP1 mutation in Renpenning syndrome and other XLMR syndromes (Kalscheuer et al. 2003) exemplifies the lumping of XLMR syndromes that has become justified on the basis of molecular studies (Stevenson 2000). As MR, microcephaly, and short stature seem to be consistent findings among individuals with PQBP1 mutations, patients with these findings should be included in any testing scheme. In a South Carolina study of mental retardation, in a South Carolina study of mental retardation, in a South Carolina study of mental retardation, among 4,008 males with MR of unknown cause, 486 (12%) have microcephaly, 350 (9%) have short stature, and 128 (3%) have both (R.E.S., unpublished data). Hence, microcephaly is the most common physical finding among males with MR of unknown cause (Stevenson et al. 2003) and is a reliably ascertained finding that may be useful in the selection of cases for PQBP1 mutation testing.

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