Journal of Pediatric Neurology 3 (2005) 121–122
IOS Press

Research Letter

ARX and other single genes in X-linked mental retardation: revisiting a population-based study

Petter Strømme*
Department of Pediatrics, Ullevl University Hospital, N0-0407 Oslo, Norway

Received 25 October 2004
Revised 2 December 2004
Accepted 10 December 2004

It has been calculated that monogenic genes for X-linked mental retardation (XLMR) account for $<$10% of male MR [1]. XLMR can be classified as syndromic, referring to conditions with distinct neurological, physical or biochemical abnormalities, or nonsyndromic (unspecified or nonspecific). More than 20 genes are known to be associated with syndromic XLMR [2] and 13 genes have so far been identified with nonsyndromic XLMR [3]. The most common XLMR condition, fragile X syndrome (FRAXA) due to mutation in the FMR1 gene, occurs in approximately 1 in 6000 males in various populations, or in 2–2.5% in cohorts of MR males [4].

Although the search for genes has been very active in recent years, mutations in a "major" causative gene underlying a larger proportion of unexplained XLMR remain to be identified. Recently, the identification of mutations in the Aristaless related homeobox gene (*ARX*) in syndromic as well as non syndromic conditions [5,6] created optimism that *ARX* could be a major gene in XLMR, particularly since the phenotypic range appeared to be very broad [7]. A review of 11 original *ARX* genotype-phenotype studies reported in the literature since 2002 revealed 31 different mutations (P. Strømme, personal communication). The commonest mutation, 431–454dup(24 bp) in exon 2 (hereafter called the 24 bp mutation), accounted for 14 families and three sporadic cases.

Information concerning the frequency of *ARX* mutations in the general population is almost non-existent. In search for *ARX* mutations Grønskov et al. [8] examined 682 *FMR1* negative MR Danish males and found only one case, a sporadic 24 bp mutation, giving a prevalence of 0.15% (95% confidence limit 0–0.45%; 95% confidence limit for prevalence was based on the Poisson distribution.) in male MR for this mutation. Partington et al. [9] screened for *ARX* mutations among 118 XLMR families, all fragile X negative, and found six families (5%; 95% confidence limit 1–9%).

In the light of the discovery of the *ARX* gene, reanalysis of data from a population-based study can provide information on the frequency of *ARX* mutations and other XLMR genes in male MR. In a cross sectional study comprising 30,037 Norwegian children (15,495 males and 14,542 females) born between 1980 and 1985 all children with MR, defined as IQ $\leqslant$ 70 after psychometric assessments ($n = 185$), were identi-

*Correspondence: Petter Strømme, M.D., PhD, Department of Pediatrics, Ullevl University Hospital, N0-0407, Oslo, Norway. Tel.: +4723015234; Fax: +4723015790; E-mail: petter.stromme@medisin.uio.no.

fied [10]. Of these 178 (104 males and 74 females) were available for etiological work up. A three-generation pedigree aiming to reveal X-linked inheritance was completed in 168 participants (94%), while 151 (84%) were tested for the fragile X syndrome. Those who were not tested had other recognizable diagnoses. Six monogenic X-linked conditions were identified: two with FRAXA and one each with FRAXE, Menkes disease, X-linked MR gyneocomastia-obesity syndrome (OMIM 309585) and X-linked infantile spasms (ISSX; OMIM 308350) [11]. The study also included three pairs of brothers, one with possible autosomal or X-linked recessive inheritance and two labeled familial MR. The ISSX patient was the proband in a XLMR family mapped to Xp11.4–Xp22.11 [12] and was subsequently shown to have the 24 bp mutation in the ARX gene [5]. Although there were five other affected males with variable neurological phenotypes, the proband was the only person in this family to comply with the age and demographic criteria to be included for the study.

The prevalence of the 24 bp mutation in the *ARX* gene in this cohort study of the general population was ∼1% (95% confidence limit 0–3%). The prevalence of FRAXA in male MR from the same cohort was 2% (95% confidence limit 0–5%), within the expected range. The prevalence of XLMR genes accounted for approximately 6% (95% confidence limit 2–10%) of male MR, also within the expected range. As there were 30 more males than females, X-linked genes accounted for 20% (95% confidence limit 6–34%) of the male excess, and thus *ARX* mutation accounted for 3% (95% confidence limit 0–9%) of the male excess. The representativity of the figures in this study is crude as the prevalence of low frequency conditions have broad confidence limits and are difficult to compare. However, the occurrence of other low frequency syndromes such as Angelman, Prader Willi and Rett syndrome were also within expected range [11].

In conclusion, as a crude estimate derived from this study, the prevalence of the 24 bp ARX mutation in male MR is 1%, or less, and is perhaps one third to half as common as the fragile X syndrome.

References

[1] J.L. Mandel and J. Chelly, Monogenic X-linked mental retardation: is it as frequent as currently estimated? The paradox of the ARX (Aristaless X) mutations, *Eur J Hum Genet* **12** (2004), 689–693.

[2] J. Chelly and J.L. Mandel, Monogenic causes of X-linked mental retardation, *Nat Rev Genet* **2** (2001), 669–680.

[3] H.H. Ropers, M. Hoeltzenbein, V. Kalsscheuer et al., Nonsyndromic mental retardation: where are the missing mutations, *Trends Genet* **19** (2003), 316–320.

[4] V. Biancalana, C. Beldjord, A. Tailanndier et al., Five years of molecular diagnosis of Fragile X syndrome (1997–2001): a collaborative study reporting 95% of the activity in France, *Am J Med Genet* **129** (2004), 218–224.

[5] P. Strømme, M.E. Mangelsdorf, M.A. Shaw et al., Mutations in the human ortholog of Aristaless cause X-linked mental retardation and epilepsy, *Nat Genet* **30** (2002), 441–445.

[6] T. Bienvenu, K. Poirier, G. Friocourt et al., ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation, *Hum Mol Genet* **11** (2002), 981–991.

[7] P. Strømme, M.E. Mangelsdorf, I.E. Scheffer and J. Gécz, Infantile spasms, dystonia, and other X-linked phenotypes caused by mutations in the Aristaless related homeobox gene, *ARX*. *Brain Dev* **24** (2002), 266–268.

[8] K. Grønskov, H. Hjalgrim, I.M. Nielsen and K. Brøndrøm-Nielsen, Screening the ARX gene in 682 retarded males, *Eur J Hum Genet* **12** (2004), 701–705.

[9] M.W. Partington, G. Turner, J. Boyle and J. Gécz, Three new families with X-linked mental retardation caused by the 428–451dup(24 bp) mutation in ARX, *Clin Genet* **66** (2004), 39–45.

[10] P. Strømme and K. Valvatne, Mental retardation in Norway: prevalence and sub-classification in a cohort of 30037 children born between 1980 and 1985, *Acta Paediatr* **87** (1998), 291–296.

[11] P. Strømme and G. Hagberg, Aetiology in severe and mild mental retardation: a population-based study of Norwegian children, *Dev Med Child Neurol* **42** (2000), 76–86.

[12] P. Strømme, K. Sundet, C. Mørk, J.J. Cassiman, J.P. Fryns and S. Claes, X-linked mental retardation and infantile spasms in a family: new clinical data and linkage to Xp11.4–Xp22.11, *J Med Genet* **36** (1999), 374–378.