A splice site mutation in the methyltransferase gene FTSJ1 in Xp11.23 is associated with non-syndromic mental retardation in a large Belgian family (MRX9).

Mental retardation is the most frequent cause of serious handicap in children and young adults. The underlying causes of this heterogeneous condition are both acquired and genetically based. A recently performed refinement of the linkage interval in a large Belgian family with mild to severe non-syndromic X linked mental retardation, classified as MRX9, revealed a candidate region of 11.3 Mb between markers DXS228 and DXS1204 on the short arm of the X chromosome. In order to identify the underlying disease gene in the MRX9 family, we established a gene catalogue for the candidate region and performed comprehensive mutation analysis by direct sequencing. A human homologue of the bacterial 23S rRNA methyltransferase Fstj, the FTSJ1 gene, is located within this region and displayed a sequence alteration in the conserved acceptor splice site of intron 3 (IVS3-2A>G) in all tested patients and carrier females of this family. In contrast, it was absent in all unaffected male family members tested. The mutation results in skipping of exon 4 and introduces a premature stop codon in exon 5, probably leading to a severely truncated protein. Our finding indicates that a protein, possibly associated with ribosomal stability, can be linked to X linked mental retardation (XLMR).