

Abstract 9

TWO INDEPENDENT MUTATIONS IN THE ZNF526 GENE CAUSE NON-SYNDROMIC AUTOSOMAL RECESSIVE MENTAL RETARDATION

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Monogenic defects are thought to be an important cause of severe MR. However, apart from X-chromosomal forms, relatively few MR genes have been identified so far. In particular, no more than five genes have been directly associated with non-syndromic autosomal recessive MR (NS-ARMR). Recently, we have identified numerous novel loci for NS-ARMR, including MRT4-11 (Najmabadi et al, Hum Genet. 2007). Here we report on two different single nucleotide changes in the *ZNF526* gene, which maps to MRT11, localized in a 10 Mbp linkage interval on chromosome 19 (19q13.2-13.32). These nucleotide changes were found to co-segregate with moderate to severe NS-ARMR in three large, apparently unrelated Iranian families and were absent in 240 control chromosomes. *ZNF526* encodes a C2H2 zinc finger protein with multiple functional domains. It is expressed in brain, has DNA binding properties and is thought to be involved in gene regulation. Both mutations affect functional domains of the gene product and impair its function, as suggested by *in silico* protein modelling and confirmed by the presence of specific changes in the gene expression patterns of lymphoblastoid cells. Several zinc finger proteins have been shown to be involved in the pathogenesis of X-linked MR, but *ZNF526* is the first to be implicated in ARMR. Moreover, *ZNF526* is only the second gene known to carry MR-causing mutations in independent families. This may suggest that *ZNF526* defects are among the more common causes of NS-ARMR, at least in the Iranian population. CHIP-seq experiments are in progress to identify regulatory targets of *ZNF526*.