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A NOVEL RECURRENT COPY NUMBER GAIN AT Xq28 IN FOUR MR FAMILIES REVEALS A DOSAGE-DEPENDENT SEVERITY OF THE PHENOTYPE AND SUGGESTS A NOVEL RECOMBINATION MECHANISM

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In a study to elucidate the genetic defects in patients with X-linked mental retardation (XLMR) we performed X chromosome-specific BAC-array-CGH and identified a 0.3 Mb inherited recurrent copy number gain at Xq28 in affected males of four unrelated XLMR families. All aberrations segregate with the disease in the families and the carrier mothers show a nonrandom X-inactivation. The aberrant region is located at 153.21 Mb to 153.53 Mb and harbors 18 genes of which three are highly expressed in brain (*RPL10*, *ATP6AP1* and *GDI1*). Interestingly, qPCR at these loci demonstrated that this region was duplicated in one family with nonsyndromic mild to moderate MR, triplicated in two other families with some additional features, while in a fourth family with a severe syndromic form of MR, it was present in four copies. Expression analysis revealed copy number-dependent increased mRNA levels in affected patients compared to control individuals, which correlates with the severity of clinical features. Our data strongly suggest that an increased expression of genes within this region results in impaired cognition in a dosage-dependent manner. Tiling resolution oligo-array analysis of the Xq28 region confirmed the qPCR data but also revealed a more complex aberration that involved two different but adjacent sets of low copy repeats (LCR) that flank the aberrations, which implies a yet unknown recombination mechanism. Finally, in patients with *MECP2* duplication the region described in this study is often completely or partially involved, but the contribution of their increased mRNA expression to the severe phenotype is probably masked by the strong effect of increased *MeCP2* levels. Our data thus demonstrate that a copy number gain of individual genes present in a contiguous genomic aberration can on itself result in a clinical phenotype too.