P3: Mutation in POLA1 in a family with X-linked syndromic mental retardation

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X-linked mental retardation (XLMR) is a heterogeneous disorder that can be classified as either nonsyndromic (NS-XLMR), when mental retardation (MR) is the only feature, or as syndromic mental retardation (S-XLMRS). In the latter, the mental retardation is associated with dysmorphic, metabolic and/or neurological features. Until now, 215 monogenic XLMR conditions have been recorded and more than 90 XLMR-associated genes have been identified of which about 70 MRXS genes. We report the results in a family presenting with X-linked mild mental retardation, short stature, microcephaly and hypergonadotrophic hypogonadism. Linkage analysis assigned the causative gene to a 6 cM interval in Xp22.1-p21.3, with a maximum LOD score of 2.61, and subsequently the two known MR genes ARX and IL1RAPL1 were excluded. To identify the causative gene, we performed a systematic sequencing analysis of the remaining 17 genes in this interval. This led to the identification of a missense mutation, c.236T>G in the POLA1 gene. To further validate the role of POLA1 in XLMR associated with microcephaly, we performed mutation analysis in additional MR patients with either a similar phenotype or linkage to the same region, as well as mouse in situ hybridisation. Our results support a role for POLA1 in neurogenesis and brain size, consistent with the phenotype observed in the patients.