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E-P24.16 Biallelic mutations in *M1AP* are associated with meiotic arrest, severely impaired spermatogenesis and male infertility

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Male infertility affects ~7% of men, but its causes remain poorly understood. The most severe form is non-obstructive azoospermia (NOA), which is, in part, caused by an arrest at meiosis, but so far only few validated causal genes have been reported. To address this gap, we performed whole exome sequencing in 58 men with unexplained meiotic arrest and identified

in three unrelated men the same homozygous frameshift variant c.676dup (p.Trp226LeufsTer4) in *M1AP*, encoding meiosis 1 arresting protein. This variant results in a truncated protein lacking 57% of its full-length as shown *in vitro* by heterologous expression of mutated M1AP. Next, we screened four large cohorts of 1904 infertile men from the International Male Infertility Genomics Consortium (IMIGC) and identified three additional cases carrying homozygous c.676dup and three carrying combinations of this and other likely causal variants in *M1AP*. Moreover, a homozygous missense variant p.(Pro389Leu) segregated with infertility in five men from a consanguineous Turkish family (LOD score = 3.28). The common phenotype between all affected men was NOA, but occasionally spermatids and rarely a few spermatozoa in the semen were observed. A similar phenotype was described for mice with disruption of *M1ap*. Collectively, these findings demonstrate that mutations in *M1AP* cause autosomal recessive severe spermatogenic failure and male infertility. In view of the evidences from several independent groups and populations, *M1AP* should be included in the growing list of validated male infertility genes.

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