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HOMOZYGOSITY MAPPING OF PRIMARY MICROCEPHALY IN 86 IRANIAN FAMILIES: NOVEL MUTATIONS AND PHENOTYPES

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Primary microcephaly (MCPH) is a genetically heterogeneous disorder showing an autosomal recessive mode of inheritance in the majority of cases. Affected individuals present with head circumferences more than three standard deviations below the age- and sex-matched population mean, accompanied by mental retardation without further associated malformations. Five genes (*MCPH1*, *CDK5RAP2*, *ASPM*, *CENPJ* and *STIL*) and two additional genomic loci (MCPH2 and 4) have been identified so far. In this study, we investigated all six loci in patients with primary microcephaly and other family members from 86 Iranian families with 2 or more affected individuals. Thorough clinical characterization and karyotype analyses were performed for all patients. For linkage analyses, several microsatellite markers were selected for each locus and used for genotyping. Our investigation enabled us to detect linkage to the *ASPM* region in thirteen families. Three families showed linkage to MCPH2. Seven families were linked to *MCPH1* and four to *CENPJ*. The remaining 59 families were not linked to any of the six known loci. Subsequent sequencing revealed 10 novel mutations in *ASPM*, seven novel mutations in *MCPH1* and one novel mutation in *CENPJ*. Additional clinical features accompanying microcephaly and MR were observed in some patients. While confirming the general prevalence of *ASPM* mutations, our results indicate that these are comparatively less frequent in the Iranian population than in others. This and the high proportion of families without apparent linkage to known loci suggest the presence of additional, probably population specific loci.