Phenotypes and genotypes in outbred and inbred Primary microcephaly: high incidence of epilepsy

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Abstract

Primary microcephaly (PM) is defined as a significant reduction in occipito-frontal circumference (OFC) of prenatal onset. Clinical and genetic heterogeneity of PM represents a diagnostic challenge. We performed detailed phenotypic and genomic analyses in a large cohort (n=169) of patients referred for PM, and could establish a molecular diagnosis in 38 patients. Pathogenic variants in ASPM and WDR62 were the most frequent causes in non-consanguineous patients in our cohort. In consanguineous patients, microarray and targeted gene panel analyses reached a diagnostic yield of 67%, which contrasts with a much lower rate in outbred patients (9%). Our series includes 15 previously unreported families and 11 novel pathogenic variants, and we identify novel candidate genes including IGF2BP3, DNAH2, and TSR1. We confirm progression of microcephaly over

time in affected children. Epilepsy was an important associated feature in our PM cohort, affecting 34% of patients, with various degrees of severity and seizure types. Our findings will help to prioritize genomic investigations, accelerate molecular diagnoses and improve management of PM patients.

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