

RARE MUTATIONS IN PATIENTS WITH BRAIN ARTERIOVENOUS MALFORMATIONS

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Background: Brain arteriovenous malformations (AVMs) are a complex tangle of abnormal arteries and veins located in the brain, and this vascular anomaly lacks an intermediate capillary network [1]. The risk of spontaneous intracranial hemorrhage caused by AVM rupture is estimated to be about 2-4% per year and can reach up to 34% under certain conditions, and hemorrhage can lead to severe irreversible neurological disability and death [2]. The mechanism of AVM formation remains unclear.

Materials and methods: This study was conducted in a cohort of three patients (AVM1–3) who underwent microsurgical resection of bAVMs at the National Centre for Neurosurgery in Astana, Kazakhstan. Genomic DNA was isolated from whole venous blood using a standard salt-out method [3]. Whole-exome sequencing was performed using the Novaseq 6000 platform (Illumina). Genetic variants were identified using the GATKv4.0.5.1 (<https://gatk.broadinstitute.org/hc/en-us>). To visualize and functionally group genes containing filtered genetic variants, we used the ClueGO plugin (version 2.5.10

Results: We selected only the loci affected by rare variants (MAF < 0.01) and then those that are most likely associated with the onset of the disease (brain AVM). In silico analysis further revealed can-

didate genes likely associated with lesion development, including COL3A1, CTNNB1, LAMA1, NPHP3, SLIT2, SLIT3, SMO, MAPK3, LRRK2, TTN, ERBB2, PARD3, and OBSL1. It is essential to focus on the genetic variants affecting the prioritized genes, ERBB2, SLIT3, SMO, MAPK3, and TTN, as mutations in these genes were predicted to be “damaging”. Most of these genes are involved in signaling pathways that control vasculogenesis and angiogenesis and work together through various signaling pathways to regulate the formation and remodeling of blood vessels during embryonic development and in response to physiological needs.

Conclusions: The results of this study indicate that sporadic arteriovenous malformations (AVMs) in the brain are a heterogeneous condition.

References

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