POSTZYGOTIC ACTIVATING VARIANTS IN MAPK PATHWAY GENES CAUSE INTRACRANIAL ANDEXTRACRANIAL VASCULAR MALFORMATIONS THAT RESPOND TO TARGETED INHIBITION

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Background Sporadic vascular malformations (VMs) are complexcongenital anomalies of blood vessels that lead to stroke, life-threatening bleeds, disfigurement, overgrowth, and/or pain. Therapeutic options are severely limited and multi-disciplinary management remains challenging, particularly for high-flowarteriovenous malformations (AVM).
Project To investigate the pathogenesis of 160 sporadic VMs in which known genetic causes had been excluded, sequencing of affected tissue DNA was undertaken using deep next generation sequencing with analysis optimised for detection of low mutant allele frequency.
Results Mosaic activating variants in *KRAS, NRAS, BRAF* and *MAP2K1* were identified, most commonly in AVM, both intracranialand extracranial. Transgenic zebrafish expressing BRAFV600E only in the vasculature recapitulated the human phenotype. Treatment of zebrafish with the BRAF inihibitor, vemurafinib, restored blood flow in AVM.
Conclusions These findings reveal an important unifying cause of sporadic vascular malformations of different clinical types, and offer the potential of personalised medical treatment for affected individuals by repurposing of existing licensed cancer therapies.