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

Great Ormond Street Hospital, London, UK10.1136/archdischild-2017-084620.30

Background Sporadic vascular malformations (VMs) are complex congenital anomalies of blood vessels that lead to stroke, life-threatening bleeds, disfigurement, overgrowth, and/or pain. Therapeutic options are severely limited and multidisciplinary management remains challenging, particularly for high-flow arteriovenous 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 intracranial and extracranial. Transgenic zebrafish expressing BRAFV600E only in the vasculature recapitulated the human phenotype. Treatment of zebrafish with the BRAF inhibitor, vemurafenib, 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.