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GENETICS

# *ACVR1* mutations—a key piece in paediatric diffuse glioma

High-grade glioma—or high-grade astrocytoma (HGA)—have a devastating prognosis, with survival ranging from 20–30% for tumours outside the brainstem, and less than 10% for diffuse intrinsic pontine gliomas (DIPGs), which arise in the brainstem and are found almost exclusively in children. Aside from radiotherapy, there is currently no effective treatment for this type of cancer, and most children will die of their tumours within 1–2 years of diagnosis. This lack of effective treatment could be due to the fact that drug development in this field has been designed based on the biology of adult glioma when, in fact, the spectrum of molecular alterations in children is very different. Now, four independent papers published in *Nature Genetics* have identified mutations in the gene *ACVR1* in patients with DIPG, revealing a crucial role of this gene in the development of this type of brain tumour. The *ACVR1* gene encodes for the activin receptor type I protein, which is a receptor of the bone morphogenetic proteins (BMPs). None of these mutations had previously been found in cancer, although they are linked to an inherited muscular disease known as fibrodysplasia ossificans progressiva.

Cynthia Hawkins and colleagues used whole-genome or whole-exome sequencing on 36 samples of DIPGs and overlaid the results with information about DNA copy number, methylation and expression. They found that DIPGs comprise three distinct methylation-based subgroups with potentially targetable genetic changes. "We had prior evidence that DIPGs were distinct from adult and cerebral paediatric glioblastoma multiforme, however, the clear role of epigenetics and the uniqueness of these tumours at the DNA mutation level were not appreciated prior to this study," says Hawkins. *ACVR1* was mutated in 20% of the samples analysed.

In turn, Baker and colleagues sequenced 127 tumour–normal pairs of HGA samples (DIPGs and other paediatric HGA that arise outside the brainstem) from 118 patients. "We also completed whole-genome or whole-exome sequencing on the matched germline DNA for 108 of these cases so that we could identify all somatic mutations," explains Baker. The authors reported recurrent somatic mutations in *ACVR1* exclusively in DIPGs, in 32% of the samples.

Jones, Grill and colleagues used only tumour material obtained from stereotactic biopsies of DIPG that are systematically and routinely carried out at diagnosis at their centre in France. "The aim was to be able to describe the initial phase of the growth of this tumour. All biopsies were obtained from patients with typical clinical and radiological features. We can therefore be sure that we describe an unbiased series of cases that represent the true nature of the disease," says Grill. They found mutations in *ACVR1* in 21% of these samples.

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In all three papers, the authors also showed that these mutations were activating and that cultured astrocytes transfected with constructs expressing ACVR1 mutants also had increased levels of phosphorylated SMAD and ID proteins, which are targets of BMP. Although Baker and colleagues showed that *Tp53*-null astrocytes remained non-tumorigenic when transfected with constructs encoding ACVR1 mutants, Hawkins and colleagues showed that the expression of mutant *ACVR1* into cultured brainstem progenitor cells increased proliferation.

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Treatment with LDN193189, a selective antagonist of the BMP pathway, reversed the BMP pathway activation caused by the expression of *ACVR1* mutants in culture. "Inhibitors of this pathway are already available so could potentially move quickly into clinical trials," remarks Hawkins.

A fourth study, by Nada Jabado and colleagues, analysed 40 midline HGA, including DIPG and non-DIPG tumours, by whole-exome sequencing and found five cases with *ACVR1* mutations.

Taken together, these four studies identify *ACVR1* mutations and aberrant BMP signalling as a new potential therapeutic target in paediatric DIPGs. "This information provides desperately needed leads for the development of improved, more selective therapy for these devastating tumours," concludes Baker.

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**Original articles** Wu, G. *et al.* The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. *Nat. Genet.* **46**, 444–450 (2014) | Buczkowicz, P. *et al.* Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations. *Nat. Genet.* **46**, 451–456 (2014) | Taylor, K. R. *et al.* Recurrent activating ACVR1 mutations in diffuse intrinsic pontine glioma. *Nat. Genet.* **46**, 457–461 (2014) | Fontebasso, A. M. *et al.* Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma. *Nat. Genet.* **46**, 462–466 (2014)