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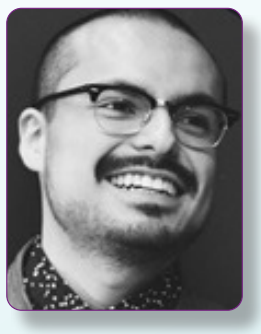
PAPER OF THE MONTH • MARCH 2026



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nature

Androgen activity in the male embryonic hindbrain drives lethal PFA ependymoma

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PFA ependymoma is a lethal brain tumour affecting babies and toddlers, with no major driver mutations and few therapeutic options. There is a marked sex-difference in incidence and outcomes: boys are not only more likely to get the disease, but they also have a worse prognosis and shorter overall survival time than girls do.

Here, we show that the tumor cells from male patients are less differentiated and more stem-like than cells from female patients. This phenotype is retained from normal hindbrain development: we find that, in the normal developing glial lineage where these tumors originate, male progenitors have a delay in maturation when compared to female progenitors.

Using the four core genotypes model —a mouse model that allows to uncouple the effects of sex chromosomes and the action of sex hormones—, we found that androgen signalling, rather than sex chromosomes, promotes stemness and prevent differentiation in the glial lineage. Importantly, this mechanism appears to be intact in PFA ependymoma tumors. Exposure to androgens promoted the growth of PFA ependymoma cells, while androgen blockade diminished both the stem-like potential and the proliferation of PFA ependymoma.

In conclusion, androgen signalling in both the normal developing hindbrain and PFA ependymoma is sufficient to promote growth and delay differentiation. This suggests that anti-androgen therapies represent a potential clinical avenue to target this currently untreatable childhood cancer.

https://www.nature.com/articles/s41586-026-10264-6