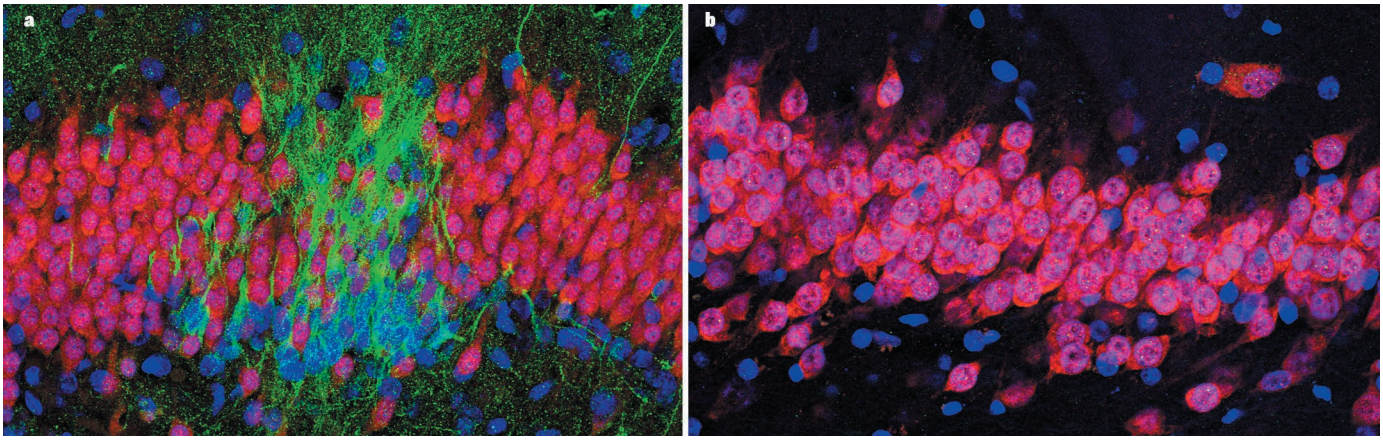

S. SORELLS *ET AL.*/*NATURE*

Figure 1 | Decreasing neurogenesis with age. Sorrells *et al.*[1] examined slices of the hippocampus from human brains at various stages of life, to investigate when new neurons are generated. Green indicates the location of the protein DCX, which is produced in new neurons; red indicates the protein NeuN, which is produced in mature neurons; blue indicates a fluorescent marker called DAPI, which stains all cell nuclei. **a**, At birth, many new neurons can be seen. **b**, By contrast, the authors observed no new neurons in the adult hippocampus.

cell. Similarly, the group demonstrated that it is possible to obtain BrdU-like immunohistochemical labelling in tissue that did not actually contain BrdU. Nonspecific labelling could therefore have led to false-positive results in previous studies.

The researchers' careful approach also speaks to the challenges of performing neurogenesis work in humans. Animal studies have shown that PSA-NCAM is modified by previous experiences[7] and that DCX degrades if tissue is not rapidly preserved[8]. An apparent loss of neurogenesis could therefore reflect changes in marker expression, especially if stringent criteria are used to define new neurons. Given that there are debates about hippocampal precursor-cell identity even in rodents[9], it is also possible that we simply do not know what to look for in humans.

Sorrells *et al.* minimized these issues in several ways. First, they observed neurogenesis in the hippocampus of infants and children, which served as a positive control. Second, they used a variety of adult samples to minimize the possibility that problems with tissue health or preservation could confound their results. Third, they used diverse markers of neurogenesis to gain multiple lines of evidence. Nonetheless, further investigation will be needed to see whether Sorrells and colleagues' conclusions will stand the test of time.

How do the authors' findings fit with the animal literature? With a bit of conceptual recalibration, they might fit quite well. Rodents are born with relatively immature nervous systems, so adult rodent neurogenesis could be a decent model of neurogenesis in children or adolescents. Given that depression, schizophrenia and Alzheimer's disease are rooted in early hippocampal defects, even neurons generated in childhood could have a key role in the aetiology of disease in humans. In addition, primate data[10] suggest that new neurons in humans could go through an extended period of maturation (years or even decades) relative to what occurs in rodents, during which time they might have enhanced plasticity and important functional properties. Thus, whereas the continual addition of new neurons might provide plasticity in adult rodents, the prolonged development of neurons could provide a similar plasticity in adult humans.

At the other end of the developmental spectrum, even in rodents, neurogenesis is very low by middle age[2]. Thus, Sorrells and colleagues' human data again are not wholly inconsistent with the animal literature. If the focus of rodent studies were shifted to identifying the mechanisms by which neurogenesis diminishes over time, and to how neurogenesis can be enhanced to offset pathology caused by age and disease, we just might be able to translate the authors' sobering findings into discoveries that improve human health. ■

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CANCER GENOMICS

Landscapes of childhood tumours

Two analyses of the genetic alterations that characterize paediatric cancers reveal key differences from adult cancers, and point to ways of optimizing therapeutic approaches to combating cancer in children. SEE ARTICLE P.321 & LETTER P.371

PRATITI BANDOPADHAYAY & MATTHEW MEYERSON

The mapping of the human genome, followed by the explosion in next-generation genome sequencing, has revolutionized our understanding of cancer. These advances have paved the way for precision-medicine approaches to treating adult cancers. Two papers in *Nature* report the first pan-cancer genomic analyses in children. In the first, Gröbner *et al.*[1] (page 321) analysed sequences of whole exomes (all the protein-coding regions in the genome) or whole genomes for 961 cancers across 24 tumour types, with an emphasis on tumours of the central nervous system. In the second, Ma *et al.*[2] (page 371) used similar analyses to characterize 1,699 cancers across 6 types of cancer tissue, particularly leukaemias.

The findings provide valuable insights into the mechanisms that shape the genomes of childhood cancers.

Adult cancers frequently involve multiple genetic alterations that together drive cancer progression, including small mutations of one or a few DNA bases, and larger changes called structural variants that span more than 1,000 bases. Such drivers can be shared across cancer types[3]. One of the most meaningful outcomes of the current studies is their confirmation that the genomic landscape of childhood cancers differs from this picture. Previous studies of individual paediatric cancer types[4–7] have revealed that they have fewer mutations and structural variants, on average, than do adult cancers[3,8], but the current pan-cancer analyses take this further, systematically highlighting several key differences between childhood and adult cancer genomes (see 'The differing genomic landscapes of childhood and adult cancers').

First, there are fewer mutations and structural variants in paediatric cancers than in adult cancers. For instance, Gröbner *et al.* report a mutation rate 14 times lower for childhood than for adult cancers. Furthermore, both groups find that the total number of mutations in paediatric-cancer genomes correlates significantly with age — consistent with the idea that cells accumulate mutations with age.

Second, paediatric cancers are frequently defined by a single driver gene. For instance, 57% of the cancers in Gröbner and colleagues' analysis harboured single driver mutations. These authors also highlight the fact that germline mutations, which are inherited from parents and are present in all cells of the body, are a causative factor in childhood cancers — 7.6% of cancers in the authors' cohort are associated with detectable germline mutations. Furthermore, paediatric cancers tend to be enriched in either mutations or structural variants, rather than a mixture of the two. Indeed, the group observes enrichment of germline mutations involved in a DNA-repair pathway called mismatch repair in cancers defined by mutations, and germline mutations in a tumour-suppressor gene, *TP53*, in cancers characterized by structural variants. These differences highlight potential mechanisms by which different paediatric cancer genomes are shaped.

Third, different genes are mutated in paediatric compared with adult cancers. Only 30% of significantly mutated genes identified by Gröbner and co-workers (those that have acquired more mutations than would have been expected to occur by chance, and so are likely to be involved in cancer progression), and only 45% of those reported by Ma and colleagues, overlap with adult pan-cancer analyses. These differences are borne out in the groups' mutation-signature analyses, which provide information about the mutational processes that lead to a particular pattern of mutations.

THE DIFFERING GENOMIC LANDSCAPES OF CHILDHOOD AND ADULT CANCERS

Two studies[1,2] have analysed genome sequences from a range of childhood cancers, and uncovered key differences from adult cancers.

Feature	Childhood	Adult
Mutation rate	Lower	Higher
Cancer-driving mutations	Frequently single	Multiple
Mutation specificity	Disease-specific	Shared

Fourth, and perhaps most intriguingly, driver mutations tend to be specific to individual paediatric cancer types, with minimal overlap across diseases. This is in contrast to adult cancers, which more frequently share mutations across types, according to Gröbner and colleagues' analysis. This finding by the current studies might reflect the differing paths to cancer development between adult and paediatric cancers. Adult cancers often arise through a multiple-hit process in which alterations in genes generally beneficial to cell survival accumulate as cells become cancerous[9]. By contrast, a model of paediatric cancers posits that, in some cases, a single, specific driver alteration might promote cancer development in certain cell lineages, if it results in aberrant gene expression during a crucial period of development[6]. Indeed, a study in mice has also highlighted the importance of developmental context and the timing of genomic perturbation in tumour development[10].

"Different genes are mutated in paediatric compared with adult cancers."

The insights gleaned from the current analyses have implications for precision-medicine approaches for childhood cancers. Gröbner *et al.* found that about 50% of the tumours that they profiled harbour genomic alterations that can be targeted (directly or indirectly) by drugs that are available or under development. This number, which is consistent with previous reports[11,12], is a cause for optimism. The findings also provide insights into how clinical assays could be designed to ensure robust detection of alterations specific to paediatric tumours. Assays must profile genes that are significantly mutated across childhood cancers, with sufficient sensitivity to detect single driver alterations in an individual's genome, and must be specifically designed to include mutations and structural variants in both coding and non-coding regions of the genome.

Furthermore, the studies reinforce the need for paediatric oncologists to consider the high incidence of germline mutations in their patients. Clinicians should offer genetic counselling (in which patients are advised about risks and management options for genetic disorders), testing for germline alterations and appropriate screening for families who are found to harbour germline mutations.

Although the current studies provide valuable insights, much work is still required to complete the picture. Gröbner and colleagues were unable to identify driver alterations in 10% of tumours, and neither group analysed enough samples in a specific cancer type to detect infrequent mutations. Childhood cancers are, by definition, rare tumours. Continued collaboration and data-sharing are required to amass information from enough tumours of each type to comprehensively identify recurrent driver alterations. Furthermore, given that both groups identified structural variants, which often occur in non-coding regions, whole-genome sequencing is needed to detect drivers outside coding regions. Data from both studies are available for review — Gröbner and colleagues' at go.nature.com/2bq3oyh, and Ma and colleagues' at go.nature.com/2svr9hh. This is a key step in paving the way for further analytical efforts across large cohorts of paediatric tumours.

Last but not least, it will be necessary to elucidate the mechanisms by which the identified genetic alterations drive childhood cancer. This will improve our ability to target these alterations therapeutically. ■

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