standardize best practices for proxy sampling, reconstructions, dating and statistical analyses. One priority should be to select key sites for proxy sampling and analysis. For example, are there crucial geographical gaps that require attention and that strike an urgent socio-economic or ecological chord[4,11]? Fortunately, several initiatives are already focusing on improving efforts to integrate models and proxy results, for example the Paleoclimate Modelling Intercomparison Project and the Past Global Changes project.

Ljungqvist *et al.* were, of course, constrained by the data available for analysis — indeed, their efforts reveal a shocking lack of data. For example, Figure 1 of their paper[3] highlights the vast geographical gaps between proxy sites. Immense areas of the Northern Hemisphere still require exploration for proxy development, many in highly populated regions. The current analysis should therefore be revisited as proxy records from these regions become available.

Nevertheless, this research is a crucial first step in the use of models and proxy data to reconstruct and explain the history of water — and not just of temperature change — through time. Future research efforts should improve, test and extend Ljungqvist and colleagues' results. Global warming will undoubtedly change Earth's water cycle, so the more that is known about the cycle's past behaviour through proxy records, and the better those changes can be modelled, the more confidence we will have in predictive models as we forge ahead into the twenty-first century. ■

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NEUROSCIENCE

Untangling autism

A clever dissection of the roles of the *Ptchd1* gene in the brains of mice demonstrates one way to untangle the complex relationships between the causes and symptoms of neurodevelopmental disorders. SEE ARTICLE P.58

SCOTT BOLKAN & JOSHUA A. GORDON

Our current understanding of neurodevelopmental disorders can be thought of as a tangled mess of threads. The clinical presentations of such disorders are so variable that people can receive the same diagnosis despite not sharing a single symptom. Furthermore, the underlying risk factors — be they genetic or environmental — can be associated with not just one, but several disorders. Untangling these threads to link cause and outcome seems a Sisyphean task, but it is a crucial one if we are to develop treatment approaches that have a solid neurobiological basis. In this issue, Wells *et al.*[1] (page 58) use a mouse model of a human genetic condition to grasp the loose end of a single thread and carefully extricate it from the tangled mess. In doing so, they map a precise set of genetically linked symptoms onto dysfunction of a neuronal structure that gates the flow of information across multiple brain circuits.

Wells and colleagues' approach is based on clinical observations[2,3] of a link between autism spectrum disorder and mutations in the *PTCHD1* gene. Autism spectrum disorder involves a tremendously debilitating disruption of social and cognitive function, and is frequently associated with several neurodevelopmental diagnoses that have overlapping symptoms, including intellectual disability and attention deficit hyperactivity disorder.

As is typical for genes associated with neurodevelopmental conditions, *PTCHD1* mutations are seen in only a small fraction of people with autism spectrum disorder[4]. Not everyone with the risk-associated gene variant develops the disorder, but the mutation does raise disease risk substantially: more than 40% of individuals with the mutation develop autism-like behaviours, compared with about 1% of the general population[5]. Nonetheless, how a single gene can alter brain function to produce particular symptoms remains unclear.

Wells *et al.* began to unravel these issues by generating mice that produce a truncated, non-functional form of the PTCHD1 protein. The authors report that *Ptchd1* mutant mice exhibit behavioural abnormalities that are largely consistent with those seen in people with autism spectrum disorder, including sleep disruption, hyper-aggression and deficits in attention and learning.

In seeking to understand how the *Ptchd1* mutation can produce such a broad set of symptoms, the authors were struck by the observation that, during early postnatal development, expression of the gene is highly enriched in a neuronal structure called the thalamic reticular nucleus (TRN) in the thalamus region of the brain. This structure sends inhibitory neuronal projections to all areas of the thalamus, and thus exerts powerful control over the flow of neuronal activity within and across brain circuits that process information

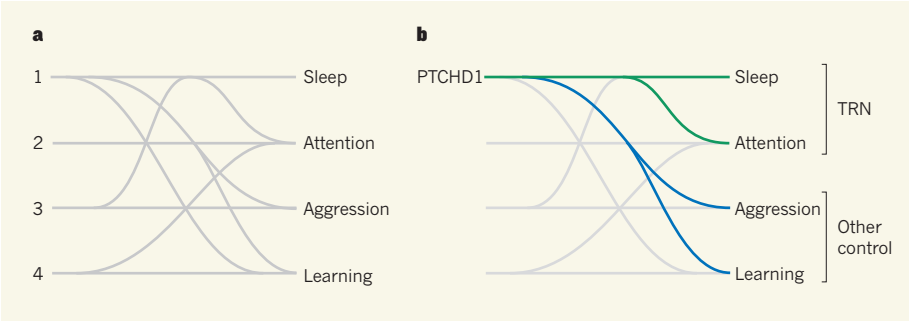

Figure 1 | Tracing the threads between causes and symptoms of autism. **a**, Autism spectrum disorder is caused by a range of environmental and genetic factors (symbolized here by numbers), each of which can lead to one or more of many symptoms. Untangling which causes lead to which symptoms is a major challenge. **b**, Wells *et al.*[1] have done just that for the PTCHD1 protein, which is mutated in some people with autism spectrum disorder. They find that, in mice, PTCHD1 regulates sleep, attention, aggression and learning. Furthermore, sleep and attention, but not aggression and learning, are mediated by PTCHD1 expression in a neuronal structure called the thalamic reticular nucleus (TRN).

about vision, movement, cognition and more. The TRN is known as the 'guardian' or 'gatekeeper' of activity in these thalamic brain circuits and has regulatory roles in sleep[6] and attentional processes[7,8]. As such, dysfunction in the TRN could plausibly produce wide-ranging behavioural abnormalities.

Focusing on the TRN, Wells *et al.* traced a route from gene to behaviour in *Ptchd1* mutant mice. The authors monitored the activity of TRN neurons, and found fewer bursts of activity in mutant animals than in controls. These changes were attributable to a drastic reduction in the activity of the SK-channel protein, which mediates passage of potassium ions across the cell membrane and normally promotes activity bursts. With reduced levels of channel activity, and reduced numbers of bursts, TRN neurons fail to properly inhibit activity in other regions of the thalamus, including the lateral geniculate nucleus — the main visual relay between the eyes and the brain's visual cortex. This failure to properly inhibit thalamic relays seems to disrupt visual attention, among other behaviours.

Which of the wide-ranging abnormalities seen in the *Ptchd1* mutant mice truly depend on this disruption of TRN function? To answer this question, Wells *et al.* generated mice that lacked the *Ptchd1* gene exclusively in the TRN. In a remarkable dissociation of symptoms, they found that TRN-restricted *Ptchd1* mutant mice display hyperactivity and deficits in sleep and attention, but do not exhibit the learning deficits and hyper-aggression observed in mice carrying the brain-wide mutation (Fig. 1). Moreover, using a pharmacological agent to restore SK-channel function in adult mice, Wells *et al.* were able to re-establish activity levels in the thalamic relays controlled by the TRN. This reversed abnormal hyperactivity and deficits in sleep and attention, but not impaired learning or hyper-aggression. Successful restoration of normal sleep and attention in adult animals raises hopes that treatments targeting the SK channel might benefit people with *PTCHD1* mutations, and perhaps also those with autism spectrum disorder caused by other factors.

The authors' study indicates that both TRN-specific deletion of *PTCHD1* and systemic enhancements in SK-channel function affect the same subset of behavioural outcomes. This consistency strongly supports the idea that *PTCHD1* exerts its effects on TRN function (and therefore on activity, sleep and attention) through the SK channel. However, the findings also argue that the effects of *PTCHD1* on learning and aggression are caused by an altogether different mechanism that both acts outside the TRN and is independent of SK-channel function. Determining which brain regions and biochemical pathways might be responsible for these behavioural changes will probably be important for fully reversing the deficits caused by *PTCHD1* mutations.

Wells *et al.* have placed their fingertips on the loose thread of *PTCHD1* expression, following it to the TRN, through the SK channel and to its end in behaviours associated with neurodevelopmental disease. In doing so, they have identified the SK channel as a potential pharmacological target for treating autism spectrum disorder, while simultaneously highlighting the usefulness of animal models of human genetic conditions for studying neurodevelopmental and psychiatric diseases. Although the role of *PTCHD1* in learning and aggression remains elusive, the current paper shows one way to navigate the daunting complexity of neuronal-circuit function to reveal the mechanisms by which gene dysfunction leads to changes in behaviour. ■

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MOLECULAR BIOLOGY

Breaks in the brain

A high-throughput approach has found clusters of DNA double-strand breaks in neural cells. Most of the clusters are in large genes that are associated with neural function, which suggests that the breaks may have tissue-specific roles.

THOMAS W. GLOVER & THOMAS E. WILSON

Studies over the past decade have revealed a surprising degree of structural variation in human genomes. Structural variants (SVs) in germline DNA are now known to be a major factor in normal genomic variation and an important class of mutation in genomic disorders, and they arise frequently in cancers. Many SVs are thought to result from DNA-replication errors[1], so they would be expected to occur at a high frequency in dividing somatic cells (those that do not undergo meiotic division). However, in contrast to heritable SVs in germline cells, little is known about somatic SVs and their impact on tissue function and disease. Writing in *Cell*, Wei *et al.*[2] provide insight into these questions by examining the landscape of DNA double-strand breaks (DSBs) that arise in mouse neural cells.

The difficulty in studying somatic SVs arises primarily from technical challenges in detecting rare events in cell populations. Sensitive sequencing technologies coupled with bioinformatic tools have begun to provide glimpses of somatic SVs *in vivo*, especially in the brain, where up to 40% of individual neurons have been found to contain megabase-scale copy-number variations (CNVs; a form of SV in which the number of copies of a genomic region varies between cells or individuals)[3,4]. However, because of the low resolution of many approaches, the true prevalence of SVs in neurons or other cells, and the mechanisms by which they arise, are unknown.

Wei *et al.* used a sensitive, targeted assay known as high-throughput genomic translocation sequencing. This method allows genome-wide detection of naturally occurring 'prey' DSBs using experimentally induced 'bait' DSBs targeted elsewhere in the genome. The two DSBs are joined by cellular DNA-repair processes, leading to a translocation between the genomic regions. Sequencing of the resulting breakpoint junction allows mapping and characterization of the DSBs at nucleotide-level resolution.

The authors first created DSBs at bait loci on three mouse chromosomes in cultured neural stem/progenitor cells (NSPCs) that lacked the protein Xrcc4, which is essential for a DSB-repair process called non-homologous end-joining (NHEJ); preventing this joining enriches for cells with rearrangements. The cells also lacked the protein p53; this lack promotes cell survival. The researchers identified thousands of prey DSBs, with 61% located close to the bait DSBs and the rest spread across the genome (Fig. 1). Strikingly, many were found within three recurrent DSB clusters (RDCs); two of these were in the *Lsamp* and *Npsa3* genes, which are unusually large genes that encode a neural-cell-specific adhesion molecule and a transcription factor, respectively. The third RDC reflected DSBs that occurred close to the bait.

When the authors applied the same procedure in mouse B cells (a type of immune cell), they found B-cell-specific RDCs but no