

# THIS WEEK

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## The mind's tangled web

*Efforts to elucidate how genes and the environment shape the development of autism, although making progress, still fall far short of their goal.*

Among psychiatric disorders, autism has received particularly strong support from government and philanthropic funders in recent years. And that investment has paid scientific dividends, above all the uncovering of genetic clues to underlying mechanisms for the disorder. But, as discussed in this special issue and in a web collection of content published this week in other Nature journals (see [nature.com/autism](http://nature.com/autism)), those developments, although pointing a way forward, have themselves revealed just how small a distance we have travelled towards a fuller mechanistic understanding.

Context, as always, is important. First, the object of study: it is clear that the diagnostic criteria for autism need to be refined and expanded, and that there is a spectrum of autistic disorders. Second, although most parents struggling with children with autism would jump at the chance to mitigate or cure the symptoms, it is not appropriate to think of autism solely as a disorder needing treatment. As psychiatrist Laurent Mottron vividly describes on page 33, people with autism bring particular talents to many professional settings, including the scientific laboratory. And that perspective plays into a range of ethical implications for the pursuit of biomarkers for the condition (P. Walsh *et al. Nature Rev. Neurosci.* **12**, 603–612; 2011). Third, the growth in the prevalence of autism can be explained only partly by changes in diagnostic practice — about 50% seems to be genuine, or at least unexplained (see page 22).

Everyone agrees that autism stems from a disruption of brain development caused by a combination of genes and environment. Since the 1970s, it has been known from studies of twins that there is a high, but not complete, degree of heritability. In recent years, well-funded and coordinated efforts, coupled with advances in technology, have led to large-scale studies of unprecedented statistical power, producing impressive data on the genetics of the condition. But those data have confirmed only that the answer is elusively complicated. With the exception of a few rare disorders, such as fragile X or Rett syndrome, which lead to forms of autism, no disruption of an individual gene, or set of genes, can reliably predict the condition. An emerging story is that the culprits could include any one of many extraordinarily rare genetic variations, and that a systems approach will be important in understanding regulatory hubs, for example (M. W. State and P. Levitt *Nature Neurosci.* <http://dx.doi.org/10.1038/nn.2924>; 2011).

Nonetheless, progress is being made in tracking the neurobiological effects of these genetic variations. Recently, mice carrying mutations in candidate genes have been produced, and have been found to show behaviours reminiscent of autism — such as a lack of interest in socializing with other mice, repetitive grooming and anxiety. These mice all have alterations in brain structure and function, and will undoubtedly be useful for testing hypotheses about the relationship between various brain circuits and autism-associated behaviour (see, for example, J. L. Neul *Nature Med.* **17**, 1353–1355; 2011). Along with these mice, cellular models derived from patients carrying certain mutations also hold promise for testing molecular hypotheses and therapies.

Encouraging as these efforts are, they cover just half of the gene–environment equation and thus will at best only ever yield part of the solution. It is widely agreed that environmental factors, through direct neurobiological mechanisms or interactions with genes, could interfere with neural development to cause autism. Many factors have been proposed, including maternal infection during pregnancy. But none of these candidates has yet been convincingly established, nor have their biological links to autism been tested mechanistically.

**“The growth in the prevalence of autism can be explained only partly by changes in diagnostic practice.”**

Clearly, nailing down a given influencing factor from our incredibly complex environment is no trivial task, possibly harder than identifying variation in the genome. It will take very large and expensive long-term studies just to narrow down the possibilities.

Some, such as the US National Institutes of Health's EARLI study (see page 22), are already under way and could yield not only valuable material for studying gene–environment interactions, but also potential mechanistic leads for biologists to pursue.

Although many scientists and funding agencies have focused their resources on apparently tractable questions in genetics and neurobiology, the attention of the public and mainstream media has been repeatedly drawn to environmental hypotheses regardless of their scientific strength, such as the discredited link to vaccinations (see page 28). It is essential that agencies and philanthropists are not similarly distracted by public mood, just as it is crucial that scientists working on possible environmental influences take great care to communicate the results of their studies properly. The need to elucidate the true environmental influences on autism is a priority, and, as our collection of articles displays, social sciences, psychology and neurobiology all have their roles. ■

## More in Montreal

*Momentum builds for ozone treaty to take on greenhouse gases.*

For more than two decades, the 1987 Montreal Protocol has served as a shining example of how to get things done on the environment in the international arena. By banding countries together to preserve Earth's shield against harmful ultraviolet rays, the agreement has already eliminated many ozone-depleting substances and should see off most of the rest by 2030. And in doing so, it has done more to reduce greenhouse-gas emissions than the 1997 Kyoto Protocol, which was signed expressly for that purpose. It is equally