Recent studies of genetic and environmental risk factors for psychiatric disorders challenge standard diagnostic classifications in psychiatry.\(^1\) Many of the strongest emergent genetic risk factors, such as copy number variants (CNVs), increase risk across a range of conditions.\(^2\) Furthermore, common risk variants, individually of small effect, can also increase risk for a range of disorders and some even span disorders as apparently diverse as autism and attention-deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder and depression.\(^3\) Environmental risk factors, such as prenatal adversities, can similarly increase liability to later neuropsychiatric illness across a variety of conditions.\(^4\)

It is clear that identified risk factors can increase vulnerability to a range of psychiatric symptoms and syndromes at different developmental stages. This means that any classification of psychiatric disorders based on aetiology will need to take into account not only the risk factors, but also the age at which they become manifest. The fact that the same risk factor might produce quite markedly different psychiatric symptoms at different ages has been predicted at least since the earliest formulations of the neurodevelopmental hypothesis of schizophrenia. This can now be seen clearly in the context of specific genetic risk factors such as deletions of chromosome 22q11.2 (22q11DS; Di George syndrome; velocardiofacial syndrome) that has been studied in more detail to date than any other CNV that is associated with psychiatric outcomes.

The example of 22q11DS

A relatively common chromosomal CNV, 22q11DS, affects approximately 1 in 4000 live births. It is associated with increased rates of cardiac abnormalities, a range of other physical consequences and intellectual disability. 22q11DS is also associated with markedly high rates of schizophreniform and affective psychosis with peak age at onset in the early 20s.\(^5\) Studies of children with 22q11DS also reveal high rates of childhood psychopathology including symptoms of ADHD, autism spectrum disorder and anxiety disorders.\(^6,7\) Strikingly, 22q11DS has also been shown to be a risk factor for early-onset Parkinson’s disease in older individuals.\(^8\) Overall, therefore, 22q11DS is associated with increased risk for a range of neuropsychiatric and neurodegenerative disorders that present across the lifespan. A similarly wide range of neuropsychiatric outcomes spanning developmental stages is also seen for other CNVs associated with psychiatric risk,\(^9\) raising the question as to how individual genetic lesions can increase risk for a range of conditions each with distinct core symptoms.

One possible explanation of the range of outcomes seen following 22q11DS and other genetic risk factors is that the phenotypic effects of the deletion are moderated by the age of penetrance in a given individual. The primary neural mechanisms involved in central brain functions such as learning and prediction are established early in life, but the relative maturation of different brain circuits and the nature of the information being laid down differs at various stages of development. Disruptions of core aspects of brain function at different ages are therefore likely to result in the emergence of different symptoms. For example, in early postnatal life key developmental achievements include the acquisition of motor skills, imitative social behaviours and language.\(^6\) These skills are typically gained in the developmental environment provided by the family and immediate social group. The impact on brain circuitry during these developmental stages is likely to be associated with outcomes associated with altered language development and basic motor and social functions such as are seen in developmental disorders including autism and ADHD. In contrast, after puberty exploration away from the family group increases and learning and prediction must be applied to a different set of circumstances.\(^7\) Disruption of normal brain function at this developmental stage is likely to reflect maturational processes occurring in the post-pubertal brain as it interacts with a wider range of environments, and may be manifest as psychosis and altered motivational states, such as mood disorders. In later life neurodegenerative processes develop in vulnerable populations and may be exacerbated by risk factors that have an impact on the development, maintenance and function of key brain circuitry.

It is not currently known whether the different conditions associated with 22q11DS arise from one primary underlying pathological deficit, or through separate mechanisms.\(^9\) There are multiple neurally expressed genes within the 22q11DS region, each with differing expression patterns and developmental trajectories and potentially having an impact on multiple different brain circuits/systems at different developmental stages, many of which may contribute to vulnerability to the range of neuropsychiatric outcomes seen in 22q11DS. However, several of the neuropsychiatric conditions associated with 22q11DS show overlap at the resolution not just of loci or even individual genes, but even of mutations with similar functional (loss-of-function) effects.\(^8\) Thus, it remains possible that deletion of either a single gene or
multiple genes within the 22q11DS region might contribute to the diverse neurodevelopmental outcomes seen in 22q11DS.

Notably, many of the neuropsychiatric outcomes seen in 22q11DS have been associated with alterations in the regulation of monoaminergic functioning. Disruption of the regulation of monoaminergic systems such as mesostriatal dopamine involved in learning and reward may therefore represent one common aspect of the vulnerability to neuropsychiatric symptoms seen in 22q11DS that would be expected to produce different outcomes at different developmental stages. However, detailed studies of monoamine levels and regulation in 22q11DS are currently lacking and more needs to be known about the basic pathophysiology in 22q11DS before any specific conclusions can be drawn.

**Age at onset**

There are a number of potential explanations as to why risk factors such as 22q11DS may lead to the emergence of neuropsychiatric symptoms at differing neurodevelopmental stages. The simplest is that for individuals with later presentations (such as schizophrenia), symptoms of earlier difficulties were present but were not sufficient for formal diagnosis or did not come to medical attention. This would reflect the more general finding that individuals destined to develop schizophrenia have a greater degree of subtle neurodevelopmental impairments years prior to illness onset in population studies.5 There is indeed some evidence that a proportion of people who develop schizophrenia in the context of 22q11DS did have earlier symptoms consistent with childhood autism spectrum disorder, although this has been reported to be the case in less than 10% of individuals in a cross-sectional retrospective study.6 Longitudinal prospective studies examining a range of neurodevelopmental outcomes are, however, required to clarify the relationship and overlap of symptoms, including subsyndromal traits, across different developmental stages within individuals.

The currently available evidence is consistent with the view that at least in some cases later neuropsychiatric presentations, such as schizophrenia or Parkinson’s disease can arise in individuals with 22q11DS without marked earlier psychiatric difficulties. This raises the issue of what might act to moderate the age of presentation in different individuals. The range of possibilities include genetic, environmental and stochastic processes. Genetic moderators could include the size of the deleted region, allelic variation in the region of the deletion on the unaffected chromosome or the moderating effect of other genetic variants in the genome. Environmental influences could include a range of early life insults, such as maternal prenatal infections or obstetric complications, which might have an impact on the same developmental pathways affected in 22q11DS. Stochastic factors operating across the highly intricate and extended course of brain development may also act to influence eventual outcome. The realisation that risk factors such as 22q11DS produce a range of different disorders according to the timing of penetrance illustrates the importance of research into identifying such key moderating influences.

**Implications for research and classification**

A clear priority for future research will be the longitudinal characterisation of psychopathology in individuals bearing genetic lesions such as CNVs conferring high risk for neuropsychiatric disorders. Only through longitudinal cohort studies of these risk factors will we truly understand the nature and interrelationship of symptom emergence over neurodevelopment. Such studies will also provide an important opportunity to study the development of associated physical comorbidities in these populations, with additional potential benefits in terms of health monitoring and intervention. Interpreting the emergence of symptoms at different developmental stages will also greatly benefit from further study of the normal development and functional maturation of brain systems such as the mesolimbic dopaminergic projections and associated cortico-striatal circuitry. Understanding of the biological effects and differential penetrance of CNVs will also be advanced by the ability to study development in meaningful cellular and animal models of these conditions.

In the longer term these findings will also have major implications for how we view the classification of psychiatric disorders.1 Current classification systems view neurodevelopmental disorders such as autism and adult disorders such as schizophrenia as distinct. However, if individual specific risk factors increase risk for both ‘developmental’ and ‘adult’ conditions dependent on the timing of onset, classifications based on aetiology will eventually need to reflect a matrix of risk including both lesion type and developmental stage.7 As the identification of genetic risk factors such as CNVs becomes more common in children and adults presenting to clinical genetic services, understanding risk across the neurodevelopmental age range and developing classification systems that reflect the true nature of risk will become an increasingly pressing clinical concern.

**References**