

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/116409/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Doherty, Joanne, Cooper, Miriam and Thapar, Anita 2018. Advances in our understanding of the genetics of childhood neurodevelopmental disorders. *Evidence-Based Mental Health* 21 (4) , pp. 171-172.  
10.1136/ebmental-2018-300067

Publishers page: <http://dx.doi.org/10.1136/ebmental-2018-300067>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



**Advances in our understanding of the genetics of child neurodevelopmental disorders**

**Joanne Doherty<sup>1</sup>, Miriam Cooper<sup>2</sup>, Anita Thapar<sup>1</sup>**

**Corresponding author: Joanne Doherty, [dohertyjl@cardiff.ac.uk](mailto:dohertyjl@cardiff.ac.uk)**

**Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ**

**<sup>1</sup> Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Wales, UK**

**<sup>2</sup> Neurodevelopmental Service, Cwm Taf University Health Board, Merthyr Tydfil, Wales, UK**

**Word count: 1274**

Child neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and intellectual disability (ID) typically are complex, heterogeneous, conditions that show considerable clinical overlap. There are both genetic and environmental contributions to their aetiology, which are not yet fully elucidated. However, immense progress has been made in our understanding of their genetic basis in the last two decades. This short review aims to synthesise the key findings in this regard, with a focus on some of the factors that are most relevant to clinical practice.

Family and twin studies provided the first evidence of the familial aggregation and heritability of child neurodevelopmental disorders. For example, the heritability estimate for ADHD is 88%[1] and for ASD it is 64-91%[2]. Families often want to know the likelihood of having a child with a neurodevelopmental problem in future if they themselves or their offspring have a neurodevelopmental disorder. First degree relatives of people with ADHD have a five to ninefold elevated risk of having ADHD themselves,[3] and siblings of those with ASD are estimated to have a tenfold elevated risk of having ASD[4]. Family studies also show shared genetic effects across disorders,[5] i.e. siblings of a person with one disorder (e.g. ADHD) are themselves at elevated risk of both that disorder and other neurodevelopmental conditions (e.g. ASD, reading disability), as well as of subthreshold traits.[6, 7]. These factors mean that parents of children with a neurodevelopmental disorder may show elevated levels of neurodevelopmental traits that do not necessarily meet criteria for a diagnosed disorder. These characteristics could impact on clinical assessment and parental ability to implement interventions.

What genetic factors contribute to this high heritability? Both common (single nucleotide polymorphisms, SNPs, >5% population frequency) and rare (<1%) genetic variants, which can be inherited or arise *de novo* in offspring, are involved in the pathogenesis of ADHD, ASD and ID. Early work into the genetic basis of neurodevelopmental disorders used linkage analysis to identify relatively high-penetrance variants associated with neurodevelopmental disorders by studying large pedigrees of affected families. Another early approach investigated candidate genes, selected based on their hypothesised role in the underlying biology of the disorder (e.g. dopamine receptor genes in ADHD). Both approaches however, have significant disadvantages and these studies, on the whole, failed to produce consistent, reproducible results. They have been superseded by genome-wide platforms that allow comparison between large samples of patients and controls to identify differences in genetic make-up without any *a priori* hypotheses about genetic susceptibility loci. Genome-wide association studies (GWAS), have so far been successful in identifying multiple common genetic risk variants for adult-onset disorders such as schizophrenia,[8] bipolar disorder[9] and many

physical illnesses such as diabetes [10]. GWAS of child neurodevelopmental disorders have somewhat lagged behind, not least because of the difficulty accumulating large samples of patients with these disorders although genome-wide significant findings have now emerged for both ADHD[11] and ASD[12]. Such findings are being used to investigate the biology and epidemiology of these disorders. Nevertheless available evidence suggests that the individual effect size of any given individual common gene variant is small, and that the genetic architecture of neurodevelopmental disorders, like other complex diseases, is explained by multiple common gene variants that have pleiotropic effects (i.e. they confer risk for various phenotypes) on multiple neuropsychiatric disorders such as depression and schizophrenia[13]. GWAS findings are increasingly being used to better understand clinical phenotypes and their boundaries. For example, when SNP effects are combined into composite measures of genetic risk[14,15] it has been shown that common polygenic variation for ADHD diagnosis confers risk for both ADHD traits and autism-related features in the general population[16] and that ASD diagnosis risk is associated with social-communication population trait levels[17]. More common gene variants will be identified as sample sizes grow with increased international collaborative efforts between research groups[18].

It has been known for a long time that genetic syndromes such as Fragile X syndrome and Tuberous Sclerosis can manifest as childhood neurodevelopmental disorders. More recently, rare chromosomal deletions and duplications (copy number variants, CNVs, <1% population frequency) also have been found to contribute to the risk for ADHD[19] ASD and ID[20]. People with neurodevelopmental disorders have a higher overall CNV burden than unaffected people as well as higher rates of specific pathogenic CNVs including deletions and duplications at chromosome 16p11.2[21] and duplications at chromosome 15q13.3[14]. These variants also have pleiotropic effects – for example, the 16p11.2 microdeletion is associated with developmental delay, cognitive impairment and ASD as well as physical manifestations including macrocephaly, obesity and seizures. Several copy number variants are highly penetrant for neurodevelopmental disorders (for example approximately 40% of children with chromosome 22q11.2 deletions meet the diagnostic criteria for ADHD and around 30% for ASD)[22] as well as for affective disorders and psychosis[23]. The relatively high penetrance of these neurodevelopmental CNVs for other psychiatric and physical health problems, together with the increased availability and reduction in cost of microarray genetic testing platforms in recent years has led to much debate about when to refer patients and their families to clinical genetic services for testing, with many arguing for a lowering of the threshold. Microarray testing has been recommended as a first-line investigation for global developmental delay (GDD) as it has a high diagnostic yield[24], particularly when compared with standard karyotyping. Current NICE guidance for ASD only recommends referral for genetic testing if dysmorphology, congenital anomalies and/or ID are also

present[25] and there are no recommendations made by NICE for testing in ADHD. The diagnostic yield seems to be highest when genetic testing is carried out in patients with multiple congenital abnormalities and/or dysmorphic features, and genetic testing should be considered even in the absence of a significant family history if a *de novo* mutation is suspected[26].

As discussed above, neither common nor rare genetic variants map onto single phenotypes on a one-to-one basis. This overlap between genetic risk factors for neurodevelopmental disorders is perhaps unsurprising given the overlapping clinical features of this spectrum of disorders. In addition, recent genetic evidence points to a gradient of psychiatric risk which not only cuts across childhood-onset disorders but also across disorders typically considered to be adult-onset, such as schizophrenia[27]. Equally, individual neurodevelopmental phenotypes can be viewed as continuously distributed risk dimensions[28]. As such, the importance of subthreshold neurodevelopmental symptomatology should not be overlooked as it indexes adverse outcomes[29]. Taken together, this evidence argues for a more dimensional approach to clinical assessment rather than one constrained by traditional diagnostic boundaries.

In summary, there have been tremendous advances in our understanding of the genetic aetiology of neurodevelopmental disorders over the last twenty years. Recognising the contribution of genetic factors can be extremely helpful for patients and their families and may help to reduce self-blame and stigma, although this needs empirical evidence. Furthermore, understanding the heritability of these disorders enables clinicians to have informed discussions with families about the risks for any future offspring, both of the index disorder and of other neurodevelopmental conditions - although at present these data do not provide personalised risk profiles. Also, genetic risks are probabilistic: not all at high genetic risk develop a disorder and not all with a disorder necessarily carry a given risk factor. Finally, although relatively rare, increased awareness and appropriate testing for neurodevelopmental CNVs is important so that affected individuals can be assessed for associated physical and psychiatric manifestations and receive appropriate genetic counselling.

In this short review, we have focussed on the genetics of neurodevelopmental disorders. However, we also acknowledge the important role that environmental factors play in the complex aetiology of these conditions. Continued investigation into the interactions between the environment and genetic factors will be an important avenue for future research.

*Competing interests: None declared.*

## References

- 1 Larsson H, Chang Z, D’Onofrio BM, *et al.* The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. *Psychol Med* 2014;**44**:2223–9.
- 2 Tick B, Bolton P, Happé F, *et al.* Heritability of autism spectrum disorders: a meta-analysis of twin studies. *J Child Psychol Psychiatry* 2016;**57**:585–95.
- 3 Faraone S V., Biederman J, Monuteaux MC. Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. *Genet Epidemiol* 2000;**18**:1–16.
- 4 Risch N, Hoffmann TJ, Anderson M, *et al.* Familial recurrence of autism spectrum disorder: evaluating genetic and environmental contributions. *Am J Psychiatry* 2014;**171**:1206–13.
- 5 Lichtenstein P, Carlström E, Råstam M, *et al.* The Genetics of Autism Spectrum Disorders and Related Neuropsychiatric Disorders in Childhood. *Am J Psychiatry* 2010;**167**:1357–63.
- 6 Ronald A, Simonoff E, Kuntsi J, *et al.* Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *J Child Psychol Psychiatry* 2008;**49**:535–42.
- 7 Taylor MJ, Charman T, Robinson EB, *et al.* Developmental associations between traits of autism spectrum disorder and attention deficit hyperactivity disorder: a genetically informative, longitudinal twin study. *Psychol Med* 2013;**43**:1735–46.
- 8 Ripke S, Neale BM, Corvin A, *et al.* Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014;**511**:421–7.
- 9 Xiao X, Wang L, Wang C, *et al.* Common variants at 2q11.2, 8q21.3, and 11q13.2 are associated with major mood disorders. *Transl Psychiatry* 2017;**7**:1273.
- 10 Fuchsberger C, Flannick J, Teslovich TM, *et al.* The genetic architecture of type 2 diabetes. *Nature* 2016;**536**:41–7.
- 11 Demontis D, Walters RK, Martin J, *et al.* Discovery Of The First Genome-Wide Significant Risk Loci For ADHD. *bioRxiv* 2017;:145581.
- 12 Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium TASDWG of TPG. Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. *Mol Autism* 2017;**8**:21.
- 13 Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 2013;**381**:1371–9.
- 14 Hamshere ML, Langley K, Martin J, *et al.* High loading of polygenic risk for ADHD in children with comorbid aggression. *Am J Psychiatry* 2013;**170**:909–16.
- 15 Anney R, Klei L, Pinto D, *et al.* Individual common variants exert weak effects on the risk for autism spectrum disorders. *Hum Mol Genet* 2012;**21**:4781–92.
- 16 Martin J, Hamshere ML, Stergiakouli E, *et al.* Genetic risk for attention-deficit/hyperactivity disorder contributes to neurodevelopmental traits in the general population. *Biol Psychiatry* 2014;**76**:664–71.
- 17 Robinson EB, St Pourcain B, Anttila V, *et al.* Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. *Nat Genet* 2016;**48**:552–5.
- 18 Sullivan PF, Agrawal A, Bulik CM, *et al.* Psychiatric Genomics: An Update and an Agenda. *Am J Psychiatry* 2018;**175**:15–27.
- 19 Williams NM, Franke B, Mick E, *et al.* Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: the role of rare variants and duplications at 15q13.3.

- Am J Psychiatry* 2012;**169**:195–204.
- 20 Girirajan S, Brkanac Z, Coe BP, *et al.* Relative burden of large CNVs on a range of neurodevelopmental phenotypes. *PLoS Genet* 2011;**7**:e1002334.
  - 21 Weiss LA, Shen Y, Korn JM, *et al.* Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med* 2008;**358**:667–75.
  - 22 Niarchou M, Zammit S, van Goozen SHM, *et al.* Psychopathology and cognition in children with 22q11.2 deletion syndrome. *Br J Psychiatry* 2014;**204**:46–54.
  - 23 Schneider M, Debbané M, Bassett AS, *et al.* Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry* 2014;**171**:627–39.
  - 24 Mithyantha R, Kneen R, McCann E, *et al.* Current evidence-based recommendations on investigating children with global developmental delay. *Arch Dis Child* 2017;**102**:1071–6.
  - 25 National Institute for Health and Care Excellence. NICE Clinical Guideline 128: Autism diagnosis in children and young people. 2011.
  - 26 Bouwkamp CG, Kievit AJA, Markx S, *et al.* Copy Number Variation in Syndromic Forms of Psychiatric Illness: The Emerging Value of Clinical Genetic Testing in Psychiatry. *Am J Psychiatry* 2017;**174**:1036–50.
  - 27 Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum:evidence from genomics. *World Psychiatry* 2017;**16**:227–35.
  - 28 Constantino JN, Todd RD. Autistic Traits in the General Population. *Arch Gen Psychiatry* 2003;**60**:524.
  - 29 Bussing R, Mason DM, Bell L, *et al.* Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. *J Am Acad Child Adolesc Psychiatry* 2010;**49**:595–605.