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DOI:

[10.1016/S2215-0366\(15\)00389-2](https://doi.org/10.1016/S2215-0366(15)00389-2)

Document Version

Peer reviewed version

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Citation for published version (APA):

Charman, T. (2015). The new genetics of autism: A translational opportunity? *The Lancet Psychiatry*, 2(10), 856-857. [https://doi.org/10.1016/S2215-0366\(15\)00389-2](https://doi.org/10.1016/S2215-0366(15)00389-2)

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The new genetics of autism: from rare syndromes to translational opportunities

Richards and colleagues¹ have made a useful contribution to our understanding of the prevalence of autism spectrum disorder (ASD) in genetic and metabolic syndromes.

Their meta-analysis demonstrates that the prevalence rates of ASD in these syndromes range from high (11% in individuals with 22q11.2 deletion syndrome) to very high (36% in tuberous sclerosis complex) to exceedingly high (61% in Rett syndrome). This is against a general population prevalence of around 1%. The findings are of clinical relevance and speak to the ‘new genetics’ of ASD that are unveiling clues to the aetiology of the disorder and hold the potential for translational discovery to develop and test new interventions².

Clinically, the high rates of ASD in these syndromes support the revisions to the DSM-5 diagnostic classification system where the ‘clinical specifiers’ that should be noted alongside an ASD diagnosis include ‘known medical or genetic conditions’³. The authors highlight that the recognition of an ASD presentation alongside the genetic/metabolic syndrome will have important implications for management, for example in terms of managing repetitive and rigid behaviours or taking account of impairments in social understanding and communicative functioning. One caveat that should be added to the conclusions of the authors is that alongside intellectual disability (ID) – another clinical specifier in DSM-5 – it is also the case that other common neurodevelopmental and neuropsychiatric conditions (e.g. attention deficit hyperactivity disorder (ADHD), anxiety disorders) that are associated both with ASD and with ID may also be common in these individuals with these syndrome with implications for management⁴. As the Richards et al. recognise, there are significant challenges to the measurement and establishment (and treatment) of both ASD and other associated disorders in individuals with significant ID and the field needs to continue to develop clinically useful solutions to such challenges, as they may offer tractable pathways to better management and treatment.

In basic and translational science terms, the possibility of reconciling our understanding of how single gene disruptions affect neurodevelopment both before and after birth – essentially a ‘bottom-up’ approach to revealing mechanisms of aetiology – with ‘top-down’ approaches such as searching for the genetic substrate of ‘idiopathic’ ASD where there is no known genetic anomaly reflects the crossroads at which the science of ASD has arrived. The fact that most genetic and genomic disorders show both variable expression and pleiotropy⁵ raises the question of the

extent to which the association the authors describe between genetic/metabolic syndromes and ASD is specific, or whether such syndromes are associated with more general neurodevelopmental disruption that results in behavioural phenotypes that include features of ASD, ADHD and ID.

Recent attempts to establish greater specificity between the behavioural phenotype of ASD – such as IQ and symptom profiles – and specific genetic substrate have proved more challenging than many hoped⁶. Whilst single gene disorders may have high penetrance in terms of being strongly associated with an ASD phenotype in individuals with such mutations – as clearly demonstrated in this article – most genetic risk for the broader population of individuals with ASD resides in common genetic variation⁷. It is also well established that de novo mutations – copy number variations (CNVs) – are also associated with the ASD phenotype⁸. CNVs that result in loss of function may be more strongly associated with ASD in combination with significant ID, whereas in individuals with ASD with higher IQs inherited genetic influences – as evidenced by higher rates of psychiatric disorders in family members – might play a more major role⁹.

A final consideration of the translational potential of better understanding how genetic and metabolic syndromes contribute to the ASD phenotype and commonly associated phenotypes is the possibility that such discoveries will offer therapeutic opportunities at a neural systems level. One area of focus that has been strongly influenced by recent findings from the study of syndromic forms of ASD are the neural pathways involved in synaptic development and functioning¹⁰. There is accumulating evidence that these pathways might also be involved in the pathogenesis of nonsyndromic

forms of ASD. After promising findings from preclinical studies within model systems and in human neuronal models, pilot trials have begun to test whether a number of compounds may have therapeutic potential in human patients. Promising targets including mGluR5 antagonists in fragile X syndrome, mTOR inhibitors in tuberous sclerosis and insulin-like growth factor in Phelan-McDermid syndrome¹¹. If these studies are successful then trials will begin with these compounds in nonsyndromic or ‘idiopathic’ patients with ASD.

Richards and colleagues have provided a state-of-the-art meta-analytic review that reinforces how commonly the ASD and other associated phenotypes are associated with rare genetic and metabolic syndromes. The challenge for clinicians and scientists in the years ahead is to further develop clinical practice and translational science to put this knowledge to good use for these individuals and those who care for them.

Word count: 790

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Abbreviations

ADHD – Attention deficit hyperactivity disorder
ASD – Autism spectrum disorder
CNV – Copy number variation
ID – Intellectual disability
IGF-1 – Insulin-like growth factor-1
PMS – Phelan-McDermid syndrome