Editor's Choice

Progress in the genetics of autism spectrum disorder

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PUBLICATION DATA
Accepted for publication 17th January 2018.
Published online 25th March 2018.

ABBREVIATIONS

ASD	Autism spectrum disorder
CNV	Copy number variant

A genetic basis for autism spectrum disorder (ASD) is now well established, and with the availability of high-throughput microarray and sequencing platforms, major advances have been made in our understanding of genetic risk factors. Rare, often de novo, copy number and single nucleotide variants are both implicated, with many ASD-implicated genes showing pleiotropy and variable penetrance. Additionally, common variants are also known to play a role in ASD's genetic etiology. These new insights into the architecture of ASD's genetic etiology offer opportunities for the identification of molecular targets for novel interventions, and provide new insight for families seeking genetic counselling.

Autism spectrum disorder (ASD) is a childhood onset, lifelong disorder that impacts socio-communicative development and is also characterized by rigidity and ritualistic/repetitive patterns of behaviour. It occurs with a population prevalence of around 1 per cent, with a male preponderance of 4 to 1.[1] In approximately 50 per cent of cases there is an association with intellectual disability, and comorbidity with neurodevelopmental and psychiatric disorders is frequent.[1] In some cases, ASD forms part of a syndrome, usually in association with known single gene disorders.[2] ASD can occur sporadically, but is often familial, with a sibling recurrence risk in the region of 10 to 20 times.[3] Recognizing these varied phenotypic manifestations, it is unsurprising that the underlying etiological architecture of ASD is also complex; it is widely accepted, however, that genetic factors play a crucial role, and that both common and rare forms of genetic variation confer susceptibility.

With the availability of affordable, high throughput microarray and whole genome sequencing platforms (Fig. 1), the spectrum of population based human genetic variation is now more fully understood. Individuals harbour in the region of 3 million genetic variants, 95 per cent of which are shared with 5 per cent or more of the population and are termed 'common variants', 4 per cent are shared with between 1 per cent and 4 per cent of the population, and 1 per cent of which are rare or unique to any one individual or their immediate family.[4] Some such variants are de novo (i.e. arise in the germline). This distinction between common and rare variation provides a useful categorization for understanding the genetic architecture of many complex genetic disorders, including ASD. Specifically, the liability to ASD is now known to involve both rare variants of moderate effect size, and common variants, individually of small effect size but cumulatively conferring susceptibility above a theoretical level of liability.[4] As discussed subsequently, much is known about the 'rare' end of the allelic spectrum of ASD's etiology, with both de novo and rare inherited variants and complex structural rearrangements identified in both sporadic and inherited forms of the disorder.[2] Additionally, common variation is now known to be etiologically important.[5]

RARE MUTATIONS IN ASD

Single gene disorders

The identification of rare de novo and inherited genetic variants that are predicted to be damaging, represents the most successful aspect of ASD gene discovery to date. Among some individuals, these risk variants form part of known genetic syndromes. Certain Mendelian genetic disorders are strongly associated with ASD, most notably Rett syndrome, among whom 40 per cent are diagnosed with ASD, and Fragile X syndrome which is associated with ASD (25%) as well as other social phenotypes (e.g. social anxiety in >40%). Many other single gene disorders are also associated with ASD, including neurofibromatosis, tuberous sclerosis, and Williams-Beuren syndrome. All of these disorders are also associated with intellectual disability, and many with other neuropsychiatric disorders. Although individually these disorders are rare, cumulatively they account for approximately 10 per cent of all cases of ASD.[2] Routine screening for Rett syndrome and Fragile X syndrome among individuals with ASD has been established practice for several years, but clinicians should be alert to the possibility of other single gene disorders that may occur sporadically.

Copy number variation

With the availability of microarray platforms offering higher resolution high-throughput genome scanning, duplication or deletion of segments of the genome have been described among individuals with ASD (Fig. 1). These range in size from cytogenetically visible rearrangements to regions of copy number variation (typically involving more than 1 kb) and smaller regions of insertion and deletion (indels, typically up to around 1 kb in length). Microarray studies largely converge on evidence for a greater burden for de novo mutations (both deletions and duplications) in families with ASD compared with controls, with the proportion of de novo copy number variants (CNVs) three to five-fold higher in cases.[6,7] Moreover, there is a higher mutational burden for large CNVs among cases of ASD compared to non-ASD controls, as well as CNVs that overlap (1) known intellectual disability and/or ASD genes, (2) pathogenic or otherwise clinically relevant genes, and (3) genes that are brain expressed and more specifically those that are structurally and/or functionally related to the postsynaptic density or chromatin remodelling/transcription regulation gene sets.[6–8] At least 5 per cent of individuals with ASD are carrying two or more penetrant mutations.[9]

Several rare recurrent, de novo exonic CNVs overlap genes that are promising candidates for ASD susceptibility, including *NRXN1*,[10] *PTCHD1*,[11] *NLGN1* genes,[12] *SHANK1*,[13] and *SHANK3*.[14] Certain loci are recurrently found to be duplicated or deleted in ASD, including 16p11.2 (around 0.8%),[15–17] 15q11-13 (around 0.5%),[18] and 22q11 (around 0.5%).[19] Mutations in these genes and loci are also observed in the general population (Table I, and see 'Knowledge translation' on next page). Other similar loci have been described, comprising small and large loci of CNV loss or gain. These loci are often pleiotropic and overlap genes listed in DECIPHER, a web-based platform for the sharing of plausibly pathogenic variants from well-phenotyped patients. They also show similar association with other neuropsychiatric disorders. Although rare in the population, variants overlapping these regions are sometimes transmitted from parents who are without apparent phenotypic consequence.[9] For example, exonic CNV deletions overlapping *NRXN1* at 2p16.3 have been described in 0.11 per cent of clinically ascertained samples, but are also seen in 0.02 per cent of population controls.[10]

What the paper adds

- A number of rare genetic variants are implicated in autism spectrum disorder (ASD), with some showing recurrence.
- Common genetic variants are also important and a number of loci are now being uncovered.
- Genetic testing for individuals with ASD offers the opportunity to identify relevant genetic etiology.

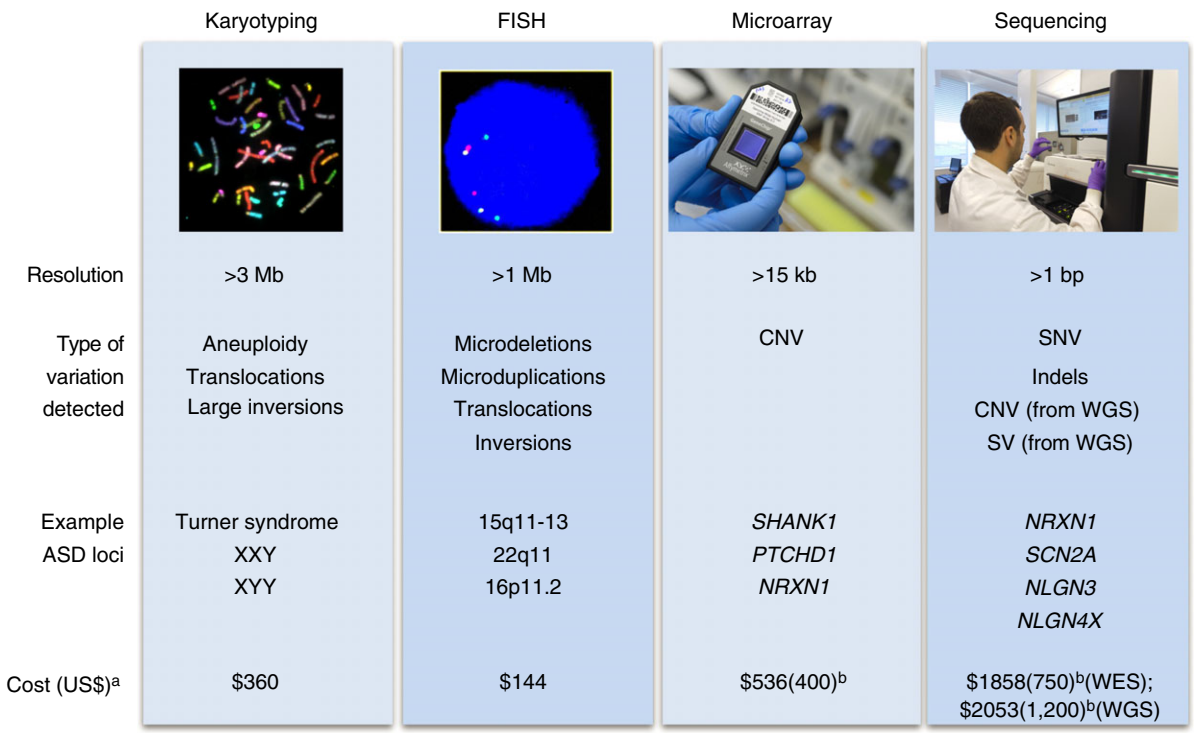

Figure 1: Genotyping platforms with details of their resolution, the types of variants detected, and example autism spectrum disorder (ASD) loci that have been identified. [a]Costs in US$ (2015) for clinical samples. [b]Costs in parenthesis for research microarray and whole exome sequencing (WES)/whole genome sequencing (WGS) samples. FISH, fluorescence in situ hybridization; Mb, megabase; kb, kilobase; bp, base pair; CNV, copy number variant; SNV, single nucleotide variation; SV, structural variation. [Colour figure can be viewed at wileyonlinelibrary.com].

Table I: Example prevalences of rare copy number variants in autism spectrum disorder (ASD) and population samples

Locus	Frequency in ASD[a] %	Frequency in population[b] %
15q13.3 deletion	0.002	0.002
15q13.3 duplication	0	<0.001
16p11.2 deletion	0.002	<0.001
16p11.2 duplication	0.002	<0.001
NRXN1 deletion	0.002	<0.001
SHANK3 deletion	0.002	Unknown

[a]Frequency based on MSSNG[9] for ASD probands (n=1739) and affected siblings (n=878). [b]Frequency based on UK Biobank samples (n=152 000).

It is therefore important to consider the penetrance of such mutations when attempting to counsel families on risk.[20] Additionally, smaller maternally inherited duplications enriched for *CHD8* gene targets show a bias in transmission to ASD probands. It is possible that this class of inherited CNV of reduced penetrance (and single nucleotide variation, see below) simply predisposes an individual to ASD, requiring additional factors (genetic or otherwise) to cause the clinical phenotype.[21]

Single nucleotide variation

Several large-scale sequencing projects have now been completed, including those that examine the entire coding region of the genome (whole exome sequencing)[22,23] and the entire genome (whole genome sequencing).[9,24,25] Among simplex families, the rates of rare de novo and inherited single nucleotide variations that are predicted damaging is higher in cases of ASD than in their unaffected siblings.[22,23] In contrast, the rate of synonymous mutations does not differ. Protein truncating single nucleotide variations that impact conserved genes and show preferential maternal transmission are enriched in ASD probands. Similar to the maternally transmitted CNVs discussed above, these may be low penetrance mutations that predispose to ASD, requiring a 'second hit' to cause the clinical phenotype.[21]

Strikingly, rates of exonic de novo mutations similar to these were also reported in a study of affected sib-pairs;[24] while in some cases an identical ASD-implicated mutation was shared between affected siblings, in others each sibling harboured unique ASD-implicated mutations. This evidence for genetic heterogeneity both between and within families, along with pleiotropy, speaks to the need for precision medicine, a personalized approach to genetics that is cognizant of the fact that assessment of an individual's complete genomic risk is required.

One important finding from sequencing based studies is the relationship between paternal age and rates of rare, de novo variants. Specifically, the majority of point mutations in ASD originate from the father, with the correlation between paternal age and number of de novo events reflecting a 1.3-fold increase in the number of de novo events for every 10 years of paternal age.[26] The evidence for a relationship between de novo mutations and maternal age is less consistent. A similar relationship is observed for de novo events in other neuropsychiatric disorders such as schizophrenia.[27]

COMMON MUTATIONS IN ASD

Among inherited forms of ASD, it is not unusual for first or second-degree relatives to share milder but related characteristics, termed the broader autism phenotype.[28] In some cases, larger extended pedigrees show the segregation of such traits, and other neuropsychiatric diagnoses, more widely.[29] A genetic underpinning for the tendency for ASD and related traits to run in families is supported by heritability estimates. The early twin studies were consistent with heritability in the region of 90 per cent, higher if lesser, subclinical degrees of socio-communicative and other impairments were included.[30] Although more recent studies have identified a larger role for shared environmental effects,[31] this is likely because of the overinclusion of concordant dizygotic twins along with different liability thresholds used in calculations. A heritability of 64 per cent to 91 per cent is supported if these potential confounds are taken into consideration.[32]

Intriguingly, autism traits are normally distributed in the general population, suggesting that clinical ASD may represent a threshold liability with underlying common polygenic variation conferring susceptibility.[33] This is supported by the strong correlation between the polygenic contribution to ASD traits in the general population and among individuals with ASD.[34] The fact that many families segregating ASD also seem to share risk for other neuropsychiatric disorders suggests that this genetic risk may be more correctly ascribed to fundamental brain-based traits (i.e. intermediate level phenotypes). There is a body of research examining these quantitative phenotypes; some have been shown to be heritable and associated with genome-wide linkage signals in families.[35–38] In general terms, however, this has not led to gene discovery in ASD.

Until very recently, the search for common variants using genome-wide association methods was largely unsuccessful. Several studies identified signals not reaching a genome-wide level of significance.[39–41] Similarly, a recent genome-wide association analysis of a discovery sample of 7387 cases of ASD failed to find individual variants that reached the genome-wide threshold; however, a meta-analysis with an independent sample (n=7783 cases of ASD) identified a genome-wide significant signal at 10q24.32 (rs1409313, odds ratio=1.12, p=1.058e-08).[42] Although this marker is intronic, it is in linkage disequilibrium with a number of other markers that span a gene-rich region. The most recent genome-wide association study comprising 18 381 cases of ASD and 27 969 controls, identified five genome-wide significant signals, with a further seven loci shared with other traits also reaching a similar level of significance. Furthermore, evidence of heterogeneity of association across phenotypic subgroups was observed; for example, the higher functioning subgroup showed an

excess of alleles that overlapped with educational attainment.[43]

Notwithstanding the negative findings, these and other genome-wide association studies estimate the contribution of common variants to ASD's heritability to be significant. For example, the recent meta-analysis described above estimated single nucleotide polymorphism-based heritability to be in the region of 32.6 per cent. Similarly, the Swedish Population-based Autism Genetics and Environment Study estimates heritability caused by common variants to be in the region of 49.4 per cent, with genetic liability spread evenly across chromosomes consistent with polygenic inheritance.[5] The contribution of common variation seems to be the same whether or not there is a background of de novo mutations.[44] However, single nucleotide polymorphism heritability is higher among those cases without intellectual disability, supporting the observation that de novo and sporadic variants are more frequently observed among cases of ASD with intellectual disability.[43]

KNOWLEDGE TRANSLATION

Interpreting results of genetic testing

One major challenge after genetic testing is the interpretation of results, and specifically, evidence of likely pathogenicity of identified variants. The American College of Medical Genetics and Genomics and the Association for Molecular Pathology have issued joint guidelines for the classification of variants that uses terms 'benign' and 'pathogenic' and the strength of the evidence in favour of each.[45] The framework utilizes information from the population frequency of variants, as well as computational in silico prediction and the results of functional studies that consider the impact of mutation on brain structure and function in vitro. In clinical terms, knowing the penetrance (i.e. the probability of a specified phenotype) of a particular mutation is important. The calculation of penetrance requires phenotyped population samples, which is often a problem considering the pleiotropy or variable expressivity associated with particular variants; subthreshold traits are likely to escape even the most detailed phenotyping. Penetrance can also be calculated by tracking inherited variants across family members,[46] which is a particularly useful strategy for rare variants.

In general terms, although several genes are now identified as ASD genes, including *NRXN1*, *SHANK1*, *SHANK3*, and *PTCHD1*, the penetrance of the underlying mutations is not well described. By way of example, deletions in *NRXN1* are relatively common in clinically identified individuals with ASD (0.45%) and intellectual disability (0.12%), as well as in other neurodevelopmental phenotypes. In contrast, the frequency in population based surveys is much less (around 0.02%). Consequently, an estimate for penetrance of *NRXN1* mutations for all neurodevelopmental phenotypes is 33 per cent. However, judging penetrance of conflated *NRXN1* mutations does run the risk of overstating (or understating) penetrance for individual variants.[20] This may be problematic for genetic counsellors who are required to make judgements about the risk of disease for an individual. Indeed, regarding *NRXN1*, among most clinical cases variants seem to cluster around exons 1 to 4 at the 5′ end of the gene, with deletions that impact the subsequent exons showing evidence of lower penetrance.[47]

Individuals with an identical mutation may still demonstrate a large degree of phenotypic variability. By way of example, the 16p11.2 locus is associated with a range of neurodevelopmental disorders and other clinical phenotypes, including intellectual disability. Haploinsufficiency at this locus shifts IQ downwards, but residual correlation with biparental IQ and ASD traits also suggest that background familial factors contribute to trait variability.[48] It is to be expected that a similar mechanism will explain phenotypic variation for other mutations. What is not entirely clear at present, however, is whether specific ASD symptoms are associated with particular genetic mutations. One recent analysis found that children with ASD who have de novo mutations had a relative strength in language but more pronounced motor deficits.[49] Similarly, among cases diagnosed with ASD, CNVs in 'ASD/intellectual disability genes' are specifically associated with communication subphenotypes.[50] Much remains to be learned about these phenotype-genotype relationships.

Providing genetic counselling for families

Genetic counsellors may be asked to advise on the recurrence risk of ASD among families who have one or more offspring already diagnosed with ASD. In families generally, the risk of having a child with ASD is related to the population prevalence, currently in the region of 1 per cent.[1] Among those children deemed 'high-risk' by way of an older sibling being diagnosed with ASD, 18.7 per cent are subsequently diagnosed with ASD. Moreover, with two older siblings with ASD, this figure goes up to 32.2 per cent.[51]

The situation is slightly different among those families where the first child already has been identified as harbouring a variant overlapping an ASD gene. For recurrent CNVs, for example, gene-specific and/or locus-specific penetrance calculations have been generated and may be useful in providing genetic counselling to families, particularly as they provide information about penetrance for ASD and other neurodevelopmental disorders.[52] Many variants, however, are categorized as 'variants of unknown significance'. In such situations, the variant cannot be used for clinical decision-making; instead, attempts to resolve variant classification are needed, and the family should be monitored. A more difficult and sensitive situation arises when genetic testing is being used for prenatal decision-making. In such situations, the weight given to variant classification should be aligned with the strength of the evidence, and in all likelihood other factors (including additional medical investigations and family circumstances) will play a bigger role in the decision-making process.

Assessment of an individual with ASD should include a thorough physical examination to document growth as well as body morphology. This may give light on the possible underlying genetic etiology. It is important to determine whether the individual has 'complex' or 'essential' ASD.[53] The term 'complex' describes the existence of dysmorphology, abnormal growth, congenital anomalies, and neurological complications. In contrast, such features are typically absent among those described as 'essential'. Categorizing in this way facilitates the decision-making process in a clinical setting (Fig. 2). For example, among individuals with head circumference greater than three standard deviations from the mean the possibility of *PTEN* mutations should be considered, and developmental regression in a female patient should alert to the possibility of a *MeCP2* mutation. For children with positive genetic test results, genetic counselling offers the opportunity to plan treatment and/or prophylactic measures for any medical conditions known to be associated with the particular gene. This may include close monitoring to prevent the onset of obesity in those with 16p11.2 mutations, mental health monitoring and intervention in those with 22q11 deletions and cardiovascular surveillance for those with 1q21.1 microdeletion syndrome.[1]

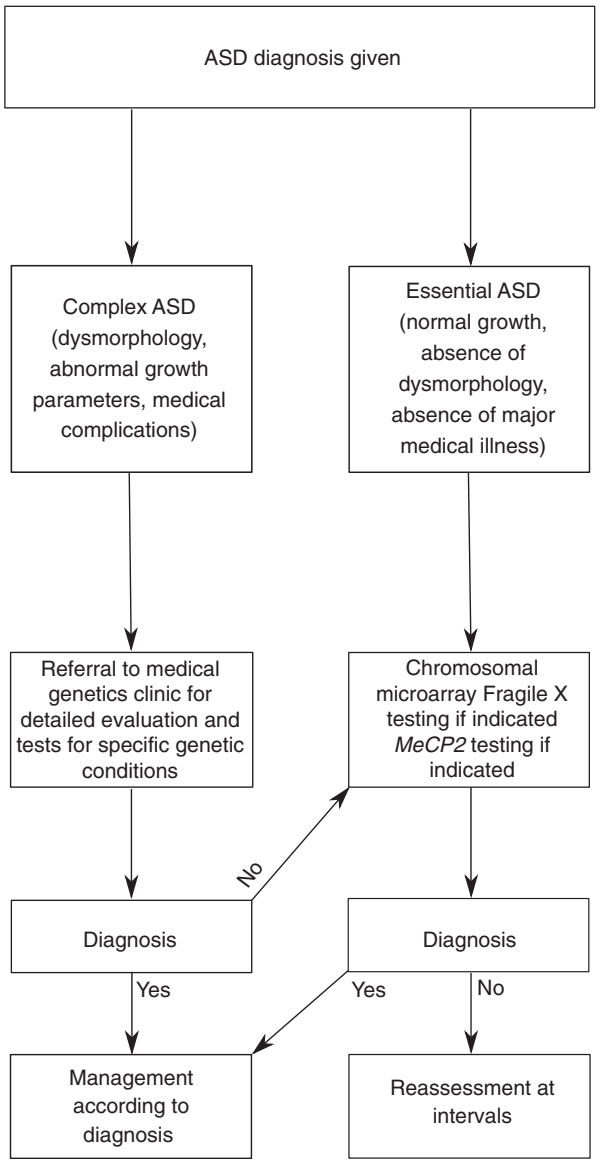

Figure 2: Flow diagram of approach to genetics investigation and evaluation for individuals with autism spectrum disorder (ASD). See main text for definition of terms 'complex' ASD and 'essential' ASD.

Diagnostic yield of genetic testing

Children with developmental vulnerabilities are increasingly likely to have genetic testing. Among those who have ASD in association with dysmorphology and additional health problems, testing for Rett syndrome, Fragile X syndrome, or one of the other single gene disorders is established practice. In recent years clinical microarray has become feasible, and is increasingly used for children diagnosed with ASD. Indeed, a published consensus statement mandates the use of clinical microarray as a first-tier diagnostic test in individuals with intellectual disability and/or ASD.[54] The diagnostic yield of such testing is higher than G-banded karyotyping in clinical cohorts. For example, in one study of 848 children with ASD evaluated by clinical microarray, 59 (7%) had results considered abnormal or possibly significant. Importantly, 83 per cent of the abnormalities detected were below the size routinely detected by karyotyping.[55] The yield of clinical microarray has also been compared with exome sequencing.[56] The yield from both were comparable (around 8%), with both showing much higher yield with complex ASD (21.9% vs 16.7% for clinical microarray and exome sequencing respectively), defined according to the presence of dysmorphology as described in Miles et al.[57]

Development of molecular compounds

The identification of ASD genes, and elaboration of their protein pathways, offers the opportunity for the development of new molecular compounds that target these protein networks. Recognizing the large number of genes identified so far, and with estimates that up to 1000 genes may be involved,[58] it is hoped that these converge on a relatively small number of functional protein networks that may be amenable to treatment, although an 'omnigenic' model has also been proposed.[59] A number of clinical trials are currently underway, principally focussing on single gene disorder causes of ASD, such as Rett syndrome (insulin-like growth factor 1 [IGF-1]), Fragile X syndrome (metabotropic glutamate receptor 5 [mGluR5] antagonists), and tuberous sclerosis (mechanistic target of rapamycin [mTOR] inhibitors).[60] The confidence that these, and other, molecular compounds may impact on symptoms rests on the evidence for early plasticity of the brain. Indeed, it has been shown, for example, that phenotypes resulting from *SHANK3* knockout can be reversed in a mouse model in adult animals,[61] supporting potential

therapeutic benefit during the period of plasticity and beyond. Similarly, inhibition of mTOR, a protein kinase, has reversed the brain changes associated with tuberous sclerosis in animal models,[62] and a reduction of mGLuR5 signalling has resulted in symptomatic improvement in knockout mice.[63] The convergence of ASD-implicated genetic variants identified so far on specific cellular processes, most notably several proteins involved in synaptic structure and function, offers the opportunity to target drug development by focussing on one or more distal target of the highly interconnected pathways involved.[64]

CONCLUSION

In summary, major advances have been made in recent years in our understanding of the genetic architecture of ASD, with strong evidence that both rare and common variants contribute to risk, and with recent microarray and whole genome sequencing platforms providing evidence to support a number of genes and loci as ASD-implicated. Despite this, much remains unknown; because of the infrequent nature of individual variants, their penetrance for ASD and related phenotypes is not well elaborated, and functional studies are only now beginning to contribute to the evidence in favour of, or against, pathogenicity. Several large-scale projects have now been initiated to help more fully realize the underlying complexity of ASD's genetic architecture.

ACKNOWLEDGEMENTS

We thank The Centre for Applied Genomics (TCAG), which is funded by Genome Canada and the Ontario Genomics Institute, Canada Foundation for Innovation (CFI), and the Ontario Research Fund of the Government of Ontario. We thank the McLaughlin Centre, University of Toronto. SWS holds the GlaxoSmithKline-CIHR Chair in Genome Sciences at the University of Toronto and The Hospital for Sick Children. SWS has been on the Scientific Advisory Board of Population Bio and Deep Genomics during the writing of this manuscript. The role included an honorarium and while it may be related to the work, it did not influence it. MWS has no interest that might be perceived as posing a conflict of bias.

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RESUMEN

PROGRESO EN LA GENÉTICA DEL TRASTORNO DEL ESPECTRO AUTISTA Actualmente se ha establecido una base genética para el trastorno del espectro autista (TEA) y, con la disponibilidad de plataformas de secuenciación y microarrays de alto rendimiento, se han logrado avances importantes en nuestra comprensión de los factores de riesgo genéticos. Raras, a menudo de novo, número de copias y variantes de nucleótido único están implicadas, con muchos genes implicados en TEA que muestran pleiotropía y penetrancia variable. Además, también se sabe que las variantes comunes desempeñan un papel en la etiología genética de TEA pero aún no se han identificado. Estos nuevos conocimientos sobre la arquitectura de la etiología genética de TEA ofrecen oportunidades para la identificación de objetivos moleculares para intervenciones novedosas, y proporcionan una nueva perspectiva para las familias que buscan asesoramiento genético.

RESUMO

PROGRESSO NA GENÉTICA DO TRANSTORNO DO ESPECTRO AUTISTA Uma base genética para o transtorno do espectro autista (TEA) agora está bem estabelecida, e com a disponibilidade de plataformas de microarray de larga escala e de sequenciamento, grandes avanços têm sido feitos para a compreensão dos fatores de risco genéticos. Variantes raras, frequentemente de novo, tanto de cópia extra quanto de nucleotídeos simples têm sido implicadas, com muitos genes relacionados ao TEA mostrando pleiotropia e penetrância variável. Adicionalmente, sabe-se que variantes comuns também desempenham um papel na etiologia genetica do TEA, mas ainda precisam ser identificadas. Estas novas descobertas sobre a arquitetura da etiologia genética do TEA oferecem oportunidades para a identificação de alvos moleculares para novas intervenções, e fornecem novas possibilidades para famílias procurando aconselhamento genético.