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Discussion

Communicating complex genomic information: A counselling approach derived from research experience with Autism Spectrum Disorder

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ABSTRACT

Individuals with Autism Spectrum Disorder (ASD) share characteristics (impairments in socialization and communication, and repetitive interests and behaviour), but differ in their developmental course, pattern of symptoms, and cognitive and language abilities. The development of standardized phenotyping has revealed ASD to clinically be vastly heterogeneous, ranging from milder presentations to more severe forms associated with profound intellectual disability. Some 100 genes have now been implicated in the etiology of ASD, and advances in genome-wide testing continue to yield new data at an unprecedented rate. As the translation of this data is incorporated into clinical care, genetic professionals/counsellors, as well as other health care providers, will benefit from guidelines and tools to effectively communicate such genomic information. Here, we present a model to facilitate communication regarding the complexities of ASD, where clinical and genetic heterogeneity, as well as overlapping neurological conditions are inherent. We outline an approach for counselling families about their genomic results grounded in our direct experience from counselling families participating in an ASD research study, and supported by rationale from the literature.

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in communication, reciprocal social interaction, and a tendency to engage in restricted and repetitive behaviours. An increase in the prevalence of ASD has been documented over the last few decades, with the most recent study in the United States reporting an incidence of 1 in 68 children [1]. ASD demonstrates heterogeneity with regard to (i) sex, with a 4:1 ratio of males over females [2], (ii) clinical expression, both between and within families (even identical twins), and (iii) genetic etiology, evident in the identification of hundreds of different genes contributing to ASD [3–5].

The inheritance of ASD is described to follow a multifactorial model in which both genetic and environmental factors, possibly acting in combination, have a role [6,7]. Data support a strong genetic basis for ASD, with estimates of heritability between ~50-90% [7–9]. Hundreds of genes have been implicated in the etiology of ASD [5,8,10–15]. Until recently, 10–15% of individuals with ASD have been found to have an identifiable genetic cause [4,16]. This includes individuals who have a single gene disorder (e.g. Fragile X syndrome, Rett syndrome) [17–20] and individuals with chromosome microdeletions/microduplications (e.g. 16p11.2 microdeletion) [11,21,22]. No single genetic cause accounts for more than 1% of ASD [4,23–26], and most individuals with an identifiable genetic cause have a syndromic form of ASD, which is associated with other physical and/or systemic features [16,27,28]. The majority of individuals who are diagnosed with ASD have non-syndromic/

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idiopathic ASD, the cause of which has been more difficult to elucidate [15,24].

Advances in next generation sequencing (NGS) technology, including whole exome and whole genome sequencing, have enabled us to identify an increasing number of genes that contribute to the etiology of idiopathic ASD [23,24,29–33]. In some instances a single (strong) genetic change (variant) is sufficient to cause ASD, however, in the majority of cases evidence suggests that ASD results from a combination of genetic variants including those of weaker effects, as well as other contributors, which we collectively refer to as environmental factors (i.e. anything non-genetic). The complexity of the genetic etiology of ASD is further confounded by the recent finding that within some families, siblings with ASD have different contributing genetic variants [23,29]. Moreover, many of the genetic variants associated with ASD have also been identified in individuals with other neurodevelopmental disorders, including intellectual disability (ID), obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD) and some psychiatric disorders (e.g. schizophrenia, bipolar disorder, depression), complicating our interpretation of the impact of these genetic variants on neurodevelopmental outcomes [10,34,35]. Additionally, comorbidity is common in ASD, in that individuals with ASD have other neurodevelopmental diagnoses (e.g. ID, OCD, ADHD) [3,36]. While furthering our knowledge regarding the genetic causes of ASD, genome sequencing data has also highlighted the need to further understand the many additional complex factors contributing to the genetic architecture of ASD [6,30,37–41].

The need to equip healthcare professionals with the knowledge and tools to effectively communicate complex genomic information is crucial and has been recognized [42–44]. As the use of NGS technology for the investigation of ASD moves from research into clinical care there will be increased demand to communicate genomic results to families and facilitate understanding of the significance of these results [45,46]. This task will fall to genetic professionals/counsellors and other health care providers in turn [47–49]. Guidelines and best practice reports on how to effectively communicate this information are limited. Existing literature centers on the consenting process for NGS and provides recommendations for topics to cover in the pre-test discussion [50]. Little is written about the post-test counselling approach, specifically regarding the challenges of how to present genomic results, how to explain their meaning, how to counsel about implications for patients and their families, and how to discuss the remaining uncertainty. Although the challenges have been recognized, no practical paradigms exist in the pediatric setting for communicating genomic data, especially for complex disorders like ASD.

Here, we present a model to facilitate communication regarding the complexities of ASD, where clinical and genetic heterogeneity, as well as overlapping neurological conditions are inherent. We outline an approach for counselling families about genomic results grounded in our experience from counselling families participating in an ASD research study with rationale from the literature. The resources and tools developed by our group, shared below, are tailored for ASD but can be adapted and applied to other neurodevelopmental conditions.

2. Conceptual model for the complexity of ASD

2.1. Complexity of ASD

ASD is a good paradigm to showcase the complexity of neurodevelopmental conditions. Not only do individuals with ASD present with a broad clinical spectrum, the genetic factors involved in ASD are varied and complex, with some variants being inherited and others occurring for the first time in the child with ASD (*de novo*). Non-syndromic forms of ASD are considered to have multifactorial inheritance, where genetic risk factors and environmental risk factors both may play a role. It is the additive effect of these factors which, upon reaching a critical threshold, lead to ASD [51].

2.2. Existing multifactorial-threshold models

The concept of multifactorial inheritance and threshold models is not unique to ASD or neurodevelopmental disorders. It applies to many complex conditions, including diabetes, cardiovascular disorders, and mental illness. A few conceptual models have been developed to help describe this complex inheritance pattern, including a jar model for mental illness [52] and balance scale model for common adult conditions like diabetes [53]. Both models depict the role of genetic and environmental factors in the contribution to risk, but have different emphasis. In the balance scale model, environmental/lifestyle factors contribute more strongly to risk and the idea that risk is not static is illustrated. Individuals have some control over their health and can make behavioural changes that impact their disease risk (i.e. exercising and dietary modifications can decrease risk, while smoking can increase risk) (Fig. 1). In the jar model (Fig. 2), the concept of

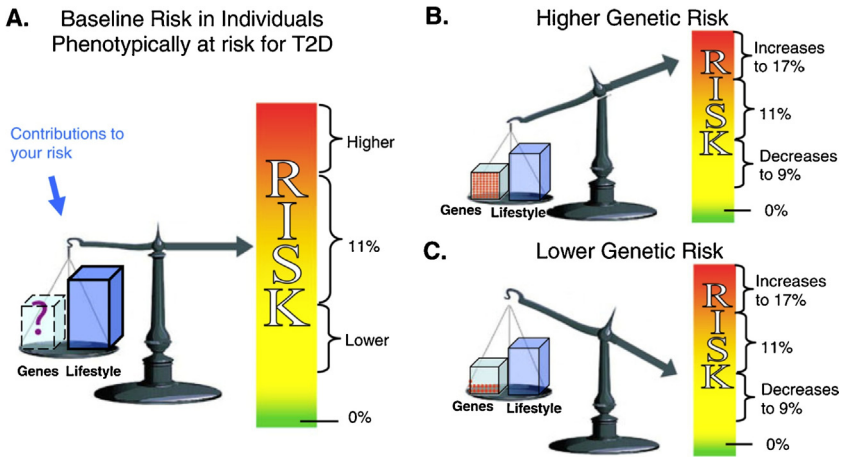


Fig. 1. Balance scale model for diabetes: [A] baseline risk for developing type 2 diabetes (T2D) [B] adjusted risk of 17% for those with a higher genetic risk [C] adjusted risk of 9% for those with a lower genetic risk [53].

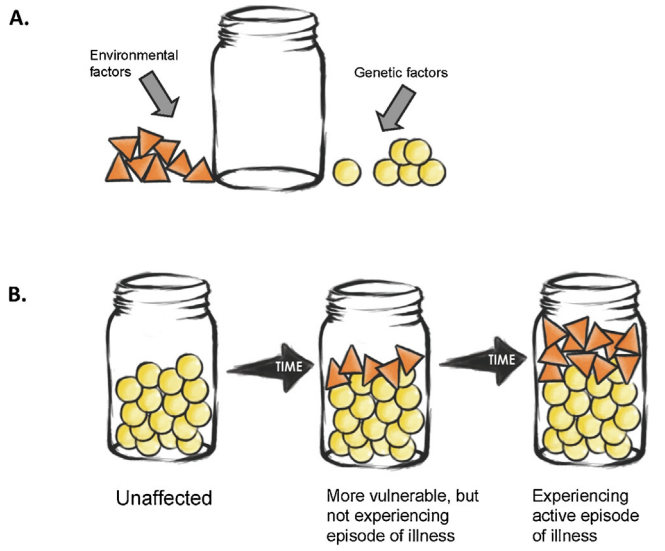


Fig. 2. Jar model for mental illness [A] The "mental illness jar" filled by two kinds of vulnerability factors [B] Only when the jar is full to the top does an individual experience an active episode of illness [52].

genetic predisposition and time are represented. All individuals are vulnerable to mental illness with susceptibility ranging from low to high depending upon one's genetic risk factors. Additional environmental factors (e.g. stress, trauma) contribute to this risk. When a threshold is reached (i.e. the jar is filled), an individual will experience an episode of mental illness. If environmental risk factors are removed, such that the jar is no longer full, the individual may go into remission, highlighting the cyclic nature of mental illness.

2.3. Cup model: a novel tool to portray the complex etiology of ASD

We have developed a new conceptual tool, which we call the "cup model" to visually portray the complex etiology of ASD. Adapted from the jar model, the cup model emphasizes the different impact of genetic variants. Some genetic variants are highly penetrant, meaning they confer a very high risk of developing ASD. Examples include variants in certain genes that are involved in brain development/function (e.g. *PTCHD1, NRXN1, SHANK2, CHD8, ARID1B, SCN2A, ADNP*) [4,11,15,29,54–61]. Other variants confer a risk for ASD, but may not be sufficient to cause ASD on their own. Environmental risk factors also have varying degrees of influence (possibly affecting the same genetic pathways), but are generally thought to be less significant than genetic factors [7]. Although neither genetic nor environmental risk factors are easily quantifiable, they can be categorized based on our current understanding. To illustrate the relative strength of these multiple risk factors, we use a cup analogy with different size balls (Fig. 3). Similar to the jar model, an individual will develop ASD if the cup is filled with enough risk factors to reach a critical threshold.

Unlike the jar model, time is not emphasized in the cup model. We know that genetic and environmental risk factors can impact neurodevelopment prenatally, perinatally and/or postnatally [7]. Additionally, once the threshold has been reached, an individual with ASD is not likely to lose their diagnosis. ASD is considered to be a lifelong condition with no definitive 'cure', although evidence-based interventions and therapies (e.g. IBI, ABA) have

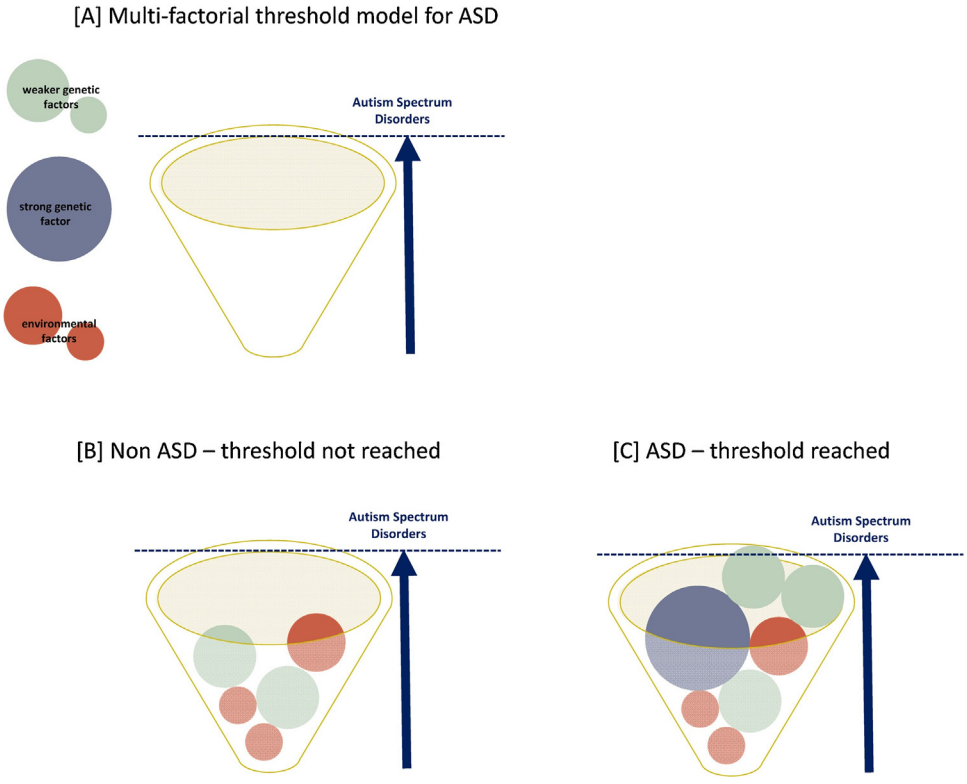


Fig. 3. Cup model for ASD [A] Each individual has an ASD risk cup with balls representing risk factors that contribute to ASD with variable degrees of impact [B] Risk cup not reaching ASD threshold – some risk factors but not enough to develop ASD [C] Risk cup reaching ASD threshold – enough risk factors to develop ASD.

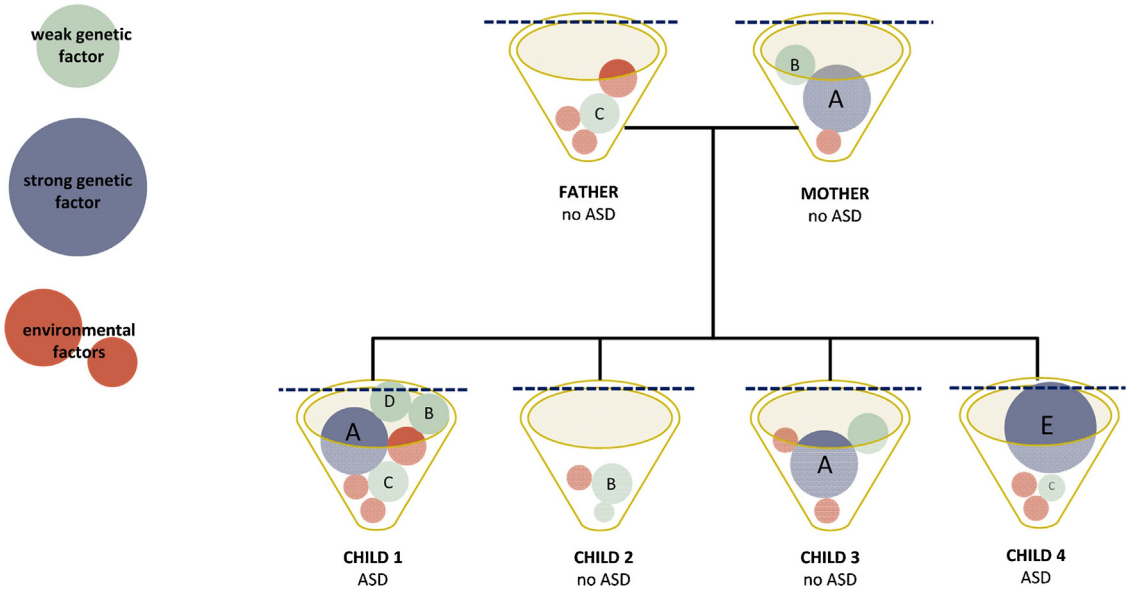


Fig. 4. Cup model illustrating reduced penetrance and genetic heterogeneity in a family with ASD. In child 1, the ASD threshold is reached as a result of a combination of genetic variants (strong and weak, both inherited and *de novo*) and environmental risk factors. In child 4, a strong *de novo* genetic variant (labeled E) is the primary contributing factor to reaching the ASD threshold.

demonstrated positive outcomes across multiple domains [62]. Even if environmental risk factors can be removed, impact during the critical window of development may have already occurred [7].

This cup model can also be used to help explain why a genetic variant thought to contribute to an individual's ASD diagnosis can also be found in family members without ASD (reduced penetrance). In Fig. 4, a genetic variant that contributes a strong risk of developing ASD (labeled A) is inherited from a parent without ASD. Child 1 with ASD has inherited this strong genetic factor (labeled A), in addition to inherited weak factors (labeled B and C), *de novo* (labeled D) genetic factor and environmental risk factors, which together push the risk above the threshold. In contrast, Child 3 who also inherited the strong genetic factor (labeled A), does not have enough additional risk factors to push the risk above the threshold. The cup model can also illustrate genetic heterogeneity in ASD, where two siblings are identified to have different genetic factors contributing to their diagnosis of ASD (i.e. Child 1 and Child 4). Each cup has a unique combination of risk factors in the same way each individual with ASD has a unique presentation of ASD.

In some families with shared ancestry (e.g. first cousin marriage), the same genetic variant may be found to be inherited from both the mother and the father (i.e. child inherits two copies of variant A, one from each parent). Emerging data are suggestive of recessive risk factors in ASD, particularly among consanguineous families [40,63–65].

Families often report no family history of ASD and consequently have a hard time understanding the contribution of specific genetic factors. This model helps families visualize the complexity of the threshold model and how it applies to their unique situation.

The cup model can also be used to demonstrate sex difference effects in ASD with females having a higher threshold (i.e. larger cup) than males (Fig. 5).

2.4. Extending the cup model to overlapping neurological phenotypes

As described above, the complexity of neurodevelopmental disorders is further evident in the discovery of shared genetic etiology across related diagnoses. Variants in the same genes have been implicated in not only ASD, but other neurodevelopmental disorders [34]. For instance, variants in the Astrotactin 2 (*ASTN2*) gene have been identified in individuals with ASD, OCD and ADHD [66]. As well, microdeletions at chromosome location 3q29 have been associated with an increased risk for ASD, as well as psychiatric disorders including bipolar disorder and schizophrenia [67]. The cup model can be used to illustrate the shared genetic basis, where one genetic

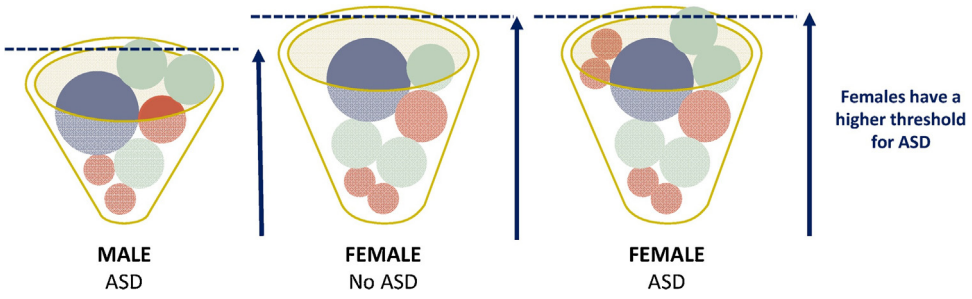


Fig. 5. The 4:1 male-to-female ratio in ASD suggests that penetrance is lower in females than in males. In the cup model this is illustrated by using a larger cup for females as they require more risk factors than males to reach the ASD threshold.

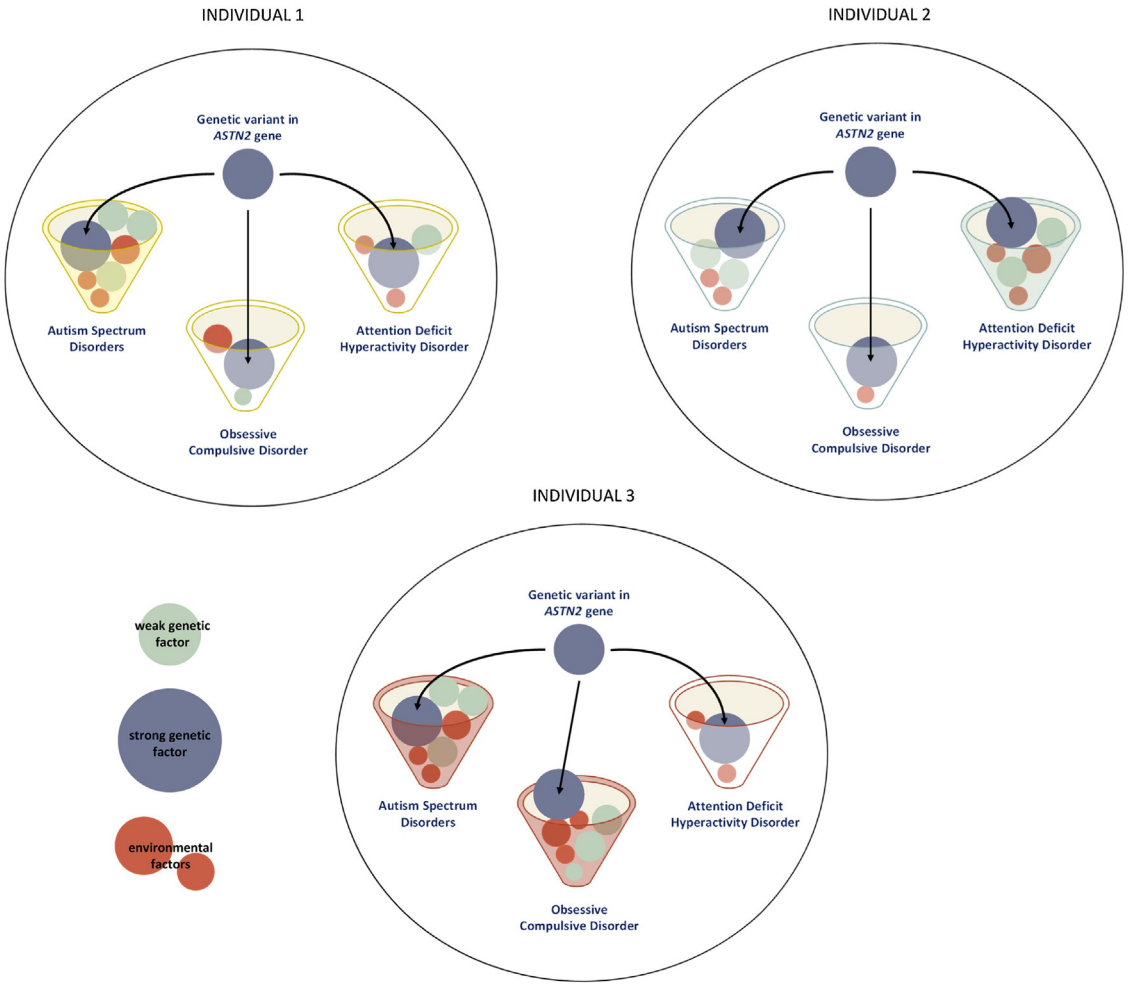


Fig. 6. Overlapping neurological phenotypes – for individual 1, the *ASTN2* variant contributes to reaching threshold in the ASD risk cup; for individual 2, the *ASTN2* variant overflows the ADHD risk cup; for individual 3 the *ASTN2* variant contributes to threshold for both ASD and OCD.

variant predisposes to several different neurodevelopmental disorders and the phenotype that manifests in a given individual depends upon the interaction with other risk factors (Fig. 6). Conceptually, each cup model is treated independently, however, it is unclear whether these conditions are truly independent (individual cups) or interact in some as yet undefined way, which may help to explain comorbidity in ASD.

3. Considerations for counselling

3.1. Genetic etiology

The rapid advancement in genome sequencing technology has enabled the identification of an increasing number of genetic factors associated with ASD and other neurodevelopmental disorders [23,24,29–33]. However, the identification of new variants is outpacing our ability to interpret their significance. Every individual in the population carries genetic variants, the majority of which do not impact health or development (benign); other variants disrupt the typical pattern of growth and development (pathogenic) and for some variants there is not enough information at present to determine their significance (variants of uncertain significance) [68,69]. In some of these cases, additional population control data, family data, or functional data may provide clarity. When interpreting the significance of variants identified in an individual with ASD, several factors should be taken into consideration including: 1) whether the variant represents a benign variation, unrelated to ASD risk 2) If pathogenic, is the variant a weak, moderate, or strong contributing risk factor 3) Is the variant known to be associated with ASD alone or reported in different neurodevelopmental disorders, which may be present in other family members. Existing databases cataloging genetic variants are critical in this evaluative process [70–72].

Researchers are starting to compile lists of ASD risk genes (e.g. Simons Foundation Autism Research Initiative, Autism Genome Project Consortium) [73], and pool variants identified through multiple sources into ASD focused databases (e.g. MSSNG project) [23] to make this information more broadly available to researchers and clinicians. It is worth noting that our understanding of the relevance of genetic variants continues to evolve as new information becomes available. Efforts are underway to develop scoring systems based on published evidence to help define the significance of ASD gene variants to facilitate interpretive consistency [74,75].

3.2. Phenotypic heterogeneity

The discovery that many of the same genomic variants (i.e. chromosome microdeletion/microduplication and single gene

Table 1
Approach for counselling about genomic results.

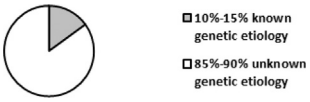
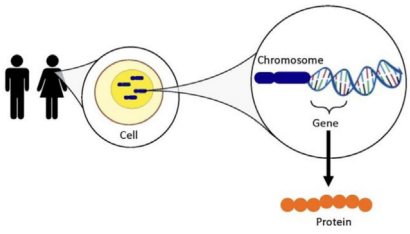
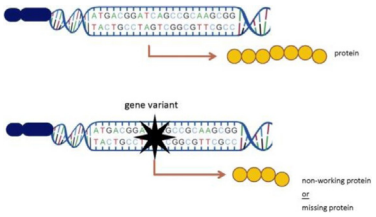
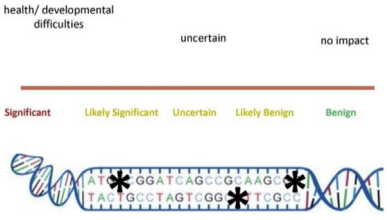
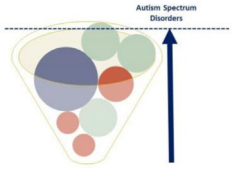
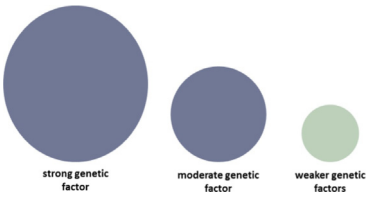
Discussion Topics	Counselling Tools	Rationale
Purpose of Genetic Testing • Review purpose of genetic testing • Explore family's expectations and hope • Discuss likelihood of identifying a genetic etiology • Discuss likelihood that results will impact medical management in ASD or impact recurrence risk		• Families may have unrealistic expectations regarding implications of genetic test results [91,99] • Important to align expectations as this influences how individuals process information [100]
General Genetic Concepts • Review cells, chromosomes, genes, proteins, variants	 	• A large portion of the general population has limited genetic literacy [94] • Understanding of some basic genetic concepts is critical for more specific discussions regarding the role of genetics in ASD
• Refer to our counselling aids found at http://www.tcag.ca/documents/projects/ • Additional counselling aids can be purchased (e.g. Greenwood Genetic Counselling Aids) and animations are available online for guidance (http://learn.genetics.utah.edu/, *www.yourgenome.org*)	http://www.tcag.ca/documents/projects/ Visual aids can be effective in explaining genetic concepts [96]	• Visual aids can be effective in explaining genetic concepts [96]
Genomic Variants • Note that we all have genetic variants		• Understanding the different types of genetic variants is key to understanding genetic contributions to ASD • It is important to recognize the distinction between certainty (bengin and pathogenic variants) and uncertainty (variants uncertain significance)
• Discuss the different categories of variants	http://www.tcag.ca/documents/projects/	
Etiology of ASD • Explore family's understanding of what causes ASD • Review multifactorial inheritance • Explain genetic heterogeneity even within members of the same family	 Cup Model	• Clarify any misconceptions regarding causes of ASD, particularly those that may contribute to feelings of guilt and blame [101–103]
• Discuss overlap of genes/variants across related conditions	http://www.tcag.ca/documents/projects/	
Genetic Tests • Explain the genomic test(s) that was utilized to investigate the genetic etiology of ASD in your patient • Use available tools to facilitate this discussion	• Ambry Genetics: What is Exome Sequencing [104] • SickKids Hospital: Exome Sequencing Animation [105]	• Understanding the scope of a test provides a foundation for discussing the results of the test

Table 1 (*Continued*)

Discussion Topics	Counselling Tools	Rationale
• Discuss the advantages and limitations of the test(s)		
Genetic Result & Significance • Discuss variant(s) identified and available information regarding contribution to ASD • Include discussion regarding any uncertainty – be cognisant that association is not causation • Summarize the impact of risk variant referring back to the cup model		• This is an important step in understanding risk information and will facilitate the discussion around recurrence risk
• Discuss what additional investigations are recommended (e.g. parental testing, functional study)	http://www.tcag.ca/documents/projects/	
Psychosocial Impact • Explore family's perception of the results and response • Refer to genetic counsellor if further support is needed • Offer genetic testing for other family members if indicated	Questions to explore: 1) What does the result mean for you and your family? 2) Does it change your understanding of what causes ASD? 3) Is having this information helpful? 4) Does it impact your decision to have other children? 5) Are there services from which you or your family would benefit?	• Given the multitude of psychosocial factors experienced by families who have a child with ASD, it is important to explore parent perceptions and responses to facilitate appropriate supports [43,103]

variants) have been identified in individuals with different neurodevelopmental and psychiatric diagnoses suggests that these diagnoses should not be viewed as causally distinct. Evidence suggests although these disorders continue to be differentiated on a clinical basis they are not dichotomous, all-or-none disorders and should be viewed as a continuum [34,76–78]. Therefore, recurrence risk estimates need to address not only the risk for ASD, but the possibility of the occurrence of other disorders along the continuum. Researchers are conducting more in-depth phenotyping of individuals with variants in ASD risk genes to capture the broader range of neurodevelopmental presentations associated with specific genes [79–81]. This data will help to elucidate the overlapping spectrum of neurodevelopmental disorders and inform more comprehensive recurrence risk estimates.

3.3. Recurrence risk

Historically, the goal of genetic testing in ASD has been to determine the underlying genetic etiology in order to inform counselling about the likelihood of recurrence for future pregnancies [82–85]. This is more readily accomplished for syndromic forms of ASD, which are attributed to a specific genetic etiology for which a mode of transmission is well defined. For instance, in a situation where ASD is a feature of an underlying syndrome with autosomal dominant inheritance, the recurrence risk may be as high as 50%. More information regarding known syndromes associated with ASD, their genetic etiologies and recurrence risks can be obtained from previous reviews [4,8,16,28].

In the case of idiopathic ASD, where there is typically a more complex interplay between genetic and environmental factors, recurrence risk is more difficult to define. For "strong" genetic factors associated with a high risk of developing ASD, the chance of passing on the gene may be easy to quantify, but the specific risk for ASD is more elusive as other genetic and environmental factors may be involved (i.e. threshold model). An additional challenge lies in predicting the clinical presentation given the phenotypic heterogeneity described above. In this situation, recurrence risk counselling would be guided by available information in the literature regarding phenotypic expression associated with the specific genetic factor. For "moderate" and "weak" genetic factors, where their contribution to ASD and other neurodevelopmental disorders is less clear, we rely upon empirical recurrence risk data. For ASD, available information from sibling studies estimates that the recurrence risk to have a second child with ASD is between 10 and 20% [86–88]. This risk has been shown to be influenced by sex with one study showing a three-fold increase in risk of ASD outcome in males relative to female siblings [87].

4. Approach to communicating genomic information

Data from the literature suggests that families value genetic testing and genetic counselling in spite of the uncertainty regarding risk estimates [89–92]. The task of explaining genomic results, in the context of a multifactorial threshold model confounded by overlapping neurodevelopmental conditions poses a daunting challenge. In Table 1, we outline our approach to communicating genomic information grounded from our experience in counselling families about microarray and genomic sequencing results through an ASD research study. The table summarizes information we consider important to discuss and provides references to counselling tools to facilitate the discussion. A qualitative study exploring participants' experiences and perceptions regarding this approach is currently underway.

It is difficult to develop a framework for clinicians to follow to effectively communicate genomic results back to families. It is well recognized that many factors contribute to how patients/participants make sense of and apply information [93]. In particular, learning styles, education level, ethnic/cultural background, economic status and personal experiences all impact how individuals understand information, particularly about health and risk [43,44,94]. Therefore, the most important component in our approach is flexibility to adapt the discussion to the family's needs/expectations in an engaged counselling model [43]. The discussion points listed in Table 1 should be tailored (simplified or elaborated) accordingly. This is particularly fundamental for families with neurodevelopmental conditions like ASD, as the

individuals receiving the information may have a milder form of ASD or a related condition on the continuum, which may impact information processing (e.g. parent with ADHD).

It is worth noting that the population on which this counselling approach has been trialed is, as a whole, information driven. The majority of families have enrolled in research after connecting with community services/support for ASD. In the clinical setting, the psychological/psychosocial implications of a new ASD diagnosis may be more pressing when counselling families, so addressing the educational component of this approach can be reserved for a later visit. Of note, this counselling approach does not include guidance regarding discussion about secondary/incidental findings, which may be identified through genomic testing. This topic is beyond the scope of this paper and has been addressed previously in the literature [95–98].

5. Conclusion

The application of genomic technologies will continue to generate even more information about the genetic contributions to ASD and other neurodevelopmental conditions. Although our understanding of the causes of ASD has increased, much uncertainty and complexity still remains, particularly regarding how much a particular variant(s) contributes to ASD and its impact on clinical presentation. Counselling families about the impact of genomic results can be challenging given the limits of our current understanding. As genetic testing for ASD is increasingly integrated into mainstream medicine, health care providers will need to acquire the knowledge and skills to discuss genetic variants with families. The counselling approach we present, which incorporates our cup model, provides clinicians and counsellors with a starting point to facilitate the discussion regarding the complex genetic etiology of ASD.

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Conflict of interest

S.W.S. is on the Scientific Advisory Boards of Autism Speaks, Deep Genomics, Lineagen, and Population Diagnostics.

References

[1] Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators, Centers for Disease Control and Prevention. Prevalence of Autism Spectrum Disorders–Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill. Summ. 2012;61:1-19.
[2] L. Zwaigenbaum, S.E. Bryson, P. Szatmari, J. Brian, I.M. Smith, et al., Sex differences in children with Autism Spectrum Disorder identified within a high-risk infant cohort, J. Autism Dev. Disord. 42 (2012) 2585–2596.
[3] E. Anagnostou, L. Zwaigenbaum, P. Szatmari, E. Fombonne, B.A. Fernandez, et al., Autism Spectrum Disorder: advances in evidence-based practice, CMAJ 186 (2014) 509–519.
[4] M.T. Carter, S.W. Scherer, Autism Spectrum Disorder in the genetics clinic: a review, Clin. Genet. 83 (2013) 399–407.
[5] Autism Genome Project Consortium, P. Szatmari, A.D. Paterson, L. Zwaigenbaum, W. Roberts, et al., Mapping autism risk loci using genetic linkage and chromosomal rearrangements, Nat. Genet. 39 (2007) 319–328.
[6] M.E. Talkowski, E.V. Minikel, J.F. Gusella, Autism Spectrum Disorder genetics: diverse genes with diverse clinical outcomes, Harv. Rev. Psychiatry 22 (2014) 65–75.
[7] S. Tordjman, E. Somogyi, N. Coulon, S. Kermarrec, D. Cohen, et al., Gene x Environment interactions in Autism Spectrum Disorders: role of epigenetic mechanisms, Front. Psychiatry. 5 (2014) 53.
[8] C.M. Freitag, W. Staal, S.M. Klauck, E. Duketis, R. Waltes, Genetics of autistic disorders: review and clinical implications, Eur. Child Adolesc. Psychiatry 19 (2010) 169–178.
[9] R.F. Gillis, G.A. Rouleau, The ongoing dissection of the genetic architecture of autistic spectrum disorder, Mol. Autism 2 (2011) (12-2392-2-12).
[10] E.H. Cook Jr., S.W. Scherer, Copy-number variations associated with neuropsychiatric conditions, Nature 455 (2008) 919–923.
[11] C.R. Marshall, A. Noor, J.B. Vincent, A.C. Lionel, L. Feuk, et al., Structural variation of chromosomes in Autism Spectrum Disorder, Am. J. Hum. Genet. 82 (2008) 477–488.
[12] J. Shen, S. Lincoln, D.T. Miller, Advances in genetic discovery and implications for counseling of patients and families with Autism Spectrum Disorders, Curr. Genet. Med. Rep. 2 (2014) 124–134.
[13] Y.H. Jiang, R.K. Yuen, X. Jin, M. Wang, N. Chen, et al., Detection of clinically relevant genetic variants in Autism Spectrum Disorder by whole-genome sequencing, Am. J. Hum. Genet. 93 (2013) 249–263.
[14] I. Iossifov, B.J. O'Roak, S.J. Sanders, M. Ronemus, N. Krumm, et al., The contribution of de novo coding mutations to Autism Spectrum Disorder, Nature 515 (2014) 216–221.
[15] J.H. Miles, Complex Autism Spectrum Disorders and cutting-edge molecular diagnostic tests, JAMA 314 (2015) 879–880.
[16] C. Betancur, Etiological heterogeneity in Autism Spectrum Disorders: more than 100 genetic and genomic disorders and still counting, Brain Res. 1380 (2011) 42–77.
[17] I. Witt-Engerstrom, C. Gillberg, Rett syndrome in Sweden, J. Autism Dev. Disord. 17 (1987) 149–150.
[18] R.H. Mount, T. Charman, R.P. Hastings, S. Reilly, H. Cass, Features of autism in Rett syndrome and severe mental retardation, J. Autism Dev. Disord. 33 (2003) 435–442.
[19] R.J. Hagerman, A.W. Jackson 3rd, A. Levitas, B. Rimland, M. Braden, An analysis of autism in fifty males with the fragile X syndrome, Am. J. Med. Genet. 23 (1986) 359–374.
[20] D.D. Hatton, J. Sideris, M. Skinner, J. Mankowski, D.B. Bailey Jr., et al., Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP, Am. J. Med. Genet. A 140A (2006) 1804–1813.
[21] R.A. Kumar, S. KaraMohamed, J. Sudi, D.F. Conrad, C. Brune, et al., Recurrent 16p11: 2 microdeletions in autism, Hum. Mol. Genet. 17 (2008) 628–638.
[22] L.A. Weiss, Y. Shen, J.M. Korn, D.E. Arking, D.T. Miller, et al., Autism Consortium Association between microdeletion and microduplication at 16p11.2 and autism, N. Engl. J. Med. 358 (2008) 667–675.
[23] R.K.C. Yuen, D. Merico, M.L. Bookman, J. Howe, B. Thiruvahindrapuram, et al., Whole genome sequencing resource identifies 18 new candidate genes for Autism Spectrum Disorder, Nat. Neurosci. 20 (2017) 602–611.
[24] K. Tammimies, C.R. Marshall, S. Walker, G. Kaur, B. Thiruvahindrapuram, et al., Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with Autism Spectrum Disorder, JAMA 314 (2015) 895–903.
[25] G. Huguet, E. Ey, T. Bourgeron, The genetic landscapes of Autism Spectrum Disorders, Annu. Rev. Genomics Hum. Genet. 14 (2013) 191–213.
[26] N.J. Mendelsohn, G.B. Schaefer, Genetic evaluation of autism, Semin. Pediatr. Neurol. 15 (2008) 27–31.
[27] F. Gurrieri, Working up autism: the practical role of medical genetics, Am. J. Med. Genet. C Semin. Med. Genet. 160C (2012) 104–110.
[28] C. Lintas, A.M. Persico, Autistic phenotypes and genetic testing: state-of-the-art for the clinical geneticist, J. Med. Genet. 46 (2009) 1–8.
[29] R.K. Yuen, B. Thiruvahindrapuram, D. Merico, S. Walker, K. Tammimies, et al., Whole-genome sequencing of quartet families with Autism Spectrum Disorder, Nat. Med. 21 (2015) 185–191.
[30] R.K. Yuen, D. Merico, H. Cao, G. Pellecchia, B. Alipanahi, et al., Genome-wide characteristics of de novo mutations in autism, NPJ Genomics Med. 1 (2016) 160271–1602710.
[31] J.D. Buxbaum, M.J. Daly, B. Devlin, T. Lehner, K. Roeder, et al., Autism Sequencing Consortium The autism sequencing consortium: large-scale, high-throughput sequencing in Autism Spectrum Disorders, Neuron 76 (2012) 1052–1056.
[32] S. De Rubeis, X. He, A.P. Goldberg, C.S. Poultney, K. Samocha, et al., Synaptic, transcriptional and chromatin genes disrupted in autism, Nature 515 (2014) 209–215.
[33] S.J. Sanders, X. He, A.J. Willsey, A.G. Ercan-Sencicek, K.E. Samocha, et al., Insights into Autism Spectrum Disorder genomic architecture and biology from 71 risk loci, Neuron 87 (2015) 1215–1233.
[34] B. Finucane, S.M. Myers, Genetic counseling for Autism Spectrum Disorder in an evolving theoretical landscape, Curr. Genet. Med. Rep. 4 (2016) 147–153.
[35] A. Guilmatre, C. Dubourg, A.L. Mosca, S. Legallic, A. Goldenberg, et al., Saugier Veber P, Campion D. Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation, Arch. Gen. Psychiatry 66 (2009) 947–956.
[36] M.C. Lai, M.V. Lombardo, Baron-Cohen S. Autism, Lancet 383 (2014) 896–910.
[37] J.A. Vorstman, J.R. Parr, D. Moreno-De-Luca, R.J. Anney, J.I. Nurnberger Jr., J.F. Hallmayer, Autism genetics: opportunities and challenges for clinical translation, Nat. Rev. Genet. (2017).

[38] M.M. Ghahramani Seno, P. Hu, F.G. Gwadry, D. Pinto, C.R. Marshall, et al., Gene and miRNA expression profiles in Autism Spectrum Disorders, Brain Res. 1380 (2011) 85–97.
[39] H.Y. Xiong, B. Alipanahi, L.J. Lee, H. Bretschneider, D. Merico, et al., RNA splicing: the human splicing code reveals new insights into the genetic determinants of disease, Science 347 (2015) 1254806.
[40] E.M. Morrow, S.Y. Yoo, S.W. Flavell, T.K. Kim, Y. Lin, et al., Identifying autism loci and genes by tracing recent shared ancestry, Science 321 (2008) 218–223.
[41] Y.J. Loke, A.J. Hannan, J.M. Craig, The role of epigenetic change in Autism Spectrum Disorders, Front. Neurol. 6 (2015) 107.
[42] S.E. Ali-Khan, A.S. Daar, C. Shuman, P.N. Ray, S.W. Scherer, Whole genome scanning: resolving clinical diagnosis and management amidst complex data, Pediatr. Res. 66 (2009) 357–363.
[43] J. Austin, A. Semaka, G. Hadjipavlou, Conceptualizing genetic counseling as psychotherapy in the era of genomic medicine, J. Genet. Couns. 23 (2014) 903–909.
[44] D.M. Lautenbach, K.D. Christensen, J.A. Sparks, R.C. Green, Communicating genetic risk information for common disorders in the era of genomic medicine, Annu. Rev. Genomics Hum. Genet. 14 (2013) 491–513.
[45] D.J. Stavropoulos, D. Merico, R. Jobling, S. Bowdin, N. Monfared, et al., Whole-genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine, NPJ Genomic Med. 1 (2016) 15012.
[46] C.R. Marshall, D.J. Stavropoulos, R. Jobling, D. Merico, S. Bowdin, et al., MG-132 Diagnostic utility of whole genome sequencing in paediatric medicine, J. Med. Genet. 52 (2015) A12–A12.
[47] B. Bernhardt, Genetic counselors and the future of clinical genomics, Genome Med. 6 (2014) 49.
[48] G.W. Hooker, K.E. Ormond, K. Sweet, B.B. Biesecker, Teaching genomic counseling: preparing the genetic counseling workforce for the genomic era, J. Genet. Couns. 23 (2014) 445–451.
[49] C.A. Shelton, D.C. Whitcomb, Evolving roles for physicians and genetic counselors in managing complex genetic disorders, Clin. Transl. Gastroenterol. 6 (2015) e124.
[50] S. Arora, E. Haverfield, G. Richard, S.B. Haga, R. Mills, Clinical and counseling experiences of early adopters of whole exome sequencing, J. Genet.Couns. 25 (2016) 337–343.
[51] S. Crawford, On the origins of autism: the quantitative threshold exposure hypothesis, Med. Hypotheses 85 (2015) 798–806.
[52] H. Peay, J. Austin, Chapter 4: Explaining How Psychiatric Illness Happens How to Talk with Families About Genetics and Psychiatric Illness, W.W. Norton & Company, 2011, pp. 87.
[53] J.L. Waxler, K.E. O'Brien, L.M. Delahanty, J.B. Meigs, J.C. Florez, et al., Genetic counseling as a tool for type 2 diabetes prevention: a genetic counseling framework for common polygenetic disorders, J. Genet. Couns. 21 (2012) 684–691.
[54] A.S. Nord, W. Roeb, D.E. Dickel, T. Walsh, M. Kusenda, et al., STAART Psychopharmacology Network, King B, King MC, McClellan JM. Reduced transcript expression of genes affected by inherited and de novo CNVs in autism, Eur. J. Hum. Genet. 19 (2011) 727–731.
[55] D. Pinto, A.T. Pagnamenta, L. Klei, R. Anney, D. Merico, et al., Functional impact of global rare copy number variation in Autism Spectrum Disorders, Nature 466 (2010) 368–372.
[56] B.J. O'Roak, L. Vives, S. Girirajan, E. Karakoc, N. Krumm, et al., Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations, Nature 485 (2012) 246–250.
[57] R.A. Barnard, M.B. Pomaville, B.J. O'Roak, Mutations and modeling of the chromatin remodeler CHD8 define an emerging autism etiology, Front. Neurosci. 9 (2015) 477.
[58] L.A. Weiss, A. Escayg, J.A. Kearney, M. Trudeau, B.T. MacDonald, et al., Sodium channels SCN1A, SCN2A and SCN3A in familial autism, Mol. Psychiatry 8 (2003) 186–194.
[59] S.J. Sanders, M.T. Murtha, A.R. Gupta, J.D. Murdoch, M.J. Raubeson, et al., De novo mutations revealed by whole-exome sequencing are strongly associated with autism, Nature 485 (2012) 237–241.
[60] C. Helsmoortel, A.T. Vulto-van Silfhout, B.P. Coe, G. Vandeweyer, L. Rooms, et al., A SWI/SNF-related autism syndrome caused by de novo mutations in ADNP, Nat. Genet. 46 (2014) 380–384.
[61] A.M. D'Gama, S. Pochareddy, M. Li, S.S. Jamuar, R.E. Reiff, et al., Targeted DNA sequencing from Autism Spectrum Disorder brains implicates multiple genetic mechanisms, Neuron 88 (2015) 910–917.
[62] B. Reichow, Overview of meta-analyses on early intensive behavioral intervention for young children with Autism Spectrum Disorders, J. Autism Dev. Disord. 42 (2012) 512–520.
[63] J.P. Casey, T. Magalhaes, J.M. Conroy, R. Regan, N. Shah, et al., A novel approach of homozygous haplotype sharing identifies candidate genes in Autism Spectrum Disorder, Hum. Genet. 131 (2012) 565–579.
[64] M.H. Chahrour, T.W. Yu, E.T. Lim, B. Ataman, M.E. Coulter, et al., Whole-exome sequencing and homozygosity analysis implicate depolarization-regulated neuronal genes in autism, PLoS Genet. 8 (2012) e1002635.
[65] E.D. Gamsiz, L.N. Sciarra, A.M. Maguire, M.F. Pescosolido, L.I. van Dyck, et al., Discovery of rare mutations in autism: elucidating neurodevelopmental mechanisms, Neurotherapeutics 12 (2015) 553–571.
[66] A.C. Lionel, K. Tammimies, A.K. Vaags, J.A. Rosenfeld, J.W. Ahn, et al., Disruption of the ASTN2/TRIM32 locus at 9q33.1 is a risk factor in males for Autism Spectrum Disorders, ADHD and other neurodevelopmental phenotypes, Hum. Mol. Genet. 23 (2014) 2752–2768.
[67] T.P. Rutkowski, J.P. Schroeder, G.M. Gafford, S.T. Warren, D. Weinshenker, T. Caspary, J.G. Mulle, Unraveling the genetic architecture of copy number variants associated with schizophrenia and other neuropsychiatric disorders, J. Neurosci. Res. 95 (2017) 1144–1160.
[68] H.M. Kearney, E.C. Thorland, K.K. Brown, F. Quintero-Rivera, S.T. South, Working Group of the American College of Medical Genetics Laboratory Quality Assurance Committee. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants, Genet. Med. 13 (2011) 680–685.
[69] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, et al., ACMG Laboratory Quality Assurance Committee: standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet. Med. 17 (2015) 405–424.
[70] W.J. Kent, C.W. Sugnet, T.S. Furey, K.M. Roskin, T.H. Pringle, A.M. Zahler, D. Haussler, The human genome browser at UCSC, Genome Res. 12 (2002) 996–1006.
[71] J.R. MacDonald, R. Ziman, R.K. Yuen, L. Feuk, S.W. Scherer, The Database of Genomic Variants: a curated collection of structural variation in the human genome, Nucl. Acids Res. 42 (2014) D986–92.
[72] M. Lek, K.J. Karczewski, E.V. Minikel, K.E. Samocha, E. Banks, et al., Exome aggregation consortium analysis of protein-coding genetic variation in 60,706 humans, Nature 536 (2016) 285–291.
[73] S.N. Basu, R. Kollu, S. Banerjee-Basu, AutDB: a gene reference resource for autism research, Nucleic Acids Res. 37 (2009) D832–6.
[74] E. Larsen, I. Menashe, M.N. Ziats, W. Pereanu, A. Packer, et al., A systematic variant annotation approach for ranking genes associated with Autism Spectrum Disorders, Mol. Autism 7 (2016) 44.
[75] B.S. Abrahams, D.E. Arking, D.B. Campbell, H.C. Mefford, E.M. Morrow, et al., SFARI Gene 2.0: a community-driven knowledgebase for the Autism Spectrum Disorders (ASDs), Mol.Autism 4 (2013) (36-2392-4-36).
[76] V. De Wolf, N. Brison, K. Devriendt, H. Peeters, Genetic counseling for susceptibility loci and neurodevelopmental disorders: the del15q11.2 as an example, Am. J. Med. Genet. A 161A (2013) 2846–2854.
[77] V.W. Hu, From genes to environment: using integrative genomics to build a systems-level understanding of Autism Spectrum Disorders, Child Dev. 84 (2013) 89–103.
[78] E.B. Robinson, B. St Pourcain, V. Anttila, J.A. Kosmicki, B. Bulik-Sullivan, et al., Genetic risk for Autism Spectrum Disorders and neuropsychiatric variation in the general population, Nat. Genet. 48 (2016) 552–555.
[79] L. Soorya, A. Kolevzon, J. Zweifach, T. Lim, Y. Dobry, et al., Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency, Mol. Autism 4 (2013) (18-2392-4-18).
[80] A. Chaudhry, A. Noor, B. Degagne, K. Baker, L.A. Bok, et al., Phenotypic spectrum associated with PTCHD1 deletions and truncating mutations includes intellectual disability and Autism Spectrum Disorder, Clin. Genet. 88 (2015) 224–233.
[81] M.A. Gillentine, L.N. Berry, R.P. Goin-Kochel, M.A. Ali, J. Ge, et al., The cognitive and behavioral phenotypes of individuals with CHRNA7 duplications, J. Autism Dev. Disord. 47 (2017) 549–562.
[82] E.S. Gershon, N. Alliey-Rodriguez, New ethical issues for genetic counseling in common mental disorders, Am. J. Psychiatry 170 (2013) 968–976.
[83] G.B. Schaefer, N.J. Mendelsohn, Professional Practice and Guidelines Committee Clinical genetics evaluation in identifying the etiology of Autism Spectrum Disorders: 2013 guideline revisions, Genet.Med 15 (2013) 399–407.
[84] W.M. McMahon, B.J. Baty, J. Botkin, Genetic counseling and ethical issues for autism, Am. J. Med. Genet. C Semin. Med. Genet. 142C (2006) 52–57.
[85] E. Simonoff, Genetic counseling in autism and pervasive developmental disorders, J. Autism Dev. Disord. 28 (1998) 447–456.
[86] J.N. Constantino, Y. Zhang, T. Frazier, A.M. Abbacchi, P. Law, Sibling recurrence and the genetic epidemiology of autism, Am. J. Psychiatry 167 (2010) 1349–1356.
[87] S. Ozonoff, G.S. Young, A. Carter, D. Messinger, N. Yirmiya, et al., Recurrence risk for Autism Spectrum Disorders: a Baby Siblings Research Consortium study, Pediatrics 128 (2011) e488–95.
[88] P. Szatmari, K. Chawarska, G. Dawson, S. Georgiades, R. Landa, et al., Prospective longitudinal studies of infant siblings of children with autism: lessons learned and future directions, J. Am. Acad. Child Adolesc. Psychiatry 55 (2016) 179–187.
[89] F.A. Miller, R.Z. Hayeems, J.P. Bytautas, What is a meaningful result: disclosing the results of genomic research in autism to research participants, Eur. J. Hum. Genet. 18 (2010) 867–871.
[90] C. Hippman, Z. Lohn, A. Ringrose, A. Inglis, J. Cheek, et al., Nothing is absolute in life: understanding uncertainty in the context of psychiatric genetic counseling from the perspective of those with serious mental illness, J. Genet. Couns 22 (2013) 625–632.
[91] R.Z. Hayeems, R. Babul-Hirji, N. Hoang, R. Weksberg, C. Shuman, Parents' experience with pediatric microarray: transferrable lessons in the era of genomic counseling, J. Genet. Couns. 25 (2016) 298–304.
[92] M. Reiff, E. Giarelli, B.A. Bernhardt, E. Easley, N.B. Spinner, et al., Parents' perceptions of the usefulness of chromosomal microarray analysis for children with Autism Spectrum Disorders, J. Autism Dev. Disord. 45 (2015) 3262–3275.

[93] J. Austin, A. Inglis, G. Hadjipavlou, Genetic counseling for common psychiatric disorders: an opportunity for interdisciplinary collaboration, Am. J. Psychiatry 171 (2014) 584–585.
[94] D.H. Lea, K.A. Kaphingst, D. Bowen, I. Lipkus, D.W. Hadley, Communicating genetic and genomic information: health literacy and numeracy considerations, Public Health. Genomics 14 (2011) 279–289.
[95] K. Burke, A. Clarke, The challenge of consent in clinical genome-wide testing, Arch. Dis. Child. 101 (2016) 1048–1052.
[96] W. Burke, A.H. Antommaria, R. Bennett, J. Botkin, E.W. Clayton, et al., Recommendations for returning genomic incidental findings? We need to talk!, Genet. Med. 15 (2013) 854–859.
[97] M.I. Roche, J.S. Berg, Incidental findings with genomic testing: implications for genetic counseling practice, Curr. Genet. Med. Rep. 3 (2015) 166–176.
[98] S. Shkedi-Rafid, S. Dheensa, G. Crawford, A. Fenwick, A. Lucassen, Defining and managing incidental findings in genetic and genomic practice, J. Med. Genet. 51 (2014) 715–723.
[99] A.M. Rosell, L.D. Pena, K. Schoch, R. Spillmann, J. Sullivan, et al., Not the end of the odyssey: parental perceptions of whole exome sequencing (WES) in pediatric undiagnosed disorders, J. Genet. Couns. 25 (2016) 1019–1031.
[100] C.M. Khan, C. Rini, B.A. Bernhardt, J.S. Roberts, K.D. Christensen, et al., How can psychological science inform research about genetic counseling for clinical genomic sequencing? J. Genet. Couns. 24 (2015) 193–204.
[101] J.W. Harrington, P.A. Patrick, K.S. Edwards, D.A. Brand, Parental beliefs about autism: implications for the treating physician, Autism 10 (2006) 452–462.
[102] L. Mercer, S. Creighton, J.J. Holden, M.E. Lewis, Parental perspectives on the causes of an Autism Spectrum Disorder in their children, J. Genet. Couns. 15 (2006) 41–50.
[103] C.G. Selkirk, P. McCarthy Veach, F. Lian, L. Schimmenti, B.S. LeRoy, Parents' perceptions of Autism Spectrum Disorder etiology and recurrence risk and effects of their perceptions on family planning: recommendations for genetic counselors, J. Genet. Couns. 18 (2009) 507–519.
[104] Ambry Genetics. Genetics 101: What is Exome Sequencing? http://www.ambrygen.com/helpful-videos-exome.
[105] The Hospital for Sick Children, Centre for Genetic Medicine. Exome Sequencing Animated Video. http://www.sickkids.ca/CGM/education/exome-animated-video.html.