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Genetic Testing and Autism: Tutorial for Communication Sciences and Disorders

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Abstract

This tutorial provides professionals in communication sciences and disorders with an overview of the molecular basis and parental perceptions of genetic testing as associated with autism. The introduction notes the prominence of genetic testing within present-day medical practices and highlights related limitations and concerns through the lens of disability critique. The body of the tutorial provides an overview of four different forms of genetic variation, highlighting the potential associations with autism and available genetic testing. In sum, most autism cases cannot be associated directly with specified forms of genetic variation but are attributed instead to multiple genetic and environmental influences working in concert. Finally, the discussion focuses on parental perceptions of the genetic testing associated with autism, both the potential benefits and harms, and emphasizes the need to integrate first-person perspectives from autistic individuals.

Keywords

autism; genetic testing; geneticization; neurodiversity; disability critique

1. Introduction

The present tutorial is aimed at providing interdisciplinary background information regarding the current landscape of genetic testing and autism. As a field, communication sciences and disorders (CSD) may seem fairly disparate from molecular genetics. However, genetic information is quickly becoming woven into our everyday discourses, medical practices, and, consequently, clinical services. The general increase in genetic testing has influenced the medical care associated with childhood developmental conditions, autism included. Three forms of genetic testing will be addressed in the present tutorial: a) prenatal

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testing, b) preimplantation genetic diagnosis on embryos produced through in vitro fertilization, and c) postnatal predictive or diagnostic testing, currently the most common form of genetic testing associated with autism.

Although research on the genetic basis of autism is usually framed as working toward prevention of disease and suffering, the clinical implications of genetic testing is often less clear to practitioners and the populations they serve. Particularly as it relates to autism, it is not always clear what genetic information can predict about key developmental outcomes, and there is understandable concern within disability communities that such information will be interpreted through the lens of current societal misconceptions and discriminatory practices. Scully in a 2008 article in *Nature Reviews Genetics* notes, “It can come as a surprise, especially to researchers with little clinical contact, that disabled people might be ambivalent or even hostile toward genetics and genetic medicine” (p.798). Pellicano and Stears (2011) highlighted developments in genetics as one of the most contentious areas of autism research, with important underlying ethical considerations. They contend that the controversy hinges on “fundamentally conflicting assumptions about the nature and desirability of neurocognitive difference” (p.271). Whereas the American Psychological Association and many associated fields describe autism as a disorder defined by deficits in social interaction and excesses in behavioral rigidity and repetition (APA, 2013), advocates within the disability rights community tend to view autism as a natural form of neurological diversity--a position commonly referred to as the neurodiversity paradigm (Donaldson, 2017; Pellicano & Stears, 2011; Robertson, 2010; Straus, 2013). The neurodiversity paradigm highlights the positive aspects of autism (e.g., ability to focus on detail, high tolerance for repetition) and emphasizes society’s role in constructing disability through discrimination and institutional barriers (e.g., privileging speech over access to augmentative and alternative communication).

The neurodiversity paradigm raises a number of concerns in relation to genetic testing, concerns referred to more broadly as the “disability critique” (Parens & Asch, 2000; Scully, 2008). Though apprehensions related to genetic testing are diverse and vary across individuals and populations, we focus here on three points that are relevant but not specific to autism. First, genetic testing has the potential to provide a powerful tool for implementing currently-existing forms of societal discrimination. For example, prenatal genetic testing for autism, if it were to become widely available, could lead to a high prevalence of elective abortions and an associated decrease in the number of autistic¹ youth. Although prenatal genetic testing is not routinely available for autism at this point, routine prenatal screening for Down syndrome has been available in the U.S. since the late 1980s (Cuckle, Wald, & Thompson, 1987) and is associated with an elective abortion rate ranging from 61–93%. (Natoli et al. 2012). Second, disability advocates suggest that finite financial and human resources currently dedicated to genetic testing and associated research would be better spent addressing critical quality of life issues for autistic individuals and their families, such

¹The use of identity-first language (“autistic individuals”), as opposed to person-first language (individual with autism), is used intentionally here to reflect the preference of those who view autism as a key aspect of their identity (Kapp et al., 2013; Kenny et al., 2016; Oakley, 2012; Sinclair, 2012). This is consistent with the American Psychological Association recommendation that authors respect “what people prefer to be called” (APA, 2010, p.72).

as social acceptance, employment options, and access to augmentative and alternative communication (cf. Pellicano, Dinsmore, & Charman, 2014; Robertson, 2010). Finally, the focus on genetics often fails to acknowledge the *social* determinants of disability, such as stigma and discriminatory practices. The tendency to isolate genetic contributions to individual differences without acknowledging important contextual factors has been referred to as *geneticization* (see Clarke, Shim, Mamo, Fosket, & Fishman, 2003; Lippman, 1991; Scully, 2006). In other words, there may be a tendency to overestimate the influence of genes on child development and related quality of life indicators. In a survey of 255 parents of children with nonsyndromic² autism, 72.7% indicated they believed genetic influences to be a cause of autism (Selkirk, Veach, Lian, Schimmenti, & LeRoy, 2009). The study also found that parents tended to overestimate their probability of having another autistic child, and at least 29% of the parents reported that their perceived “risk” of having another autistic child affected their family planning to some extent.

The ubiquity of genetic testing paired with the tendency to oversimplify the role of genetics in human development together underscore the need to increase genetic literacy amongst allied health professionals, particularly those who feature prominently in the lives of autistic children and their families. Reiff et al. (2017) noted that “Healthcare providers of families undergoing testing should be aware of the ways in which the genetic information can influence attitudes and decisions about care and treatment and be prepared to communicate and to provide explanations, education and guidance about how genetic information can be understood...” p.1460). Because communication differences are often one of the first noted developmental features of autism, speech-language pathologists are at the forefront of diagnosis and early intervention. Speech-language pathologists would benefit from an overview of what forms of genetic testing are currently available for autism, as well as the benefits and harms perceived by family members.

This tutorial provides a brief overview of the genetic basis for individual difference—beginning with chromosome number and moving through an increasingly granular focus on copy number variants, single gene conditions, and single nucleotide polymorphisms (SNPs). In each case, we first provide a brief description of the underlying molecular genetic background before summarizing relevant autism literature and then specifying associated genetic test procedures (see Table 1 for an overview). We follow this review with a discussion of parental perspectives on genetic testing for autism and highlight the need to integrate first-person perspectives from autistic individuals.

2. Chromosomal Variation

2.1. Genetic Background: Chromosomes and Meiotic Division

As human beings, we have 46 microscopic “bundles of genetic material” known as chromosomes (see Figure 1)³. As a general rule, we inherit 23 chromosomes from our

²Also referred to as “essential” or “idiopathic” autism, meaning the autistic features have not been associated with a single gene condition and are likely due to a combination of multiple genetic and environmental factors (see Carter & Scherer, 2013; Moeschler et al., 2014; Rosti, Sadek, Vaux, & Gleeson, 2014; Selkirk et al. 2009)

³An interactive website for exploring the size of chromosomes and other cellular material including the egg and sperm is available at <http://learn.genetics.utah.edu/content/cells/scale/>

mother and 23 from our father when their respective germ cells, the egg and sperm, unite to form a single cell. The resulting zygote contains all the genetic material needed to create a human life. The 23 pairs of chromosomes are referred to by number, organized longest to shortest, with the exception of the X and Y chromosomes which are listed as the twenty-third chromosome despite their intermediate length. Specifically, two X chromosomes are associated with female biological sex; whereas one X and one Y are associated with male biological sex.

All 46 chromosomes are neatly packed into the nucleus of nearly every cell in our body. The creation of sperm and egg through the process of meiosis serves to halve the genetic contribution of each parent to 23 chromosomes. Consequently, when egg and sperm unite through fertilization, the original number of 46 chromosomes is restored. Occasionally during the body's production of egg and sperm, chromosomes are partitioned unevenly, the most recognized result being trisomy (an extra chromosome present) or monosomy (the absence of a chromosome)⁴. One of the most familiar examples of chromosome variation is Down syndrome, which is attributed to a partial or full extra copy of chromosome 2⁵. Chromosomal variation is relatively common in pregnancy with the majority of cases thought to result in miscarriage (Nagaoka, Hassold, & Hunt, 2012). It is estimated that 1 of 150 live births has a chromosomal variation of symptomatic significance (Norton & Rink, 2015).

2.2. Relevance to Autism

There is no one-on-one correspondence between chromosomal variation and autism in the way there is for Down syndrome. However, there is an increased prevalence of autism, 16%, in individuals with Down syndrome (Richards, Jones, Groves, Moss, & Oliver, 2015). Similarly, studies have documented an increased prevalence of autism in children either missing a sex chromosome or having an extra X or Y chromosome (Bishop et al., 2011; Bishop & Scerif, 2011; Cordeiro, Tartaglia, Roeltgen, & Ross, 2012; Lee et al., 2012; Marko & Skuse, 2006). Although not directly tied to autism, we review here the prenatal testing associated with chromosomal variation because the underlying procedures serve as means of collecting relevant genetic data for other forms of genetic testing.

2.3. Current Prenatal Testing for Chromosomal Variation

Prenatal screening for chromosomal variation is one of the first opportunities parents have to learn about their child's genetic make-up, and the process has typically focused on Down syndrome, with a more recent inclusion of other trisomies. During early pregnancy, mothers have routinely been offered a blood test referred to as the quad screen (aka, quadruple screen, AFP4, or multiple marker). This procedure is presented as a screening for Down syndrome, Trisomy 18, and neural tube or abdominal wall defects, based on the presence of four small molecules known as metabolites within the mother's blood (i.e., alpha-fetoprotein, human chorionic gonadotropin, estriol and inhibin A). In addition, fetal

⁴The unexpected translocations and rearrangements of large sections of DNA which can occur during meiosis can also be referred to as chromosomal variations.

⁵In a small minority of cases, Down syndrome can occur *after* fertilization during the process of rapid cell division known as mitosis. In such cases, the additional genetic material is only in a portion of the individual's cells.

ultrasound measurements of the space at the back of the neck (i.e., nuchal translucency) is often provided as an additional indicator of chromosomal variation. This anatomical region tends to be more fluid filled in fetuses with a genetic trisomy or monosomy due to association with heart complications or differences in fetal mobility (Berger, 1999; Wiechec, Knafel, Nocun, Wiercinska, Ludwin, & Ludwin, 2017).

Definitive prenatal testing for the presence of chromosome variation requires direct analysis of fetal tissue, which has traditionally been performed through amniocentesis or chorionic villus sampling (Norton & Rink, 2015). Amniocentesis uses a needle to extract amniotic fluid directly from the womb, which contains shed fetal cells for analysis, or chorionic villus sampling, which directly samples cells from the placenta via access through the cervix or the abdominal wall. Although both procedures include potential medical risks, including miscarriage, current guidelines from the American College of Obstetricians indicate that such diagnostic testing should be available to all pregnant women (American College of Obstetricians and Gynecologists, 2007; Norton & Risk, 2015).

Procedures for early genetic screening are changing as less invasive measures become available, such as direct analysis of fetal DNA found in maternal blood samples. Specifically, a study by Norton et al., (2015) using cell-free DNA found in maternal blood documented the ability to identify trisomies (specifically of chromosomes 13, 18, and 21) with higher accuracy than standard screening procedures (i.e., quad screen and nuchal translucency); see also Nicolaides, Musci, Struble, Syngelaki, and Gil (2013) and Nicolaides, Syngelaki, Gil, Atanasova, and Markova (2013) for similar procedures used to detect a missing or extra sex chromosome.

3. Copy Number Variants

3.1. Genetic Background: Meiotic Recombination

The 46 human chromosomes are comprised of anti-parallel strands of deoxyribonucleic acid, more commonly referred to simply as DNA. In addition to halving the chromosome number, meiosis also serves to ‘scramble’ the DNA of each parent such that the germ cells receive a hybrid chromosome rather than an exact duplicate of the chromosome from either parent (Figure 2). During the scrambling process, referred to as recombination, the matching chromosomes align based on sequences of base pairs, breaking, intermingling, and then rejoining. Misalignment of the matching chromosomes during the recombination process can lead to deletion or duplication of segments of DNA (Fig. 3).

Duplication or deletion of discrete regions of DNA, usually containing up to 50 genes, are referred to as Copy Number Variants, abbreviated as CNVs (Eichler, 2008). In contrast to chromosomal disorders, which are defined by the addition or loss of large sections of or entire chromosomes (e.g., Down Syndrome), we are referring to CNVs as differences that affect a relatively small fraction of the total genes within a chromosome⁶. CNVs are named according to the chromosome number, the chromosome arm designation (p for the short arm; q for the long arm), and a number that represents the distance from the centromere (i.e.,

⁶Note that CNVs can be considered a subtype of chromosomal variation (see for example Betancur, 2011)

the constricted point on the chromosome) where they are located. Consequently, the CNV 16p11.2 is located on the short arm of chromosome 16, region 1, band 1, sub band 2. It is closer to the centromere than CNV 16p12.1 as increasing numbers represent increased distance from the centromere. Copy number variants are considered relatively widespread in the human genome and do not necessarily imply clinical significance (Kearney, Thorland, Brown, Quintero-Rivera, & South, 2011).

3.2. Relevance to Autism Research

Recent estimates suggest that approximately 7–18% of autism cases are associated with CNVs (Shen et al., 2010). Two of the most common examples include a duplication or triplication of a region on the long arm of chromosome 15 (specifically 15q11-13) and a duplication or deletion of the short arm of chromosome 16 (specifically 16p11.2). Other CNVs associated with autism have been found across a number of chromosomal regions (Betancur, 2011; Carter & Scherer, 2013; Parikshak et al., 2016; Pinto et al., 2010; Rosti et al., 2014; Sanders et al., 2011; Sanders et al., 2015; Turner et al., 2017); see Table 1. In addition, a number of CNVs associated with autism have also been linked to medical complications such as cardiac abnormalities (Geschwind & State, 2015). Therefore, although they are uncommon, identifying CNVs can have substantial implications for medical intervention. Readers are referred to the Online Mendelian Inheritance in Man (OMIM; <http://www.omim.org>) as a publicly-available and fairly comprehensive on-line resource linking clinical profiles and specific forms of genetic variation.

Despite associations between certain CNVs and specified symptoms/traits, the presence of a specific CNV often does not correlate perfectly with specific symptoms or an autism diagnosis, a fact attributed to variable expressivity and incomplete penetrance (Betancur, 2011; Carter & Scherer, 2013; Kearney et al., 2011; Sanders et al., 2011; Visser, de Vries, & Veltman, 2010). In other words, one individual with a specified CNV may be diagnosed with autism, while a family member with the same CNV may not. Reasons for such differences may be attributed to environmental factors or other forms of genetic variation.

3.3. Genetic Testing via Chromosomal Microarray Analysis

Clinically, assessments for CNVs most often occur postnatally when medical specialists suspect genetic contributions to neurodevelopmental differences, perhaps due to family history, unusual physical features, affected organ systems, or extent of cognitive differences (Miller et al., 2010; Moeschler et al., 2014). Molecular tests for CNVs, such as chromosomal microarrays (CMA), compare sections of DNA between individuals, such as the affected individual and a comparison DNA sample from an unaffected individual. The arrays may be designed to cover the entire genome or target specific locations on the genome associated with developmental differences. Either way, the process “flags” sections of DNA that differ between the affected individual and the comparison sample. DNA samples are usually taken from a child blood sample, but they can also be taken prenatally from amniocentesis or chorionic villus sampling. Although chromosomal microarrays can detect relatively small regions of genetic variation (~30,000 base pairs), they will not identify variation at the level of specific base pairs, which is associated with single gene disorders.

4. Single Gene Conditions

4.1. Genetic Background: DNA, Base Pairs, and Mutations

In total, human DNA includes 6 billion base pairs, which can be conceptualized as specific chemical structures with strong bonding preferences: adenine (A), which consistently partners with thymine (T), and guanine (G), which consistently partners with cytosine (C); see Figure 1. These base attractions are key to the continual process of DNA replication in which the two strands are “unzipped” and then rebuilt by attracting a new string of complementary base pairs. Such replication is at the heart of the body’s constant process of growth, renewal, and as it turns out, potential for change.

The sheer volume of replication throughout the body’s approximately 100 trillion cells is bound to lead to variants or “mutations,” despite a number of built-in mechanisms to ensure DNA replication fidelity. In general, mutations are considered any change in the base pairs of DNA—a deletion, a substitution, a duplication, or a rearrangement of segments of DNA (Fig. 2). In general, the term ‘gene’ describes a discrete section of DNA that ultimately encodes a protein. Genes are named for the protein they encode or for the condition with which they have been associated. For example, the gene associated with Rett syndrome is named *MECP2* after the methyl CpG binding protein that it encodes.

Despite our focus here on single gene conditions, it is important to note that each human being has on average 60 new (i.e., de novo) mutations that are distinct from those of their parents, most of which do not seem to lead to symptomatic difference (Conrad et al., 2011). The frequency of such genetic variation can make it difficult to differentiate which mutations, if any, are contributing to an individual’s developmental differences.

4.2. Relevance to Autism Research

Various reviews have provided a summary of the numerous “candidate genes” that have been associated with autism (Betancur, 2011; Blasi et al., 2006; Geschwind & State, 2015; Lim et al., 2013; Sanders et al., 2015; Yu et al., 2013). However, each rare genetic variant accounts for only a small number of cases, and none of them have been linked exclusively with autism. As summarized by Geschwind and State (2015), these candidate genes tend to affect how DNA is packaged (chromatin modification), how neurons ‘talk’ to one another in the brain (synaptic function), how other genes are regulated (e.g. by FMRP and RBFOX), and how early embryonic development unfolds (see also Persico & Bourgeron, 2006; Rosti et al., 2014; Sahin & Sur, 2015).

Similar to CNVs, identifying single gene conditions can help flag potential medical complications, a point which is often emphasized in genetics literature (Betancur, 2011; Carter & Scherer, 2013; Rosti et al., 2014). For example, a mutation in the tumor suppressor gene, *PTEN* has been associated with a group of conditions referred to collectively as *PTEN* hamartoma tumor syndromes. Given the function of this gene and its pattern of inheritance, identifying a mutation in this gene can be important for cancer surveillance, both in the affected individual and potentially other family members (Miles, 2011). In the case of Fragile X, the *FMR1* gene is “turned off” by a DNA replication error (i.e., trinucleotide repeat expansions). The silenced gene in Fragile X syndrome indirectly affects the

expression of approximately 800 genes in the brain (Brown et al., 2001; Darnell et al., 2011). Identifying Fragile X syndrome in an autistic child has implications for some family members who might be at increased chance of developing Fragile X tremor ataxia syndrome (FXTAS), an adult-onset neurodegenerative disorder (Greco et al., 2006).

4.3. Testing for Candidate Genes via Sequencing

Genetic testing for single-point mutations and small deletions is conducted via sequencing, which is expensive and often difficult to interpret. Although there are some relatively straightforward examples (see 4.2), often it is unclear whether a change from the reference sequence is symptomatic or not. Sequencing determines the precise identity (A, C, G, or T) and order of base pairs within an individual's DNA and compares that order to an identified standard, either family members or a reference database. Similar to microarray analyses, DNA samples are usually taken from a child blood sample, but they could also be taken prenatally from amniocentesis or chorionic villus sampling. Sections of DNA that diverge from an identified standard or from the unaffected parents are flagged as potential contributors to the autistic phenotype. Although sequencing can be completed on an individual's entire genome, for clinical purposes it often focuses exclusively on the regions of the genome that code for proteins (i.e., exons), and sometimes only on a very specific targeted region. For example, a mother who knows she is genetically predisposed to have a child with the Fragile X variation may opt for prenatal testing specific to this genetic region (Gutiérrez, Bajaj, & Klugman, 2013).

For efficiency in terms of cost and time, sequencing can be focused on specific candidate genes that have been associated with certain conditions by past research (e.g., autism, intellectual disability, epilepsy). Many of these comprise the 61–107 genes that are screened for by next generation sequencing (NGS) in clinical panels. For many diagnostic categories, autism especially, the list of candidate genes is a shifting landscape, and different companies include different candidate genes within their panels.

An additional challenge related to genetic sequencing is that everyone is expected to have a number of new genetic mutations in comparison to their parents, as previously mentioned. Consequently, changes found in the affected child that are not found in either parent are only suggestive, not definitive, of causation. Changes common to all three (parents plus child) are likely to be considered insignificant common variation. Accordingly, comparisons to parental or reference DNA sequences is likely to uncover a number of “variants of uncertain significance,” meaning differences that may or may not be contributing to the symptoms of interest, because they have not been previously described in the literature.

In summary, as many as 15–25% of autism cases may be attributable to rare genetic factors like de novo mutations or rare copy number variations (Cook Jr & Scherer, 2008; Shen et al., 2010). From a genetic standpoint, remaining cases must be due to a combination of environmental factors and numerous common genetic variants.

5. Common Polymorphisms

5.1. Genetic Background: Alleles and Single Nucleotide Polymorphisms (SNPs)

In our focus on human differences, it is easy to lose sight of the overwhelming genetic similarity across humans. As a result of sequencing the human genome, completed in the early part of the 21st century, human beings were found to be approximately 99.5% identical (International Human Genome Sequencing Consortium, 2001; Levy et al., 2007; Venter et al., 2001). Despite such similarity, entire disciplines, such as CSD, have sprung up surrounding the study of individuals' differences, which, from a genetic standpoint, boils down to less than 0.5% of our DNA.

Of interest, all of the genetic variation in humans started out as a 'mutation', meaning, an 'error' in DNA synthesis, for example an adenine inserted instead of a guanine (Fig.2, right). Over hundreds of thousands of years, selection acted on individuals with that mutation, and if they were able to reproduce, the number of individuals with that mutation increased. Such allelic variation has given rise to such differences as eye color, blood type, and how quickly one metabolizes caffeine. As a matter of semantics, once 1% or greater of the population has a given mutation, the mutation is christened a 'variant' or 'polymorphism.' In other words, yesterday's mutations have become today's common variants.

Whereas the previous section focused on uncommon mutations considered to be symptomatic, this section focuses on common allelic variation that is thought to contribute to autistic characteristics in concert with a host of other genetic and environmental factors. This common type of genetic variation among humans is frequently referred to in genetics literature as single nucleotide polymorphisms, or most simply, SNPs (pronounced 'snips'), and they present in every 300–1000 bases of our genome (A, C, G or T); see The International SNP Map Working Group (2001). In sum, SNPs are small genetic differences that are not considered mutations because of their relatively high frequency in the population and the lack of associated symptomology, at least in isolation.

5.2. Relevance to Autism Research

A large number of SNPs have been associated with autism through a procedure known as Genome Wide Association Studies, or GWAS for short (Abrahams & Geschwind, 2008; Klei et al., 2012). Specifically, this procedure compares the prevalence of SNPs across a large number of individuals, both with and without autism diagnoses. The variations that appear more commonly in autistic individuals, compared to nonautistic controls, provide potential insight into the genetic etiology of the autistic phenotype (Fig 4). Despite the potential contribution of such studies, the associations are not necessarily causal, especially if key factors such as ethnic background are not controlled between the autistic and non-autistic groups (cf. Skafidas, Testa, Zantomio, Chana, Everall, & Pantelis, 2014; Behard, Jankovic, Lowe, & Geschwind, 2014; Robinson et al., 2014).

Associating autism with a number of common variants helps explain the tendency of autism to run in families (Lyll, Constantino, Weisskopf, Roberts, Ascherio, & Santangelo, 2014). In fact, the reported odds of having another autistic child is estimated at 18.7% in siblings of autistic children without an identified genetic syndrome (Ozonoff et al., 2011), potentially

reflecting both shared genes and family environment. In contrast, new mutations arising in germ cells, either through DNA replication or recombination, is not likely to reoccur, and the chance of having another autistic child would be similar to the probability in the general population.

5.3. Genetic Testing for Common Variants

Unlike single-gene conditions, there is no mainstream medical testing focused explicitly on the common variants (i.e., SNPs) associated with autism. However, at least one company, Integrigen, has developed and marketed a genetic “test,” ARISk®, that intentionally screens for a large number of the common variants associated with autism using DNA obtained from a cheek swab (Integrigen, 2016). Although the exact genes queried are not specified on the company’s website, a list of publications by researchers associated with the company gives potential insight into the genes and algorithms employed (Carayol et al., 2014; Liebaert et al., 2012). The test is being marketed as a means to postnatally identify the “risk of autism spectrum disorders in children who have signs of developmental delay, a clinical suspicion of autism, or an older sibling previously diagnosed with an ASD” (Integrigen, 2016). The site also states that the genetic results are intended to be used together with a clinical evaluation, specifically for children 48 months or younger, and is not available for prenatal testing. Particularly in light of the low sensitivity that has been associated with this test (Hughes, 2012; Liebaert et al. 2012), it is difficult to envision the test’s utility. However, given the proliferation of genetic testing, it seems quite possible that similar tests will be available in the future.

6. Perspectives on Genetic Testing and Autism

Although sequencing of the human genome was completed over a decade ago, we are still in the cradle of the genomic revolution. Identifying the genetic basis of complex behavioral diagnoses such as autism has proven challenging. Although a relatively small percentage of autism cases is associated with chromosomal variation, specific copy number variants and single gene conditions (~15–25%), none are specific to autism. The majority of cases of autism appear consistent with a multifactorial model in which a relatively large number of common variants work in concert with environmental factors. In short, established genetic testing will not determine *if* a child is autistic, but in as many as one quarter of the cases, it may provide at least partial explanation for *why* a child is autistic.

Current best practices for autism diagnosis continue to rely on behavioral assessment from a multidisciplinary team of professionals, ideally including a communication specialist such as a speech-language pathologist (ASHA, 2016; Rosti et al., 2014). Such assessments can provide critical information regarding what supports are needed to help maximize positive quality of life outcomes (Filipek et al., 2000). Although genetic counseling is not within the scope of practice for speech-language pathologists, it *is* the responsibility of the SLP to help families make informed decisions related to their child’s communication difficulties and to “discuss, evaluate, and address” related emotions (ASHA, 2016). Consequently, having a basic understanding of the potential benefits and harms associated with genetic testing for autism, especially as it relates to autistic individuals and their families, is warranted.

6.1. Parental Perspectives

Although many publications have touched on the benefits and harms associated with genetic testing more broadly, we review here five key studies that directly queried family members regarding their experience with genetic testing and autism. First, we provide a brief summary of each study followed by a synthesis of the perceived benefits and harms associated with genetic testing (see Table 2). Chen, Xu, Huang, and Dhar (2013) presented itself as the first study to directly interview parents of autistic children regarding their awareness, attitudes, and experiences with genetic testing. Of the 42 parents interviewed, approximately half had never heard of genetic testing for autism and only 12 had been through the process with their children.

Reiff et al. (2015) was the only study identified in which all the parents interviewed had completed genetic testing and received results on their autistic children. Specifically, the study conducted semi-structured phone interviews and surveys with 57 parents of autistic children who had received chromosomal microarray analysis (CMA) results, purposefully sampled to represent varied results (“pathogenic,” negative, or variant of uncertain significance). Using the same data, Reiff et al. (2017) provided a more focused analysis on parental beliefs about causality and prognosis after genetic testing.

Also focused on CMA, Xu, Mitchell, Richman, and Clawson (2016) completed face-to-face interviews with 45 parents of autistic children from North Carolina regarding their perceptions of CMA. None of the parents had undergone genetic testing. Some information was given to parents about CMA before the interview, but the nature of that information was not specified in the publication. The study was notable for the diversity of the participants in regard to household income, education, and race/ethnicity.

Instead of focusing on CMA, a study by Narcisa et al., (2012), sponsored directly by the company that designed ARISK®, assessed parental attitudes about the genetic screening of younger siblings of autistic children. They surveyed 162 parents at large (28.7% with prior genetic testing experience), with only 72 parents addressing questions related to the genetic assessment of younger siblings.

Finally, a study by Miller, Hayeems, and Bytauas (2010) conducted focus groups and semi-structured interviews with 34 parents of autistic individuals to explore their expectations regarding participation in genetic research, with an emphasis on findings of uncertain clinical significance. This study integrated interview findings from researchers as well, and it was unclear how many, if any, of the parent participants had actually received their individual results.

6.1.1. Potential Benefits—Across studies, a frequently perceived benefit of genetic testing reported by parents was that it could help answer the causal question of “why” an individual is autistic (Chen et al., 2013; Miller et al., 2010; Reiff et al., 2017; Xu et al., 2016). Of interest however, findings from Reiff et al. (2017) noted a tendency for families to incorporate the test findings into their current narrative about what caused their child’s autism: “Thus, parents’ etiological belief models proved to be highly durable, even in the face of new or conflicting information from the CMA testing” (p.1457). Related to causality,

parents in Reiff et al. 2015 reported that the discovery of a significant genetic variant can offer a tangible label for a genetic condition and help alleviate feelings of parental guilt for some individuals. Though such cases of significant genetic variation are relatively rare, when identified, parents note that such results can also help identify associated health risks, such as heart or kidney problems, which could lead to clear courses of medical intervention (Chen et al., 2013; Reiff et al., 2015; Xu et al., 2016).

Another potential benefit of genetic testing reported by parents is that significant genetic findings may help provide access to supports and services, such as early intervention (Reiff et al., 2015, Narcisa et al. 2012; Xu et al., 2016). Genetic information has also been perceived by parents as helpful in family planning, both in deciding whether or not to have other children (Chen et al., 2013; Reiff et al., 2015; Xu et al., 2016), and considering what outcomes they might expect for their current child (Reiff, 2017, Xu et al., 2016). In particular, Reiff et al. (2015) indicated that identifying genetic variants might lead to increased acceptance of a child's differences, whereas failing to find a genetic variant of significance might increase one's sense of optimism for a more positive prognosis (Narcisa et al. 2012, Reiff et al., 2017). Finally, a couple parents perceived potential in genetic testing for advancing medical knowledge, thereby increasing hope for their own child (Reiff et al., 2017) or providing some benefit to other families (Xu et al., 2016).

6.1.2. Potential Harms—As one might anticipate, potential benefits are often partnered with potential harms. Approximately one quarter of parents from Chen et al. (2013) who had experience with genetic testing for their autistic child, reported that they opposed it. One of the most commonly reported potential harms associated with parental experience with genetic testing was “no clear value” (Chen et al., 2013; Reiff et al., 2017, Narcisa et al. 2012). In addition, parents reported that awaiting results and uncertain findings can lead to confusion and anxiety (Chen et al., 2013; Reiff et al., 2017, Narcisa et al. 2012; Xu et al., 2016). Even “negative” results revealing no significant genetic variation can be misleading. Reiff et al. (2015) found that several parents who had received negative results inaccurately believed that a genetic causation had been ruled out—thus highlighting the need for genetic counseling regardless of the outcome. In contrast to the reported benefits of receiving a tangible label for a genetic condition, some parents reported being wary of giving their children a label (Narcisa et al., 2012), perhaps in part due to concerns related to stigma and the sense of predetermination/immutability that often accompanies genetic findings (Chen et al., 2013; Reiff et al., 2017). Consistent with the concept of geneticization, some parents from Chen et al. (2013) reported concern that genetic findings might lead people to ignore other potential influences on a child's development, and negatively affect how individuals perceive and interact with their child.

Whereas some parents perceived genetic findings as a way to alleviate guilt, others reported concern that unexpected genetic information may be revealed about other family members, and that such findings may lead to attribution of blame (Chen et al., 2013; Reiff et al., 2015; Reiff et al., 2017). Parents from Chen et al. (2013) also reported concern that identifying specific forms of genetic variation might have negative implications for insurance eligibility. Finally, parents within Xu et al. (2016) expressed concern about the pain and stress associated with having their child's blood drawn and noted “barriers” to the implementation

of genetic testing. Specifically, parents were concerned about the cost of the testing, transportation/scheduling issues, and their own lack of knowledge about the genetic testing under consideration.

6.2. First-person perspectives

Notably missing from the scientific literature on genetic testing and autism is first-person perspectives from autistic individuals themselves. Parent perspectives, while valuable, are likely guided by a somewhat distinct bioethical context (see Singh, 2015). What is available from autistic individuals is often published through on-line blog posts, statements via self-advocacy groups such as the Autistic Self Advocacy Network, or documented within social science research, namely disability studies. Such resources tend to highlight that autistic individuals are in the best position to judge the nature of their disability and the quality of their lives.

Whereas medical practice and genetic research tend to construct a narrative of prevention and cure around autism as a disease, many proponents within the autism rights movement view it as a form of natural neurological variation (i.e., neurodiversity) that can confer individual and societal benefits (Armstrong, 2015; Bagatell, 2010; Hillary, 2015; Hurlbutt & Chalmers, 2002; Kanazawa & Vandermassen, 2005; Ronald, Happé, & Plomin, 2005; Silberman, 2015; Sinclair, 2012; Soloman, 2012). For example, common autistic attributes such as attention to detail, an aptitude for learning new technology, and thinking outside the box have been associated with success in varied employment settings (Armstrong, 2010; Kelland, 2013; Silberman, 2015). One of the most well-known examples comes from autistic author and animal scientist Temple Grandin who has discussed how her autism has informed her research on animal behavior (Grandin, 2009).

Discussions of genetic testing elicit understandable tension between efforts to reduce human suffering and to value human variation. Grandin noted poignantly in her interview with Ira Flatow on National Public Radio in 2006, “I feel very strongly that if you got rid of all of the autistic genetics you're not going to have any scientists. There'd be no computer people. You'd lose a lot of artists and musicians. There'd be a horrible price to pay.” In short, genetic testing increases the likelihood of fewer autistic children being born, whether through parents' informed decisions not to have more children, IVF embryo selection processes, or termination of pregnancies. Although there is not current prenatal testing for autism per se, there are opportunities for genetic testing of related conditions such as fragile X, and the sequencing of fetal DNA in maternal serum during the first trimester increases possibilities for prenatal testing.

7. Recommendations

In sum, the topic of genetic testing and autism raises a number of practical, ethical, and even philosophical issues for individuals, families, and society more broadly. How then can practitioners help guide families in the midst of this complicated terrain? We highlight here three explicit recommendations for practitioners to help guide families when the topic of genetic testing and autism arises.

- First, consider sharing all or part of this tutorial as a means of providing important background information. In particular, Table 1 offers a summary of key molecular genetic information and associated genetic testing, and Table 2 offers a summary of key research on parent perceptions of the benefits and harms associated with genetic testing.
- Second, advise families to consult with a genetic counselor. Such professionals are in the best position to answer questions about the nature and accuracy of the test(s) being considered, the probability of finding a significant result, and how results may or may not change one's course of care. Together these resources will help decrease common misconceptions, such as the idea that significant genetic findings indicate immutable quality of life outcomes or that a lack of significant genetic findings indicate no genetic factors at play.
- Third, encourage individuals to seek first-person perspectives from autistic individuals about quality of life issues in general and views on genetic testing in particular. In addition to autistic individuals in one's own community, there is a growing list of books, YouTube videos, and blogs published by authors who identify as autistic⁷.

Conclusion

To recap, the present tutorial provides professionals in CSD with a basic overview of the molecular basis and parental perceptions surrounding genetic testing and autism. Based on current medical practices, genetic testing may offer direct implications in a minority of cases of autism that are associated with certain CNVs and single-gene conditions. However, the implications of genetic testing are less clear in the majority of autism cases, and genetics alone are not likely to answer the fundamental questions about how best to construct a quality life. Even when an explicit genetic mutation is identified, it may reveal relatively little in terms of the questions parents are most interested in, such as an individual child's potential quality of life (cf. DuBois & Antes, 2015; Scully, 2008). As service providers and communication specialists, clinicians are in a unique position to support autistic individuals and their families--finding ways for their perspectives and voices to contribute to the personal and societal conversations about both the potential benefits and harms afforded by genetic testing.

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⁷Actually Autistic Blogs, available at <https://anautismobserver.wordpress.com/>, provides a list of blogs written by autistic individuals that is searchable by topic

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Learning Outcomes

Readers will a) gain an interdisciplinary introduction to the landscape of genetic testing and autism, b) become familiar with the different forms of genetic testing currently available, c) be able to highlight potential benefits and harms associated with genetic testing, and d) be able to offer three explicit recommendations for individuals and families considering genetic testing related to autism.

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Figure 1.

Schematic of a cell with chromosomes in the nucleus. One enlarged chromosome is shown to be composed of tightly wound DNA that is made up of A-T and C-G base pairs.

Figure 2.

Schematic of meiosis. An example of a pair of chromosomes: a maternally inherited chromosome (white) and a paternally inherited chromosome (black) in the individual making germ cells, also known as gametes. The first step of meiosis is DNA replication where an exact copy of each chromosome is made. During replication, variants can occur such as the introduction of an A instead of a G (right) in the newly synthesized strand of DNA. This results in a base substitution. The cell that receives the bottom strand will have a SNP at that position. Recombination between the two chromosomes leads to genetic diversity. However, misalignment of the chromosomes during recombination can lead to duplication or deletions of DNA segments, which are the source of copy number variants. Also note that incomplete separation or partitioning of the chromosomes during meiosis is what leads to an extra chromosome, as in the case of Down syndrome.

Figure 3.

Misalignment of chromosomes during recombination can lead to duplication or deletions, which are the source of copy number variants. A) typical alignment of the maternal and paternal chromosomes during meiosis. Very similar repeats are shown by the arrows: their unique identity is indicated by color. B) atypical chromosome misalignment caused by the repeats mismatching during meiosis. The recombination event is shown by the blue vertical bar. The resulting chromosomes are shown on the right. The duplicated region is shown in the blue circles. Note that the bottom chromosome is deleted for this region. C) Shown here are 3 alleles with 4 copies, 2 copies or one copy, respectively, of a specific region (stippled). Without more information, it is unclear whether the stippled region was duplicated in alleles A and B or deleted in Allele C.

Figure 4.

Schematic showing how association tests work in a simplified 4-allele system. The four alleles are found distributed in a significantly different way in the autistic group (right) compared to the control group (left). Over-representation of allele 1 in the autistic population suggests an association with autism. Further tests would need to be done to show causation.

Table 1

Overview of the four types of genetic variance discussed in this tutorial including the associated background information, related autism research, and related genetic testing

Form of Variance	Background Info	Relevant Autism Research	Related Genetic Testing
Chromosomal Variation	Chromosomes Meiotic division	Studies have documented an increased prevalence of autism in children with Down syndrome or variation in sex chromosome number.	Quad screen Nuchal translucency measurements
Copy Number Variants	Meiotic recombination	CNVs are associated with 7–18% of autism cases, in particular 1q21, 2q37, 3q29, 7q11.23, 15q11-13, 16p11.2, 17q12, & 22q11.2.	Chromosomal microarray
Single Gene Conditions	DNA Base pairs Mutation	Rare genetic variants account for only a small number of cases; none have been linked exclusively with autism. Some have significant medical complications.	DNA Sequencing
Common Polymorphisms	Alleles Single Nucleotide Polymorphisms	A large number of SNPs appear more prevalent in autistic individuals compared non-autistic individuals. May explain the tendency of autistic traits to run in families.	Currently no mainstream testing available, but at least one company has developed and marketed a genetic “test” that intentionally screens for a large number of the common variants associated with autism (Integrigen, 2016).

Table 2

Summary of parental perceptions of benefits and harms associated with genetic testing based on five key studies

<u>Potential Benefits</u>
• Can help answer the causal question of “why” an individual is autistic
• Can offer a tangible label for a genetic condition
• Can help alleviate feelings of parental guilt
• Can help identify associated health risks
• May help provide access to supports and services
• May provide helpful information for family planning
• Finding a significant genetic variation may lead to increased acceptance of a child’s differences
• Might help rule out negative prognostic indicators
• May help advance medical knowledge
<u>Potential Harms</u>
• May offer no clear value
• Awaiting results and interpreting findings can cause confusion and anxiety
• Findings of no significant genetic variation can be misleading
• Being labeled with a genetic condition can elicit stigma and a sense of immutability
• Genetic findings can lead to unexpected genetic knowledge about other family members and potential attribution of blame
• Genetic findings may have negative repercussions for insurance eligibility
• Pain and stress associated with the test procedure itself (e.g., blood draw)