A Systematic Review of Emotions, Attitudes, and Decisions Regarding Genetic Tests Associated With Autism Spectrum Disorders

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1. Introduction

Autism Spectrum Disorders (ASD) represent a range of conditions characterized by social, communication, and behavioral impairments (Miles, 2011). Strong evidence suggests that ASD is among the most heritable neurodevelopmental conditions, with a high prevalence (1 in 68 children) in the U.S. (Vande Wydeven et al., 2012; Developmental DMNSY and Investigators P., 2014). ASD within a family is associated with an increased recurrence risk of 2 - 9% for one child diagnosed with ASD and 25 - 35% if two or more children are affected in a family (Ozonoff et al., 2011; Wydeven et al., 2012).

Until recently, no single laboratory test could diagnose ASD and the recommendations for clinical tests varied widely. Recently, a relatively novel technology providing higher resolution and better diagnostic yield than traditional tests (Shen et al., 2010) has become available, namely *chromosomal microarray technology* (CMA). CMA is now recommended as the first-tier test for identifying ASD by the American College of Medical Genetics and Genomics) as well as by the International Standard Cytogenetic Array Consortium (Schaefer et al., 2013; Miller et al., 2010).

CMA has the potential to identify ASD etiology, promote early diagnosis, and help develop timely treatment plans (Johnson et al., 2011). With current technology, it is estimated that a specific etiology can be identified in 30-40% of individuals tested (Schaefer et al., 2013). However, similar to other genetic tests, CMA for ASD might involve a number of ethical, legal, and social implications, such as discrimination and insurance concerns (Marchant and Robert, 2008). The scientific literature has extensively documented several psychological factors, such as stronger perceived disease risk, greater anxiety over the disease, or urge for emotional relief (Jones and Clayton, 2012b; Marchant and Robert, 2008; Lerman et al., 1997), as influencing the uptake of genetic tests, in general. However, psychological factors associated with decisions regarding testing for ASD remain relatively unexamined.

Decisions to undergo autism genetic testing may be more complex than decisions associated with other conditions because (i) ASD have a multifactorial etiology (Silvia et al., 2014) (i.e., there may be more than one gene involved); (ii) the current technology yields a relatively low detection rate (compared with single-gene disorders, such as Down syndrome and cystic fibrosis); (iii) the tests are unable to determine disease severity (Jordan and Tsai, 2010), and (iv) the tests lack evidence of clinical utility (Jordan and Tsai, 2010; Maya et al., 2010). Given these test constraints, ASD-affected people, their families, and at-risk populations might experience a host of unique psychological factors associated with the decision to undergo genetic testing for the disorders (Marchant and Robert, 2008; Reiff et al., 2012). The purpose of this review, therefore, was to (i) systematically synthesize a decade of empirical literature (2003-2014) regarding the emotional factors, attitudes, and intention toward autism genetic testing (including Fragile X, Karyotype, and chromosomal microarray technology tests), and (ii) assess the methodological quality of the reviewed studies.

2. Methods

2.1 Search strategy & inclusion criteria

Employing Garrard's Matrix method (Garrard, 2013), the review proceeded in 3 steps: 1) searching four primary OVID databases including MEDLINE (OVID), EMBASE (OVID), PsycINFO (PROQUEST), and CINAHL (Ebsco), using the search terms "autism genetic testing", "genetic testing for ASD"; labels for the three first-tier tests ("Fragile X", "Karyotype", and "CMA" for ASD"); "cognition" ("attitudes" or "perceptions"), and "decision-making" ("intention"); 2) assessing whether studies met our inclusion and exclusion criteria, and 3) conducting backward and forward searches in the Scopus database.

The studies included in this review met the following criteria: (a) reported empirical data related to emotional factors, attitudes, and decisions for undergoing genetic testing; (b) were published after 2003 (the year the International HapMap Project was completed); and (c) published in English. Studies were excluded if they: (a) focused on emotional factors, attitudes, or decisions unrelated to undergoing autism genetic testing (e.g., people's attitudes/decisions *after* obtaining the genetic test results, as well as treatment decisions, clinical decisions, or reproductive decisions); (b) focused on health care providers' emotions, attitudes, and intention regarding autism genetic testing; and (c) reported reviews, abstracts, brief reports, commentaries, or letters to the editors. We also did not include articles that investigated the psychological wellbeing and coping strategies of having a child or children with genetic disorders. In addition, we excluded studies that only examined post-test psychological states, such as worries about the test results and anxieties over carrying faulty genes.

2.2 Extraction & synthesis

Appendix A presents the matrix of reviewed studies with data on first authors, targeted genetic tests, recruitment criteria and sample source, sample size, study design, pre-test counseling, as well as test uptake rate. Appendix B displays each study according to the factors examined in this review, namely, emotions, attitudes, and intention of undergoing genetic testing. To ensure the reliability of data extraction, two of the authors independently synthesized data from four of the 17 reviewed studies (~ 23%). A Cohen's kappa of .80 indicated adequate inter-rater reliability (Landis and Koch, 1977), and differences were resolved before analyses.

2.3 Methodological quality assessment

Five criteria assessed each reviewed study's methodological quality: sample size, response rate, reporting of data validity/reliability, and theory use for quantitative studies. For qualitative studies we assessed sample diversity, data saturation, trustworthiness, researcher's disclosure, and application of theory. All studies were assigned a methodological quality score (MQS). Maximum scores were 7 and 6 points, for quantitative and qualitative studies, respectively.

3. Results

3.1. Study characteristics

From 2,747 reports obtained in the initial searches, 17 reports formed the final sample after eliminating duplicates and screening according to the inclusion/exclusion criteria. Although only studies published since 2003 were eligible for inclusion, all 17 reports were published after 2005, with 65% (n=11) appearing in the last five years. The majority (76.5 %; n=13) were conducted in the U.S. and the remainder (n=4), in Australia.

Two studies specifically assessed autism genetic testing. Chen and colleagues (2013) explored awareness of and attitudes toward autism genetic testing among 42 parents of children with at least one ASD-affected child.

Narcisa et al. (2012) conducted a web-based survey of 162 parents of ASD-affected children. Most reviewed studies (88.2%, n = 15) examined participants' perspectives on genetic testing for Fragile X syndrome (FX): 60% (*n*=9) examined attitudes or test intention regarding carrier testing (58.8%, *n*=7) or prenatal screening (11.8%, *n*=2). Three studies (20%) focused on newborn screening and 3 studies (20%) investigated carrier, prenatal, and newborn screenings.

Most studies employed female participants (70.1%, *n*=12), did not specify the carrier or non-carrier status of the samples (53%, *n*=9), and were conducted among non-affected populations. Only six studies (35.3%) were conducted with participants who were FX carriers or had children affected with genetic disorders, and 2 studies (11.7%) had mixed populations, including participants who were both FX carriers and non-carriers. Altogether, 41.2% of the studies (*n*=7) recruited samples from clinical settings,
5 studies (29.4%) used samples from the general public, 3 studies (17.7%) employed participants from universities or national research centers, and two studies (11.8%) used community-based samples.

Study samples ranged in numbers from 12 to 29,103 participants ranging from 21 to 89 years of age. Thirteen studies (76.5%) provided detailed information on participants' ethnicity and eight studies (47.1%) had Caucasians as the major ethnicity in their samples. Five studies (29.4%) detailed participants' household income. Seven (41.2%) studies employed a qualitative design, ten studies (58.8%) employed questionnaires, and one study included a mixed methods approach. Altogether, three (17.6%) studies mentioned adopting theory.

3.2 Emotions

Altogether 12 emotional constructs were targeted for study, among the reviewed reports. Most studies (72.8%) were conducted prospectively, (e.g. asking the participants how they might feel when they take the test), but three (27.2%) studies examined participants' emotional responses retrospectively, after having taken the test. Below we present the emotions examined, organized by frequency of occurrence.

3.2.1. Anxiety, fear and worry —Anxiety was the most frequently reported emotion (29.4%, *n*=5). Christie et al (2013) claimed that some mothers felt anxious regarding possible test outcomes for newborn screening for FX syndrome, although the authors found no variability by social economic status or educational levels. Conversely, Metcalf et al. (2008) identified a reduced anxiety score for women who tested for FX syndrome. Worry was mentioned in three studies (17.6%). As Bailey et al. (2011) discussed, a substantial portion (44.4%) of study participants did not want to screen for FX, because it would cause them to worry. Similarly, Skinner and his colleagues (2011) found that parents worried about how others might treat them and how they might treat their potentially affected children. Fear emerged in two (11.8%) studies. The specific kind of fear mentioned included fear of lacking feedback with regard to the test, fear of being discriminated, and fear related to problems with health insurance (Anido et al., 2007; Johnson et al., 2008). As Chen and colleagues (2013) pinpointed, a few parents of children with ASD mentioned they feared their life insurance would be suspended, or they would have to pay more premiums, if the genetic tests were positive.

3.2.2. Uncertainty — Uncertainty was identified in 5 studies (29.4%) as salient. For instance, parents in a study by Christie et al. (2013) used expressions such as "horrible" or "grief and initial confusion" to describe how they might feel if their newborns' test results were positive.

3.2.3. Feelings about the parent-child bonding — In three studies (17.6%), parent-child bonding was identified as an emotional factor associated with genetic testing. Christie et al. (2013), found that most respondents (84%) believed a positive screening result would not affect bonding with their newborns.

The remaining emotions were each discussed in a single study (5.8%) and most of them had a negative impact on participants' attitudes and intention to undergo genetic testing. For instance, Pastore and colleagues (2008) reported three emotional responses, i.e., *feeling regretful* or *feeling angry* about not learning sooner that FX might be related to their infertility and *feeling upset* if FX ran in the family.

3.3. Attitudes

Eight studies investigated participants' attitudes toward undergoing genetic testing. Both positive (47.1%, *n*=8) and negative attitudes (29.4%, *n*=5) were reported. Eight studies reported positive attitudes and listed participants' perceived benefits or positive outcomes pertaining to the test.

These perceived benefits or outcomes can be placed into five categories: (1) testing helps to ascertain one's carrier status (reported in 5 studies); (2) testing helps making reproductive decisions (*n*=5); (3) testing helps advance research (*n*=4); (4) testing can facilitate early diagnosis, intervention, and timely treatment (*n*=4); (5) testing may prepare parents for the birth of an affected child (*n*=3).

Six studies discussed negative attitudes, perceived barriers or concerns related to the uptake of a test. One specific barrier was perception of potential harm caused by undergoing the test (mentioned in 5 studies); another barrier was concern related to the characteristics of the current tests, such as their reliability (*n*=2). Concerns related to the value of the test were documented as barriers (*n*=2), as well as concerns about the societal implications of the genetic test (*n*=2). Issues related to eugenics and dilemmas for people with disabilities and their families were two specific worries identified (Archibald et al., 2009; Chen et al., 2013). Lastly, concerns related to religious and cultural beliefs were also documented in one study. Chen and colleagues (2007) mentioned that religious and cultural influences (e.g., the notion of destiny) played a role in Asian parents' negative attitudes towards genetic testing.

3.4. Intention to undergo genetic testing

Nine studies (52.9%) measured participants' intention to test and provided their reasons for accepting or declining the tests. Perceived benefits, mentioned in nine studies as a reason to undergo testing, related to early diagnosis, better preparation, and informed reproductive decisions. Most women (91.7%) agreed to participate in newborn screening tests in Bailey et al.'s study (2013). Parents in that study mentioned that knowing the baby's FX carrier status could help them prepare better for possible challenges. Perceived risk motivated intentions to test in four studies. For example, participants in the studies by Bailey et al. (2011) and Skinner et al. (2003), who believed that FX screening would pose minimal risk, were supportive of undergoing the tests.

Subjective norms were identified by three studies as motivating intention to test. Chen and colleagues (2013) found that recommendations from health care providers and influence from family members could affect participants' decisions regarding testing. Removal of perceived barriers also were identified in three studies as reasons for testing. For example, Metcalfe et al. (2008) mentioned that since testing was free of charge (in Australia?), the mothers in their study would like to undergo carrier screening for FX syndrome.

Perceived barriers was the most frequently cited reason for *not* having the intention to test (*n*=7).These perceived barriers included inconvenience, problems with the current status of genetic testing, lack of relevance, confidentiality issues, bad timing, concerns related to the genetic diseases, and cost. The second most cited reason (*n*=5) was the negative emotions associated with the test. These negative emotions included "do not want to worry," "fear," "lack of trust," and "feeling uncertain." (Skinner et al., 2003; Bailey Jr et al., 2013; Metcalfe et al., 2008; Johnson et al., 2008). Other emotions mentioned were fear of lack of feedback, fear of absence of follow-up, and ostracism (Johnson et al., 2008).

3.5. Methodological Quality Scores (MQS)

The average MQS for the 17 reviewed studies was 2.56 (*SD*=1.8; maximum score=7) for the quantitative studies and 3.25 (*SD*=1.4; maximum score=6) for qualitative studies. Altogether, 60% (6/10) of the quantitative studies utilized large samples (>300), but only one study (10%) reported response rates. Among the 10 quantitative studies, two reported data validity (content validity) but none discussed data reliability. Also, none of the quantitative studies reported utilizing a theoretical framework. Among the 7 qualitative studies reviewed, 5 examined homogenous samples and 3, heterogeneous samples. Most qualitative studies (87.5%) provided information on sample diversity, data saturation, trustworthiness, researchers; disclosure, and use of theory in analyses. While researcher disclosure is important in qualitative studies, only one (12.5%) reported the author's positionality.

Discussion

In our systematic review, we found that feelings of anxiety, fear, and worry were the most prominent emotions around testing and both positive and negative attitudes would affect test intentions. In particular, perceived benefits of the test were associated with intention to test and perceived barriers was the biggest reason for not having the intention to test. We found the majority of studies reporting participants as having positive attitudes toward genetic testing for ASD and FX syndrome. In addition, the studies documented a high acceptance rate, suggesting participants' willingness to undergo the tests. This finding was consistent with other studies documenting that the general public holds positive attitudes toward genetic testing for various conditions.

However, as pinpointed by Bailey et al. (2011), the stage of the participants' life in which genetic testing is offered, is an important factor that might influence attitudes and decisions to test. Considering the impact of stages of life on testing decisions, screening might need to be offered multiple times and with varying approaches to facilitate better informed decisions.

Overall, we identified the need for future research examining associations between emotional factors and intentions to undergo ASD genetic testing, particularly, among ASD-affected populations. In addition to a lack of literature in this research area, we identified a weaknesses in the overall quality of the existing studies which suggests the need for increased methodological rigor in this body of knowledge.

This review's strength lies in it being the first to systematically assess the emotions, attitudes, and intentions regarding autism genetic testing among at-risk groups and the general population. Despite its contributions, this review has important limitations. First, although we conducted an exhaustive search for relevant reports, we might have inadvertently overlooked publications due to the constraints of the search terms. Second, we limited the search to empirical studies published in English; therefore, selection bias might have occurred and excluded studies published in other languages.

Overall, we found that a limited number of quantitative studies reported information on data validity, data reliability, and response rates. This omission leaves readers uncertain regarding the internal and external validity of the data and of the studies' findings. Although qualitative studies should provide information on indicators of quality, only one study provided a "researcher disclosure"— one of the most important indicators of trustworthiness in qualitative studies (Lincoln, 1985).

Second, with the exception of two studies, the majority did not utilize a theoretical framework. Recently, genomics authorities such as the National Human Genome Research Institute, have recommended expanding existing theories for better understanding of the factors that might affect people's intention to undergo genetic testing (Wade et al., 2012; Sagi et al., 1992). Future research in this area should not only employ existing theories to test their adequacy, but also make contributions to refining these theories and/or developing new ones.

Third, this review documents the relative neglect of emotional factors as focal variables in studies of genetic test uptake. One reason for this oversight might be the lack of benchmarks or criteria for assessing emotional factors related to the uptake of autism genetic testing. Compared to a significant body of research evaluating emotional responses to genetic tests for Huntington's Disease or inherited cancers (Schlich-Bakker et al., 2006a; Pasacreta, 2003; Meiser and Dunn, 2001; Broadstock et al., 2000) there are no similar studies of emotional responses to autism genetic testing. Hill and colleagues conducted a systematic literature review exploring psychosocial aspects related to the uptake of FX screening and mutation frequency (Hill et al., 2010b). Although this review demonstrated psychosocial variables were associated with screening for FXS, it was not designed to explore the emotional factors and attitudes that determine participants' decisions associated with FX test decisions.

Furthermore, this review also detected lack of variability in the studies' samples, given that almost half of the samples were predominately comprised of Caucasian participants. Among the limited studies that recruited ethnic minorities, variations in attitudes between Caucasian and other ethnic groups were observed. As Skinner et al (2011) identified, African American participants tended to be less likely to accept screenings for FX compared with their Caucasian counterparts. Johnson and colleagues (2008) purposely recruited Native Americans and African Americans in their study and contended that these minority groups appeared to be more hesitant to undergo genetic testing. These findings are in line with recent research on attitudes toward genetic testing conducted in the U.S. that showed variability in viewpoints among ethnic minorities. (Hudson, et al, 2004) Future research on autism genetic testing should consider investigating a wide spectrum of ethnicities to specifically address its role, and that of culture in general, in genetic-related viewpoints.

As the availability of genetic tests for ASD increases and families face increasingly complex decisions related to genetic testing, the findings from this review suggest important directions for research, education, and counseling of both affected and non-affected populations.

Specifically, more studies are needed to (i) examine emotions related to the intention to undergo genetic testing for ASD among affected populations; (ii) integrate the under-investigated emotional factors into theories explaining genetic test decisions associated with ASD; and (iii) evaluate moderation effects of demographic factors. Addressing these dimensions is crucial for achieving a clearer understanding of parents' intention with regard to genetic testing for ASD for ASD-affected families and communities in various settings and geographical locations.

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Figure 1 Flowchart of selection process