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Reference:

Hens Kristien, Peeters H., Dierickx K..- The ethics of complexity : genetics and autism, a literature review
American journal of medical genetics: part B: neuropsychiatric genetics - ISSN 1552-4841 - 171:3(2016), p. 305-316
Full text (Publishers DOI): http://dx.doi.org/doi:10.1002/ajmg.b.32432

The ethics of complexity. Genetics and autism, a literature review.

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Running title: genetics and autism, a literature review

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Key words

Ethics, autism, genetic counceling, research ethics, reproduction, review

Abstract

It is commonly believed that the aetiology of autism is at least partly explained through genetics. Given the complexity of autism and the variability of the autistic phenotype, genetic research and counselling in this field are also complex and associated with specific ethical questions. Although the ethics of autism genetics, especially with regard to reproductive choices, has been widely discussed on the public fora, an in depth philosophical or bioethical reflection on all aspects of the theme seems to be missing. With this literature review we wanted to map the basic questions and answers that exist in the bioethical literature on autism genetics, research, counselling and reproduction, and provide suggestions as to how the discussion can proceed. We found 19 papers that fitted the description of 'bioethics literature focusing on autism genetics', and analyzed their content to distill arguments and themes. We concluded that because of the complexity of autism, and the uncertainty with regard to its status, more ethical reflection is needed before definite conclusions and recommendations can be drawn. Moreover, there is a dearth of bioethical empirical studies querying the opinions of all parties, including people with autism themselves. Such empirical bioethical studies should be urgently done before bioethical conclusions regarding the aims and desirability of research into autism genes can be done. Also, fundamental philosophical reflection on concepts of disease should accompany research into the etiology of autism.

Introduction

Autism and autism spectrum disorder (ASD) are concepts that are in flux (Verhoeff, 2013; Kenny et al., 2015). Some decades ago, the diagnosis was invariably connected with intellectual disability. Today, autism is considered a spectrum condition, but, as Waltz argues, "no agreement has been reached about even the most basic issues, such as causation." (Waltz, 2013). A diagnosis of autism is done through behavioral observation, ideally by a multidisciplinary team. In the most recent version of the DSM, DSM-V, the following behavioral characteristics are described: persistent deficits in social communication and social interaction across multiple contexts and restricted, repetitive patterns of behaviour, interests, or activities (American Psychiatric Association, 2013). Several theories explaining this behavior have been suggested. The most well-known is the *theory of mind* hypothesis, which states that autistic individuals lack a fully functioning theory of mind, and hence have difficulties in assuming the perspective of others. The *weak central coherence* thesis states that persons with autism have a detail-focused processing style but may fail to see the whole and therefore focus on details, even if they are irrelevant for the whole. The *weak executive function* thesis states that individuals with autism have problems planning and organizing and keeping track of several activities at the same time (Barnbaum, 2008). Recently, the *intense world* theory postulates

that autistic individuals have hyper functioning amygdalae, leading to the autistic's brain extreme reaction to stimuli, and hence to multiple deficits in the ability to process sensory information in a modulated way (Markram et al., 2007).

As of today no single explanation for the etiology of autism exists, although the original view that autism is as a psychogenic disorder is now considered obsolete. For quite some time is has been acknowledged that autism is at least partially genetic. Early evidence for this was the association with particular genetic syndromes and the high heritability of autism that could be derived from the larger concordance observed in monozygotic versus dizygotic twins. Recent advances in technology have resulted in increasing knowledge about the genetic causes of ASDs. Known variants conferring susceptibility include genomic copy number variants (CNVs) and sequence variants (Ronemus et al., 2014; Chung et al., 2014; Sebat et al., 2007). These represent a spectrum of *de novo* and inherited variants with different effect sizes ranging from high penetrance as close to the large effect of a mutation in a monogenic disease, to a small risk variant in a polygenic or multifactorial condition. The latter is on its own useless for risk prediction in an individual. Besides variation in the DNA code, DNA methylation, chromatin modification and other epigenetic modifications seem to play a role. In addition, some studies estimated 10-20% of the etiologic factors for ASDs to be of non-genetic origin, e.g., perinatal problems (Kolevzon A et al., 2007), intra-uterine testosterone levels (Auyeung et al., 2009; Baron-Cohen et al., 2015), immune dysfunction (Goines and Van de Water, 2010), pesticides (Roberts et al., 2007), in utero exposure to medication (Bromley et al., 2013; Rai et al., 2013), alterations to the gut microbiome (Mayer et al., 2014), and many others as reviewed by Herbert (Herbert, 2010). Also non-biological environmental factors as the social environment may contribute to the presence of ASDs. Cultural expectations also influence whether specific characteristics are thought to be different or aberrant (Norbury and Sparks, 2013).

The fact that the aetiology of autism is so complex calls for adequate genetic counselling to help families understand genetics and inheritance patterns (McGrath et al., 2009; Mercer et al., 2006). However, genetic counselling for ASD is hampered by the large phenotypic and genetic heterogeneity. In particular the genetic risk variants are currently challenging for clinical geneticists because they are often inherited from a parent without a diagnosis of ASD and lack phenotypic specificity. In the absence of a genetic cause, proband specific- or family specific characteristics might be indicative for a certain underlying genetic mechanism. In this respect it is important to assess syndromic versus non-syndromic ASD, sporadic versus familial ASD and ASD with or without intellectual disability/developmental delay.

One of the difficulties in understanding autism is that the concept itself is vague. In fact, philosophers and clinicians question whether there really is one common characteristic that can be found in all

autistic people, and that can be considered as the 'essence' of autism (Cushing, 2013). Also, the status of autism is being discussed. Many people, some with the diagnosis of autism, claim that autism is not a disease or a disability, but rather a difference that has both negative and positive sides. In this respect, the question of the desirability of genetic research and the aim of such research (cure or prevention) in the field of autism has been extensively discussed on the public fora. This has led to a polarized debate with seemingly irreconcilable viewpoints as expressed by some parents of autistic children, and members of the neurodiversity movement (Waltz, 2013).

Bioethics is the field of study that reflects on medical advances and practices. Genetics is one of the topics that has gained much attention from bioethicists. They have reflected on the task of genetic counsellors, the extent and aim of genetic testing, the aim and conditions for genetic research and whether and which reproductive options are ethical. With regard to autism genetics, many questions are still open and bioethics literature on the topic is scarce. What is the aim of autism research? Should autism be prevented or cured? How to ethically conduct research in the field of autism? Which reproductive options should be available for reproducers with family members with a diagnosis of autism?

Although autism and autism genetics have been widely discussed on the public fora, an in depth philosophical or bioethical reflection on all aspects of the theme seems to be missing. With this study we wanted to map the basic questions and answers that exist in the bioethical literature on autism genetics. We found that indeed such literature is scarce and that to adequately answer existing challenges, a fundamental reflection on the impact of the complexity of autism is needed. In the rest of this paper we will use the term *autism* to refer to the spectrum of conditions under the heading of Autism Spectrum Disorders in the DSM-V. We will use both the terms autistic persons and persons with autism, as some individuals may prefer the former and others the latter (Pellicano and Stears, 2011; Kenny et al., 2015).

Methodology

To find the relevant literature, we used the query "ethics AND (autism OR ASD OR autism spectrum disorder) AND (genetics OR genome)". We limited our search to papers from 2000 up till 18/12/2014. Databases queried were PubMed, Web Of Science, Embase, Psychinfo, Sociological Abstracts, Philosopher's index. We left out papers specifically focusing on one syndrome associated with autism, such as Fragile-X. After this initial search, we read the abstracts and kept all papers that had either 'ethics' and 'autism' in their abstract. We also kept only papers that were bioethical in nature, either in the tradition of empirical bioethics or theoretical bioethics. After reading the resulting papers, two papers were not included after reading, as they discussed general principles rather than

applying them to ASD specifically (Miller et al., 2012a, 2012b). For that reason, also a paper discussing the establishment of a neurological-psychiatric biobank was left out after reading (Molnar and Bencsik, 2006).

Results

General

We found 19 papers that fitted the description of 'bioethical literature focusing on autism genetics'. An overview is provided in table 1. Of these 19 papers, 12 were published in a medical journal, whereas 7 were published in a journal on ethics, philosophy or law. Five papers were studies in empirical ethics, of which 3 where qualitative studies (2 interview studies and one study of research papers), and 2 were surveys. 14 papers contained ethical analysis. 11 papers had as a main focus on genetic research ethics, five dealt with genetic testing and counseling and three focused specifically on reproductive ethics.

Autism research

Aim of the research

Aims of genetic research of autism as mentioned in the papers are the fact that research will provide *clues in molecular pathways*, so that infants at risk can be detected before signs of autism emerge, in order to allow *for early intervention* (Pellicano and Stears, 2011). Better understanding of the etiology of autism will also lead to more *effective treatments* (Pellicano and Stears, 2011; Marchant and Robert, 2008; Gershon and Alliey-Rodriguez, 2013), such as *pharmacogenetic treatments* (Marchant and Robert, 2008). Understanding genetic variants can help *to better understand potential environmental, demographic and behavioral factors* that affect autism development and risk (Marchant and Robert, 2008). Also, understanding the correlation between genetic variants may be used *to classify subtypes of autism* (Marchant and Robert, 2008). It may also help *delineate disease versus non disease status of autism traits* (Walsh et al., 2011). Research may help to better understand whether autism can be adequately defined by a complex set of common biological pathways or is better conceived as a heterogeneous collection of disparate entities, but whether one considers autism as one condition or different conditions can also influence the interpretation of research findings (Miller et al., 2010). With regard to the aim of research to 'cure' an individual, Perry mentions the fact that being cured from autism, should this be possible, will change the identity of the (especially adult) individual. She states that this may be undesirable, as autism could be considered an important part of one's identity (Perry, 2012). In this respect, Walsh et al. state that research should focus on those forms of prevention, cure and amelioration that protect the positive

aspects of autism while working against the negative. They question whether, in the context of autism, to make people fit in more with specific cultural norms really is an important research goal (Walsh et al., 2011).

Return of results

Eight papers out of 19 focus specifically on the return or results in autism research, of which the majority were papers describing empirical studies. Of these papers, Hayeems and colleagues did not focus on the specifics of autism, but use a survey of autism and cystic fibrosis researchers as a way of studying the opinions of researchers on the issue of return of research results in general. They state that such results should be returned, if they are clinically relevant, but also claim that the clinical significance of research results is influenced by both scientific as well as contextual factors (Hayeems et al., 2011). Miller et al found in an empirical study that genetic research results that could explain the cause of autism warrant disclosure to identify and manage reproductive risk. They state, however, that there is a risk that researchers and participants may have different theories about the role of genetics in autism (Miller et al., 2010). Also Tabor and Cho mention the danger that researchers may overstate causality (Tabor and Cho, 2007). But they also note that the complexity of autism genetics and the uncertainty of the meaning of findings could also be an incentive for further participation in research (Tabor et al., 2011).

In empirical research by Tabor et al, parents quoted the hope that return of genetic results would lead to some direct clinical benefit, such as better intervention and services (Tabor et al., 2011). However, in an investigation on the ethics of autism results in low and middle income countries, Daley et al. state that such findings may, in these countries, lead to less support and services, as some schools would use a diagnosis of autism as a justification for removal of a child, stating that they are not trained to work with such children. Also, a diagnosis may reduce marriability in cultures where arranged marriages are common (Daley et al., 2013; Gershon and Alliey-Rodriguez, 2013). Other negative consequences of the feedback of return of result are the psychological impact of genetic results, including blame, guilt and fault, worry, stress, fear, and depression. (Tabor et al., 2011; Marchant and Robert, 2008; Scherer and Dawson, 2011). Such knowledge may be unwanted by siblings and adults without a diagnosis of ASD (Chen et al., 2003) and whether or not there is a responsibility of communicating findings to other family members is an open question (Marchant and Robert, 2008). The potential misuse of this information by third parties and the impact on future employability or insurability is mentioned in two papers (McMahon W.M. et al., 2006; Marchant and Robert, 2008). However, in a survey of 158 parents of autistic children, Baret and Godard found that the majority of participants did not perceive a negative impact regarding the reception of research results and did not have unrealistic expectations (Baret and Godard, 2011). Another potential

consequence of receiving and knowing genetic research results is that it can influence reproductive planning. In the interview study by Tabor et al parents think such information is good to know, but they also believe that the possibility to make reproductive decisions based on information about autism genes is potentially harmful for their children, other children and society (Tabor et al., 2011).

Ethics of how research is performed

With regard to informed consent and the question how to inform participants, authors thought it necessary that researchers clearly state their research goals (Pellicano and Stears, 2011) and also communicate the limits of what is known (Scherer and Dawson, 2011). Marchant and Robert mention that as the field and the condition is complex, this may make the consent process complex (Marchant and Robert, 2008). Researchers should also make clear how and if their results are generalizable (Tabor and Cho, 2007). With regard to the use of microarrays to study autism genes, Tabor and Cho state that the use of such arrays must be made explicit in the consent, and that, as array findings require validation on genomic DNA, the way in which people with interesting results are recontacted must be well thought through, as this may alarm them (Tabor and Cho, 2007). Also, if samples are stored for future use, this must be mentioned in the consent (Marchant and Robert, 2008). The information in the consent must be suitable for lay audience, including individuals with autism and intellectual and language disabilities. Hence, it should reflect an understanding of how individuals with autism process information (Scherer and Dawson, 2011). As participants are often children, their assent should in principle be sought. However, some children may not be capable of assent: Chen et al. state that what may appear to be dissent to participation may be a reflection of fear of anxiety rather than a refusal to continue research participation (Chen et al., 2003). Perry questions the limits of parental consent in the light of the genetic identity of the future adult: as autism is chronic, pediatric interventions to test treatments ought to consider the future identity of the individual. She questions whether parents can actually consent to interventions that may influence this adult identity (Perry, 2012).

Genetic autism research often implies that family members are also asked to participate in the research. Chen argues that only enrolling families with children with autism is unfair, but also enrolling healthy siblings in such research may be unfair. Such siblings are enrolled because they are considered as ‘higher risk’, but the categorization of these siblings as such is not yet universally accepted. Moreover, there is a risk of stigma for these siblings if they are enrolled because they are considered as higher risk. (Chen et al., 2003). It may also be better to recruit family members through participants, so that they are not directly contacted by researchers, as this may violate their privacy (McMahon W.M. et al., 2006).

With regards to risks and harms that research may cause, parents in the interview study of Tabor mention the stress of blood draws and the fact that this takes up time of families that already are heavily occupied with the care of a child with challenges (Tabor et al., 2011). Chen et al mention the fact that it may be difficult for these children to sit still for brain scans. They state that therefore sedation may be approvable for brain imaging studies for children with autism, but not for the children that are used as controls (Chen et al., 2003). Because of the specifics of dealing with children with autism, providing training or using staff experienced with children with autism should be considered (Tabor et al., 2011), but skilled professionals are often unavailable in low and middle income countries (Daley et al., 2013).

Input of affected parties

Autism research affects parents and individuals with autism. It is therefore imperative that there is systematic input of the community affected by autism (Walsh et al., 2011) , and of empirical research on the opinions on genetic testing with ASD families and ASD individuals (Scherer and Dawson, 2011), and, in the context of low and middle income context, collaborative partnership with local organizations (Daley et al., 2013). Pellicano and colleagues describe three fundamental principles in this partnering: there should be an open acknowledgement of the inevitability of disagreement. There should also be an acknowledgment that key research participants have a disadvantage in the dialogue with respect to the researchers, because they may lack scientific knowledge, and reasonable adjustments should be done to the nature of the dialogue to respond to that disadvantage. Also, the relative impact of research on the life experience of the different partners in the process should be acknowledged (Pellicano and Stears, 2011).

Genetic testing and genetic counseling

The fact that autism may be caused by genetic and/or environmental factors make risk communication in genetic counseling complex (McMahon W.M. et al., 2006; Tabor and Cho, 2007). Recent discoveries in relation to autism genetics have caused a shift in the practice of genetic counseling: before, genetic counseling consisted of a risk calculation based on family history, whereas now, also estimates based on test results in specific individuals can be used (Gershon and Alliey-Rodriguez, 2013). A first aim of such tests is to identify a so called monogenic form of autism, to allow for an adequate plan of action (McMahon W.M. et al., 2006; Pellicano and Stears, 2011). As Scherer and Dawson argue, genetic information to confirm a diagnosis may allow people to be better prepared for the child's challenges and begin behavioral interventions at an early age (Scherer and Dawson, 2011). A benefit of finding genetic or other biological markers for autism may be that it can aid the efficiency of the diagnostic process and thus help to avoid diagnostic Odysseys (Marchant and Robert, 2008; Walsh et al., 2011). Another reason for testing is that parents want to know the cause

and want to know how likely it is that their other children are affected, and what to tell other family members of the risk (Scherer and Dawson, 2011). If the genetic mutation has occurred *de novo*, it may also relieve parents of a feeling of responsibility (Marchant and Robert, 2008; Scherer and Dawson, 2011). However, in case of an inherited mutation, it may increase feelings of guilt in the parent who is the carrier (Marchant and Robert, 2008; McMahon et al., 2006), and can lead to stigmatization within families (Gershon and Alliey-Rodriguez, 2013).

Papers also discussed the issue of genetic testing for autism as such, regardless of whether the child was diagnosed or not. In this respect Jordan an Tsai state, in the context of a discussion on commercial testing for autism, that testing for a condition is worthwhile if therapy is available and if the test allows a choice of the best treatment (Jordan and Tsai, 2010). Hence, early detection and intensive treatment early in the cause of the condition has shown to result in improved outcomes (Marchant and Robert, 2008). However, as for now, the ability to test for autism will precede the ability to respond to this information (McMahon W.M. et al., 2006). Some authors state that as autism is a multifactorial condition, and that genes merely convey susceptibility, such tests may yield many false positives or negatives and as such may have limited clinical validity (Marchant and Robert, 2008; McMahon W.M. et al., 2006; Rossi et al., 2013; Jordan and Tsai, 2010). Authors also ask whether some children that were tested positive for genetic susceptibility, but that will never develop the condition be unnecessary stigmatized (Jordan and Tsai, 2010; Rossi et al., 2013; Marchant and Robert, 2008). Several papers state that a positive test can influence the parent-child interaction and lead to anxiety and worry (Rossi et al., 2013). After a positive genetic test early in life it may take a long time to decide whether the child really has autism, and the outcome of the test may influence how others make decisions on the tested child's behalf (Jordan and Tsai, 2010; Marchant and Robert, 2008; McMahon et al., 2006), and may thus influence the right of the child to an open future (Rossi, Newschaffer, and Yudell 2013). And even in case of a true positive, Tabor and Cho ask whether we understand normal variation enough to know what is abnormal or pathogenic (Tabor and Cho, 2007), and some forms of autism may be unnecessary pathologized (Rossi et al., 2013). Walsh et al. in this respect state that a biological label should not fix and define potential treatments of individuals who are considered to be at risk of developing autism (Walsh et al., 2011).

Other ethical issues surrounding testing for autism genes include the fact that if such testing is introduced as population screening, such as newborn screening, this may lead to the stigmatization of whole communities (Gershon and Alliey-Rodriguez, 2013). There is also the possibility that tests for autism will be offered over the counter, without proper counseling (Jordan and Tsai, 2010; Marchant and Robert, 2008), or that third parties such as schools may have an interest in genetic testing results (Marchant and Robert, 2008). Daley at al. point out that a genetic diagnosis may

actually reduce the availability of services for the patient in question in low and middle income countries such as India (Daley et al., 2013). Finally, Pellicano and colleagues argue that few studies have investigated the beliefs regarding genetic testing in the autism communities themselves, and that such investigation is urgently needed (Pellicano and Stears, 2011).

Reproductive choices

The discovery of genetic or familial risk factors may influence family planning. Reproducers may use this information to forgo reproduction or to prevent the birth of a or another child with autism by prenatal diagnosis or preimplantation genetic diagnosis (PGD) (Rossi et al., 2013; Pellicano and Stears, 2011; Walsh, 2010; Amor and Cameron, 2008; Daley et al., 2013; Jaarsma and Welin, 2013; Marchant and Robert, 2008; Gershon and Alliey-Rodriguez, 2013; McMahon et al., 2006). PGD can be performed on the basis of a specific genetic mutation or on the basis of sex selection, as the condition is four times more frequent in boys (Amor and Cameron, 2008). Amor and Cameron have laid out general principles for non-Mendelian disorders for which PGD gender selection can be sought, using autism as an example of such disorder (Amor and Cameron, 2008). Daley et al. state that in India, a prenatal genetic test for autism will readily find receptive market in India, as abortion for disability is there considered by many as an "acceptable health intervention"(Daley et al., 2013). However, the variability of the phenotype and the possibility of false positives and negatives makes prenatal screening and diagnosis for autism problematic and may generate unnecessary anxiety (Walsh et al., 2011; Jordan and Tsai, 2010). Rossi et all fear that the inability to associate genetic risk factors with specific phenotypes may increase to possibility of selective abortions, as risk averse parents will not know how severely their child will be affected (Rossi et al., 2013). Also, the possibility of abortion for autism may have implications on how children and adults with the condition will view their intrinsic value as human beings (Marchant and Robert, 2008). In the interview study by Tabor and al, some parents of autistic children expressed concern that genetic information is used for reproductive planning, and that this may be a potential harm to their children, other children with autism and society (Tabor et al., 2011). Gershon and Alliey-Rodriguez state that a genetic test revealing a high probability is not a good basis for a prenatal tests and abortion, but admit that the acceptability of such choice depends on the specific history of the family (Gershon and Alliey-Rodriguez, 2013).

Two papers use Asperger's syndrome to demonstrate their disagreement with the application of certain ethical principles in the context of embryo selection or termination of pregnancy. Jaarsma and Welin discuss whether reproducers can choose an embryo predisposed for Asperger's over an embryo not thus disposed. They agree that it is wrong to willingly bring into the world a child lacking a central human capability, such as deafness, following their principle of *human capabilities*.

However, they state that people with Asperger's syndrome do have such capabilities and that deliberately selecting such embryo to be transferred to the womb can be defended (Jaarsma and Welin, 2013). Walsh uses the example of Asperger's syndrome to disagree with the supposed obligation not to bring disabled lives into the world: she states that although people with Asperger syndrome have certain challenges these are intricately linked with potentially exceptional abilities. Hence, there is no obligation to avoid the birth of such individuals, either through embryo selection or termination of pregnancy, or even through a cure in utero (Walsh, 2010).

Discussion

Complexity

In their perspective in *Nature*, Walsh et al specify four ethical issues related to research into biomarkers for autism: the heterogeneity of the condition, which results in a complex phenotypic picture of autism, the question what value should be placed on autism as a condition (is it a disability or a difference), reproductive choice in the light of uncertainty regarding reproductive risk, and how, in the light of this complexity, research should be translated into clinical practice (Walsh et al., 2011). Indeed, all papers reviewed demonstrate how the complexity of autism is a key issue when trying to come to grips with the ethical aspects of the genetics of the condition. This complexity applies to several areas. To start, the *etiology* of autism is complex. Although genetic components have been found that can explain autism in some cases, environmental issues also play a role. This complicates genetic counseling and risk communication and may limit the usefulness of genetic research. Next, there is the question, as also raised by Walsh et al, as to *how to value autism as a condition*. Hence, Pellicano and Stears argue that the ethical questions surrounding autism are "unlikely to be resolved as they depend on fundamentally conflicting assumptions about the nature and desirability of neurocognitive difference." (Pellicano and Stears, 2011). In the papers reviewed, autism was sometimes defined as a *disease* or a *disability* or, in the case of mild autism or Asperger's syndrome, a *difference* which has, next to challenges, also advantages, a view also shared by Simon Baron-Cohen who states that in subjects with autism without developmental delay, such as Asperger syndrome, systemizing is either intact or superior (Baron-Cohen, 2004, 2000). Whether a condition is considered a disability or a mere difference has ethical implications. But also the terms 'disease' and 'disability' have different meanings and require different approaches. A *disease* is more readily associated with a cure, whereas a *disability*, as disability rights activist have claimed, has a strong social component, implying that accommodating for difference rather than curing an entire phenotype may be more appropriate. But *disease* and *disability* still suggest challenges and problems for the individual: a view that is not shared by many neurodiversity activists who state that autism

may just be a variation of the normal (Savarese, 2013). Also, besides the complexity with regard to the nature of autism itself, 'autism' refers to a broad spectrum of characteristics, not all of which may be disabling (Baron-Cohen, 2004, 2000). Indeed, even the often used distinction between high functioning (or 'mild') and low functioning autism has been challenged recently by accounts of individuals that are considered to be low functioning, as it makes assumptions about a person's potential. In the case of so-called 'high functioning' autism, the use of this term may lead to society disabling these individuals even further by creating a false impression that they do not need additional support (Savarese, 2013; Kenny et al., 2015).

Walsh et al mention that there may be *many autisms*, possibly with different biological origins (Walsh et al., 2011). This has certain methodological repercussions for genetic autism research, as it makes obvious the need for a good phenotypical description of participants in genetic testing. It also begs the question whether, if certain types of autism spectrum disorder are not pathological, this warrants genetic research for these types at all. Indeed, genetic research into non-medical characteristics or character traits, such as is done in behavioral genetics, needs to answer to different ethical challenges than research into conditions to be treated or prevented (DeCamp and Sugarman, 2004). Moreover, in a historical analysis on the concept of autism Verhoeff has questioned the very idea that autism is a discrete entity that can be understood better as science progresses and knowledge accumulates, as the concept of autism has meant different things in different times. What is considered essential in autism has undergone major changes that are not properly described as mere broadening of the concept or inclusion of milder forms (Verhoeff, 2013).

The aims of genetic research

Since research for autism genes is typically done on children, such research must follow ethical principles for pediatric research (Hens et al., 2013). Some of the papers we found discussed these principles but not in a systematic way. One of the principles is that research, if done on children, should not be able to be done equally well with adult participants (*subsidiarity principle*). As most people actually diagnosed with ASD are still in fact be children, it may be unattainable to reach a high enough number of participants if this research is only done on adults. Another general principle is that the research must *benefit* the child or children with similar conditions. In the case of genetic research in general this is difficult to achieve, as there are often many steps between finding an associated gene to better treatment or cure. Outcomes of fundamental research mentioned in the papers are the development of better treatments, specifically pharmacogenetic treatments, or better association between genotype and phenotype which may lead to better predictions and better treatment plans (Jeste S.S. and Geschwind D.H., 2014; Chung et al., 2014; Gurrieri, 2012). Genetic knowledge will also better help families make reproductive decisions, but this is not always a benefit

to the children with ASD themselves. With regard to returning research results, in the case of autism research, there seems to be a consensus that such results must be clinically relevant (Hayeems et al., 2011). But in the light of the complexity of autism whether or not a genetic result will be clinically relevant is a difficult question, and one which has not yet been resolved in any of the papers reviewed. Does this mean that it needs to be relevant to the children themselves? This would imply that only genetic results that are associated with a specific phenotype that is well known with regard to treatment plans, such as is the case with syndromic autism, e.g. with Fragile-X should be returned. Or does clinically relevant also mean relevant for parents and family members? Another question that arises is what action should be taken if genetic predispositions are found in samples from subjects without a diagnosis. In this respect, Chen and all question whether healthy siblings should be enrolled into prospective longitudinal research studies, because they are considered 'at risk'. They state that categorizing children at risk for a disorder as having 'a condition' is not currently universally accepted (Chen et al., 2003). This is a similar question to whether a presymptomatic genetic test for autism, should it exist, should be used. Should people or parents of people with such diagnosis be warned and sent for further behavioral observation and testing? Can testing of genes or other biological markers ever replace diagnostic testing based on behavioral observation? Several papers mention the danger of presymptomatic testing for autism genes: this can lead to anxiety and to the fact that caregivers will behave differently towards their children, which in itself will influence how the child develops. Indeed, in their assessment of commercial tests for autism, Jordan and Tsai explicitly mention that a positive result from a genetic test of autism may burden children and their family and pressure them into seeking more psychiatric evaluations and diagnosis, and the children may be stigmatized and regarded as 'sick, abnormal or different' from their siblings or classmates (Jordan and Tsai, 2010). In the context of labelling of children with Asperger's syndrome, Molloy & Vasil have argued already in 2002 that this syndrome may be socially constructed as a disorder, and that representing children as having Asperger's may have social implications. They state that not enough knowledge is available on how the involuntary labelling of a child with AS affects that child's quality of life (Molloy and Vasil, 2002). As such, the fact that a diagnostic label is accompanied by a genetic label may have even more adverse effects on the child's self-perception.

Pediatric research ethics

Other issues with regard to research ethics that are specific to research in autism genes include difficulties related to informed consent and minimal risk. As many of the research on autism genes will be done with autistic children as research participants, their caregivers will have to give *proxy consent* to the research. Proxy consent may be conceived in two ways: first, parents may consent to what they deem is in the best interest of the child. As we have specified in the previous paragraph,

this is difficult to apply to fundamental genetic research. Or parents may try to find out what their child would wish if she were to be adult. In the case of severe intellectual disability, the latter approach will be difficult. However, as Alexandra Perry argues, autistic children may grow up to be adults who are able to cope with their autism very well, and who see it as an integral part of their identity (Perry, 2012). Hence, if parents consent to research that would have as an aim curing or eradicating autism this may clash with the future wishes of the child. Authors also mention that as individuals with autism process information differently, information and consent forms should be adapted to their needs. In a paper on risk communication in autism research in general, Yudell et al. acknowledge that risk communication, in the context of research findings, must be tailored to different communities and populations. They state that many individuals have low literacy and some will not be capable of reading, hence, easy read information will have to be provided. And those with impaired receptive language skills may be helped by the use of photos, visual stories and cartoons (Yudell et al., 2013).

Another general principle of non-therapeutics pediatric research is that it should be *minimal risk*. Such risk may be different for children with autism than for other children. For example the risk of trauma of blood draws is mentioned by some authors. In this respect, Chen et al. state that what may appear to be dissent to participation may be a reflection of fear of anxiety rather than a refusal to continue research participation (Chen et al., 2003). But maybe fear or anxiety in itself can be considered higher than minimal risk and is a sufficient reason to allow children to dissent to participate in research. Tabor et al therefore state the importance that researchers should be experienced with or trained to handle children with autism (Tabor et al., 2011). Overall, we conclude that there is a need for a more general best practice guide addressing the ethical questions of autism research, as the general guidelines may be insufficient.

Reproductive decision making

Papers did not explicitly mention the facilitation of preimplantation genetic screening and diagnosis and prenatal screening and diagnosis as an aim of genetic research. But it is inevitable that genetic counseling and testing will influence reproductive decision making for families with children with autism (Hoffmann T.J. et al., 2014), and that some reproducers will want to make use of these techniques. The desirability of these options, however, is complicated by the fact that at present very few genetic variants, except in the case of some monogenic conditions with autism, can predict the severity of the phenotype. Savulescu & Kahane, use their principle of *procreative beneficence* to argue that reproducers have all reasons to make use of such test to present the birth of children disposed to autism or Asperger's, as they believe that this reduces their potential wellbeing (Jaarsma and Welin, 2013). In her book *Autism and Ethics*, which relies heavily on the Theory of Mind,

Elizabeth Barnbaum states that such screening and prevention of autism is allowed, based on the principle of a child's right to an open future: as, according to her, autistic children lack certain social skills, their future is presumably less open than that of children without autism (Barnbaum, 2008). Two papers challenge the assumptions of this thesis. Jaarsma and Welin argue that people with "mild" autism or Asperger's syndrome have capabilities that will allow them to live a fulfilling life (Jaarsma and Welin, 2013). However, Lim has challenged the idea of deciding on accommodation or cure based on IQ or on categorizing between high and low functioning, and argues that further research is needed as to what it would mean to accommodate *all* autistics (Lim, 2015). Walsh argues that with Asperger syndrome, challenges and strengths of the phenotype are intrinsically linked, and that to avoid the former, society will miss out the latter (Walsh, 2010). But wellbeing of individuals is never completely context independent, and a fundamental reflection on the extent to which societal accommodation is possible is needed (Lim, 2015). As Bumiller has stated: if parents have a choice between giving birth to a normal child and an autistic child who may suffer stigma for being different, then, under current social conditions, there is essentially no choice at all, even if these parents would not object to raising a child with autism as such (Bumiller, 2009).

Involvement of all parties

Several papers mention the need to involve all parties that are affected by genetic research and genetic testing for autism, such as parents and autistic individuals themselves. For example, Walsh et al state that existing and new research knowledge should be contextualized within the real-life experience of affected families (Walsh et al., 2011b). Pellicano et al acknowledge that there will necessarily be some disagreement amongst these parties (Pellicano and Stears, 2011). Indeed, the clash between parents seeking a 'cure' for their child's autism and individuals with autism who state that their autism is part of their identity and need not be cured is well documented. Moreover, they argue, a large proportion of autistics are unable to participate to the debate due to difficulties with communicating. Some parents organizations actively promote biomedical research, but are heavily criticized by autistic persons (neurodiversity movement), who often fear the eugenic implications of research to find a cure or to enable prevention, as they see autism as a desirable genetic variation (Bumiller, 2009; Perry, 2012). It has been extensively argued that bioethical conclusions on issues related to disability cannot be solved without input from the affected parties themselves, and that a mere theoretical approach to bioethics is insufficient as such approach cannot lay bare all relevant ethical aspects of a given phenomenon (Scully, 2008). Therefore, we state that in order for bioethical reflection on autism and autism genetics to move forward, a necessary next step is empirical bioethical research querying the experiences, values and opinions of people with the condition.

Our study has several limitations. By focusing on bioethical themes in bioethics literature, we may have left out relevant philosophical or sociological papers. By limiting our search to papers in peer reviewed journals we may have skipped relevant book chapters. However, with this literature review we believe to have mapped the basic questions and answers that exist in the bioethical literature on autism genetics, research, counselling and reproduction. We have found 19 papers that fitted the description of 'bioethics literature focusing on autism genetics', and have analyzed their content to distill arguments and themes. We state that a thorough reflection on the aims and goals of autism genetics research is needed, and that researchers should make sure that research is conducted in a way that respects the specific ways autistic people process information. Also, the implications for probands and families of genetic findings should be considered before genetic testing is undertaken. Moreover, what autism genetics may mean for presymptomatic screening and reproductive choice is as of yet undecided and in need of further investigation. We conclude that because of the complexity of autism, and the uncertainty with regard to how to value autism, more ethical reflection is needed before definite conclusions and recommendations can be drawn. Moreover, at the moment there is a dearth of empirical studies querying the opinions of all parties, including also so-called low functioning autistic people. Such empirical studies should be urgently done before bioethical conclusions regarding the aims and desirability of research into autism genes and regarding reproductive choices can be drawn. Also, fundamental philosophical reflection on concepts of disease should accompany research into the etiology of autism.

Conflict of interest

We declare no conflict of interest

Acknowledgement

This work was supported by an 'Opening the Future' grant donated by the Leuven University Fund. Kristien Hens is supported by a Belgian Federal Science Policy Office (BELSPO) 'Back to Belgium' grant. Hilde Peeters is a Senior Clinical Investigator of The Research Foundation - Flanders (FWO). We would like to thank the anonymous reviewer for her or his valuable comments on a first draft of this manuscript.

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