Journal of Autism and Developmental Disorders
https://doi.org/10.1007/s10803-020-04589-y

ORIGINAL PAPER

Factors Affecting Family Compliance with Genetic Testing of Children Diagnosed with Autism Spectrum Disorder

Yonah Hendel[1,2] · Gal Meiri[2,3] · Hagit Flusser[2,4] · Analya Michaelovski[2,4] · Ilan Dinstein[2,5,6] · Idan Menashe[2,6,7]

Abstract

There is broad consensus about the importance of post-diagnostic genetic testing for children with ASD. However, the extent of compliance with these tests and the factors affecting compliance have rarely been examined. We surveyed a sample of 114 families with a child with ASD in Israel, where such genetic testing is funded by the government. We found that only one-third of these families completed post-diagnosis genetic testing for their child. The main factor influencing compliance was the doctor's recommendation (OR 11.6; 95% CI 3.2–42.4; $p < 0.001$). Furthermore, > 50% of the non-compliant families reported that genetic testing was irrelevant to them. Our findings highlight the importance of providing clear recommendations and explanations regarding the benefits and relevance of post-diagnosis genetic testing for children with ASD.

Keywords Autism spectrum disorder · Genetic testing · Compliance

Introduction

Autism spectrum disorder (ASD) is an early onset neurodevelopmental disorder with an estimated prevalence of 1–2% (Baio et al. 2018; Elsabbagh et al. 2012; Kogan et al. 2018). Although the etiology of ASD has remained elusive, it is commonly accepted that genetics plays an important role in its pathophysiology although, estimates about the heritability of the disorder vary significantly (Bai et al. 2019; Colvert et al. 2015; Hallmayer et al. 2011; Hansen et al. 2019; Sandin et al. 2014; Tick et al. 2016; Yip et al. 2018). In addition, genetic causes of ASD are extremely heterogeneous (de la Torre-Ubieta et al. 2016; Devlin and Scherer 2012; Goldstein et al. 2019). In approximately 10% of cases, ASD is an inherent outcome of an identifiable genetic syndrome, such as fragile X syndrome (Bagni and Zukin 2019), tuberous sclerosis (Curatolo et al. 2010), or other syndromes (Moss and Howlin 2009). Another type of genetic variation that has consistently been associated with ASD is copy number variation (CNV) (Girirajan et al. 2013; Marshall and Scherer 2012; Menashe et al. 2013; Pinto et al. 2010). In addition, rare, loss-of-function single-nucleotide variations (SNV) in a variety of genes have recently been implicated in ASD susceptibility (Muers 2012; O'Roak et al. 2011; Sanders et al. 2012; Satterstrom et al. 2020). In summary, as of January 2020, 1141 genes and 2274 CNV loci have been associated with ASD susceptibility (Abrahams et al. 2013; Basu et al. 2009).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10803-020-04589-y) contains supplementary material, which is available to authorized users.

Yonah Hendel and Gal Meiri contributed equally to this manuscript.

✉ Idan Menashe
idanmen@bgu.ac.il

[1] Joyce & Irving Goldman Medical School, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[2] National Autism Research Center of Israel, Ben-Gurion University, Beer-Sheva, Israel

[3] Pre-School Psychiatry Unit, Soroka University Medical Center, Beer-Sheva, Israel

[4] Child Development Center, Soroka University Medical Center, Beer-Sheva, Israel

[5] Psychology Department, and Cognitive and Brain Sciences Department, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[6] Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[7] Public Health Department, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Published online: 10 July 2020

Altogether, these genetic variations are found in 10–25% of ASD patients (Devlin and Scherer 2012; Geschwind 2011; Goldstein et al. 2019; Huguet et al. 2013).

Given the significant role of genetic variations in ASD susceptibility, there is currently broad consensus about the need for post-diagnostic genetic testing for ASD and its benefits for affected children and their families (Tchaconas and Adesman 2017). For example, finding an ASD susceptibility genetic variation in an affected child may help the family in their family planning decisions. In addition, identification of a possible genetic cause of ASD may provide a degree of relief in some cases, even though in others it may lead to feelings of guilt (Bauer and Msall 2011). Therefore, in 2011, the American College of Medical Genetics outlined its recommendations for postnatal clinical evaluation of constitutional genomic abnormalities in children with ASD or other developmental delays (Kearney et al. 2011).

A number of factors can influence the extent of compliance with genetic testing in ASD. Family-related factors include cultural and community habits (Zamora et al. 2016), alongside personal views and beliefs (May et al. 2012). In parallel, children with ASD tend to exhibit an aversion to and fear of any kind of medical examination, which affect their compliance with these tests (Davit et al. 2011). Furthermore, some unique characteristics of the genetic testing of ASD patients may impact negatively on parental compliance; these include limited predictive utility, stigmatization and misinterpretation of findings (May et al. 2012). Finally, a lack of familiarity and compliance with clinical diagnostic guidelines for ASD on the part of child neurologists and developmental pediatricians may result in reduced referrals of affected families to genentic testing (Tchaconas and Adesman 2017).

In Israel, the Ministry of Health recommends that all children who are diagnosed with ASD undergo genetic evaluation, which includes a test for fragile X syndrome and a chromosomal microarray analysis (CMA) for the detection of CNVs associated with ASD (Ministry of Health, Israel 2013). In some cases, additional tests such as a karyotype or a test for specific genetic syndrome associated with ASD will also be performed. In accordance with the National Health Insurance Law (Ministry of Health, Israel 1995), these tests are provided free of charge for children who are diagnosed with ASD. However, the extent of compliance of families with these recommendations and the factors affecting this compliance remain to be clarified. We, therefore, conducted a survey of a representative sample of families with one or more children with ASD living in southern Israel with the aim to gain a better understanding of the factors affecting their compliance with the recommendation for ASD genetic testing.

Methods

Participants and Data Collection

Study participants were drawn from the database of the National Autism Research Center of Israel (NARCIS), which contains comprehensive clinical data on all children diagnosed with ASD at the Soroka University Medical Center (SUMC) (Meiri et al. 2017). The parents or legal guardians of approximately 70% of these children have signed an informed consent form that allows researchers of the NARCIS to contact them for research purposes. For this study, we examined families enrolled in the NARCIS database between January 2015 and December 2018. Consequently, 383 families were eligible to participate in the survey at the time of the study (Fig. 1). The survey was performed by telephone using the number/s provided by the father/mother/guardian of the child at the time of enrollment into the database. If one parent did not respond to the request to take part in our survey, then the other parent was contacted. If both parents did not respond, a second attempt was made to call them.

For 183 of the 383 families (47.8%), no-one replied or was available at the phone numbers provided. Out of the 200 parents/guardians who did reply to the call, 120 (60%) completed the questionnaire during the first call or during a subsequent call; 76 (38%) claimed that the call had been made at an inconvenient time and failed to reply to a repeat call; and 4 (2%) said they were not interested in participating in this survey. Six families that participated in the survey (3%) could not recall whether their child had had a post-diagnosis genetic test and were therefore excluded from the study (Fig. 1). The remaining 114 families were asked to answer a questionnaire that included questions regarding: (1) the understanding of parents about the purpose of genetic testing and its relevance to them; (2) the level of compliance with the genetic testing and the reasons underlying the compliance/non-compliance; and (3) the family's genetic background. In addition, the responders were asked to answer 10 true/false questions about human genetics that had been adapted from an existing survey instrument (Fitzgerald-Butt et al. 2016), as a means to assess the parents' knowledge of human genetics. The questionnaire used in this study is provided in the supplementary material.

The sociodemographic characteristics of the families participating in the survey and the clinical data about the affected child, such as age at diagnosis and ADOS-2 comparison score (Lord et al. 2000), were obtained from the NARCIS database (Meiri et al. 2017). The socio-economic level (1-lowest to 10-highest) was set according to the criteria of the Israeli Central Bureau of Statistics (Israel 2008).

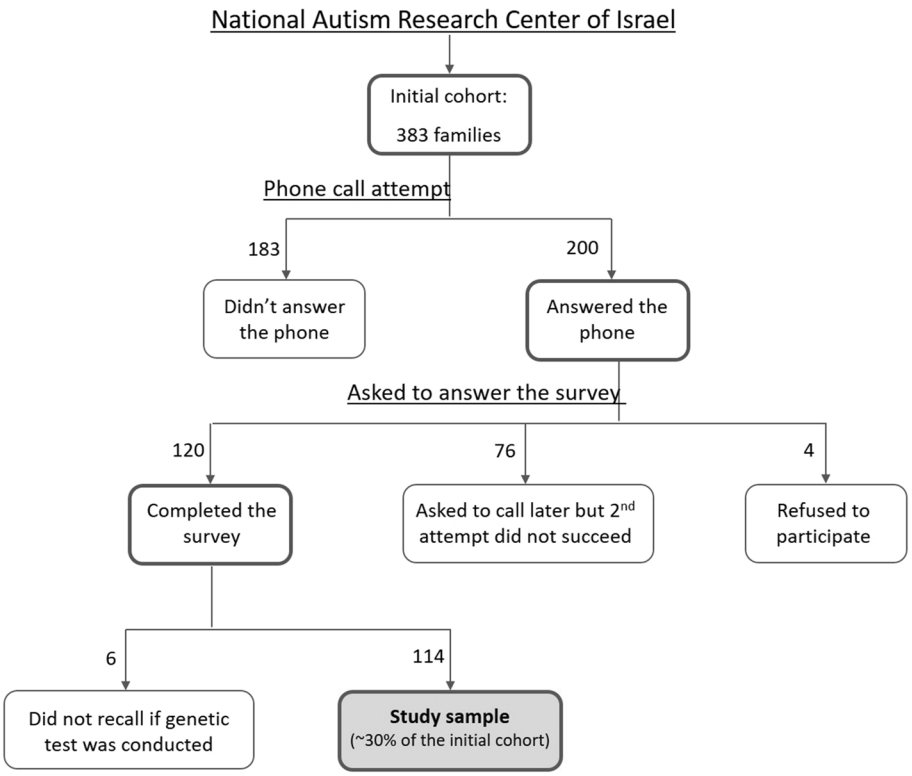

Fig. 1 A flowchart of the study sample. Attempts were made to survey by telephone 383 families with a child diagnosed with ASD that are registered in database of the National Autism Research Center of Israel. Of these, 200 families (52.2%) responded to the initial telephone call, and 120 of these (60%) completed the survey. Six families that did not remember whether their child had had a post-diagnosis genetic test were excluded from further analysis. Overall, 114 families that completed the survey were included in this study (Shaded shape)

Statistical Analysis

We used standard univariate statistical tests to compare sociodemographic and clinical characteristics as well as questionnaire outcomes between groups. Specifically, a two-sided Student's *t* test was used to compare the means of normally distributed variables, and a non-parametric Mann–Whitney test was used if parametric assumptions could not be satisfied. Pearson's Chi square test for contingency tables or the Fisher Exact test was used to compare rates of nominal variables between the groups. Finally, a multivariate logistic regression model was used to assess the odds ratio of these parameters on family compliance with genetic testing for their child. The results of this analysis are presented with 95% confidence intervals (CI), as appropriate. All statistical tests and/or CI s were performed at $\alpha = 0.05$ (2-sided). All p values reported were rounded down to two decimal places. The data were analyzed using IBM SPSS Statistics software.

Ethical Considerations

The SUMC Helsinki Committee approved the trial protocol (SOR 222-14).

Results

Sample Characteristics

Table 1 presents the basic demographic characteristics of the research cohort. Notably, the 114 families that responded to our telephone questionnaire did not differ in most of these characteristics from the other families in the NARCIS database. The only difference was in parental age, which was slightly higher in the families that did respond to the questionnaire (37.95 vs. 36.4 and 41.16 vs. 39.3 years for mothers and fathers in the responding and not-responding groups respectively; p value < 0.05).

Table 2 presents the characteristics of the 114 families that responded to our phone survey. Of these, only 38 families (33.3%) reported a post-ASD diagnosis genetic test for their child. This group included five families that had scheduled an appointment for a genetic test but had not completed it by the time of the study. The study revealed that mothers were twice more likely to answer the questionnaire than fathers, with no significant difference between families that had done a genetic test for their child and families that had not. There were no significant differences in the

Table 1 Cohort characteristics

Variable			All (n = 383)	Did not respond (n = 269)	Responded (n = 114)	p value
Age at diagnosis, mean (SD), years			2.8 (1.29)	2.85 (1.33)	2.68 (1.18)	0.38[a]
ADOS score—mean (SD)			7.36 (2.2)	7.36 (2.16)	7.38 (2.31)	0.8[b]
ADOS score—median (IQR)			8 (6–9)	8 (6–9)	8 (6–9)	
Other siblings diagnosed with ASD, n (%)			23 (6%)	15 (5.6%)	8 (7%)	0.59[c]
Ethnicity, n (%)	Jewish		280 (73.1%)	198 (73.6%)	82 (71.9%)	0.74[c]
	Non-Jewish		103 (26.9%)	71 (26.4%)	32 (28.1%)	
Mother	Age, mean (SD), years		36.94 (6.23)	36.4 (6.17)	37.95 (6.25)	0.04[a]
	Origin, n (%)	Israel	241 (74.4%)	165 (77.1%)	76 (69.1%)	0.12[c]
		Other	83 (25.6%)	49 (22.9%)	34 (30.9%)	
	Education, median (IQR) years		12 (12–15)	12 (12–15)	12 (12–15)	0.29[b]
	Address, n (%)	Urban	302 (91.5%)	200 (92.2%)	102 (90.3%)	0.56[c]
		Rural	28 (8.5%)	17 (7.8%)	11 (9.7%)	
Father	Age, mean (SD), years		39.95 (7.8)	39.3 (7.66)	41.16 (7.97)	0.02[a]
	Origin, n (%)	Israel	234 (77.5%)	151 (77.4%)	83 (77.6%)	0.98[c]
		Other	88 (22.5%)	44 (22.6%)	24 (22.4%)	
	Education, median (IQR) years		12 (12–15)	12 (12–15)	12 (12–15)	0.75[b]
	Address, n (%)	Urban	271 (90%)	175 (90.7%)	96 (88.9%)	0.62[c]
		Rural	30 (10%)	18 (9.3%)	12 (11.1%)	
Number of working parents, mean (SD)			1.47 (0.59)	1.48 (0.6)	1.45 (0.57)	0.73[b]
Socioeconomic level, median (IQR)			5 (3–5)	5 (3–5)	5 (1–5)	0.97[b]

Comparison of survey responders to non-responders

[a]t-test

[b]Mann–Whitney test

[c]Chi square test

sociodemographic characteristics between families that reported to have done a post-ASD diagnosis genetic test for their child and families that had not.

Personal Questionnaire

Table 3 presents the results of our survey. The majority (92%) of families that performed genetic testing reported that they did so because of their doctor's recommendation, while this rate was reduced to half (50%) in families that did not comply with the recommendation. Similar differences were seen between the two groups when families were asked if the doctor had explained the importance of the genetic test (79% vs. 38% respectively; p value < 0.001). Most families in the survey thought that the reason for the genetic test was for research purposes (57%) or for "understanding the cause" (53.5%), while less than half of the families thought it was for family planning (48%) or therapy adjustment (32.5%). All of these reasons were cited more frequently in the families that completed genetic testing but the "doctor's recommendation" variable alone remained significant in a multivariate logistic regression analysis (Table 4).

The leading reasons given by the families for not performing the genetic testing (Q11 in the questionnaire) was the "irrelevance" of the test for them (55%) and "no recommendation by the doctor" (36%) (Table 3). Reasons cited less often by these families were that they could not find the time to do so (8%) or that the child was not cooperative (8%). Yet another reason—one cited by three families (3.9%)—was objection in principle (due to religious or cultural reasons).

Since the Israel Ministry of Health guides doctors to recommend the genetic test to families when their child is diagnosed with ASD, it was surprising that 36% of families did not recall such a recommendation. To further examine this issue, we checked available medical records and found that in two-thirds of these cases a recommendation had been noted in their medical file.

Genetic Knowledge Questionnaire

Results of the genetic knowledge questionnaire varied considerably with few people having zero correct answers, while others were correct in all ten questions. Nevertheless,

Table 2 Sample characteristics

Variable			All (n = 114)	Non-tested (n = 76)	Tested (n = 38)	p value
Interviewed parent, n (%)	Mother		78 (68.4%)	51 (67.1%)	27 (71.1%)	0.69[c]
	Father		36 (31.6%)	25 (32.9%)	11 (28.9%)	
Age at diagnosis, mean (SD), years			2.68 (1.18)	2.68 (1.14)	2.68 (1.27)	0.93[a]
ADOS score—mean (SD)			7.38 (2.31)	7.5 (2.09)	7.11 (2.75)	0.9[b]
ADOS score—median (IQR)			8 (6–9)	8 (6–9)	8 (4.75–9)	
Other siblings diagnosed with ASD, n (%)			8 (7%)	5 (6.6%)	3 (7.9%)	1[c]
Treated child is youngest in the family, n (%)	No		38 (34.5%)	25 (33.8%)	13 (36.1%)	0.81[c]
	Yes		72 (65.5%)	49 (66.2%)	23 (63.9%)	
Total number of children, median (IQR)			2 (2–3)	2 (2–3)	2 (2–3)	0.6[b]
Ethnicity, n (%)	Jewish		82 (71.9%)	58 (76.3%)	24 (63.2%)	0.14[c]
	Non-Jewish		32 (28.1%)	18 (23.7%)	14 (36.8%)	
Mother	Age, mean (SD), years		37.95 (6.25)	38.27 (6.45)	37.32 (5.86)	0.48[a]
	Origin, n (%)	Israel	76 (69.1%)	51 (70.8%)	25 (65.8%)	0.59[c]
		Other	34 (30.9%)	21 (29.2%)	13 (34.2%)	
	Education, median (IQR) years		12 (12–15)	12 (12–15)	12.5 (11.5–15.25)	0.98[b]
	Address, n (%)	Urban	102 (90.3%)	68 (90.7%)	34 (89.5%)	1[c]
		Rural	11 (9.7%)	7 (9.3%)	4 (10.5%)	
Father	Age, mean (SD), years		41.16 (7.97)	40.92 (7.18)	41.66 (9.48)	0.97_a
	Origin, n (%)	Israel	83 (77.6%)	56 (78.9%)	27 (75%)	0.65[c]
		Other	24 (22.4%)	15 (21.1%)	9 (25%)	
	Education, median (IQR) years		12 (12–15)	12 (12–15)	12 (12–15)	0.75[b]
	Address, n (%)	Urban	96 (88.9%)	66 (90.4%)	30 (85.7%)	0.47[c]
		Rural	12 (11.1%)	7 (9.6%)	5 (14.3%)	
Number of working parents, mean (SD)			1.45 (0.57)	1.5 (0.51)	1.36 (0.67)	0.65[b]
Socioeconomic level, median (IQR)			5 (1–5)	5 (3–5)	4.5 (1–5)	0.35[b]

Comparison of genetic testing compliant vs. non-compliant families

[a]t-test

[b]Mann–Whitney test

[c]Chi square test

families of both the tested and non-tested groups did not vary significantly in their genetic knowledge, with both groups having identical median and interquartile rage of correct answers to the questionnaire (Table 3).

Results of the Genetic Tests

Of the 38 families that did the genetic test, five (13.1%) reported the following positive findings (i.e., identification of known ASD susceptibility genetic variations): 16p11.2 duplication, 15q duplication, Rett syndrome, 14q11.2 deletion, and myotonic dystrophy type 1.

Discussion

The main objective of this study was to examine the rate of compliance with the recommendation for genetic testing and the factors that influence such compliance in southern Israel. Surprisingly, the compliance rate in our study was as low as 33.3%. While this rate is similar to the compliance rate with ASD genetic testing reported in the USA (Zhao et al. 2019), we expected it to be higher for our cohort, since in Israel these tests are free [covered by the National Insurance Law (Israel 1995)], while in the USA they are usually paid for by the family's private health insurance. The rate of pathogenic CNVs found in our sample (~8%) was slightly lower than the rates reported in the USA (~15%) (Chong et al. 2014; Miller et al. 2010). This difference can be explained by the fact that in the US, CMA are usually conducted to children with both ASD and intellectual disability while in Israel, all children with ASD are eligible for such genetic test. Indeed, a study that performed CMA in a heterogenous group of children with ASD, found a diagnostic yield of CMA that was similar to ours (9.3%, 95% CI 6.1–13.5%) (Tammimies et al. 2015), suggesting a global contribution of CNVs to ASD susceptibility of ~10% of cases. The identification of Rett syndrome and myotonic dystrophy type 1 in

Table 3 Telephone survey results

Variable		All (n = 114)	Non-tested (n = 76)	Tested (n = 38)	p value
Pre-pregnancy genetic testing, n (%)	No testing	55 (48.7%)	37 (49.3%)	18 (47.4%)	0.84[c]
	As advised	55 (48.7%)	36 (48%)	19 (50%)	0.84[c]
	More than advised	3 (2.7%)	2 (2.7%)	1 (2.6%)	0.74[d]
Doctor recommended genetic testing n (%)		73 (64%)	38 (50%)	35 (92.1%)	<0.001[c]
Doctor explained the importance of genetic testing n (%)		55 (48.2%)	29 (38.2%)	30 (78.9%)	<0.001[c]
What do you think is the reason for testing, n (%)	No reason	33 (28.9%)	27 (35.5%)	6 (15.8%)	0.03[c]
	Research	65 (57%)	37 (48.7%)	28 (73.7%)	0.004[c]
	Understanding the cause	61 (53.5%)	35 (46.1%)	26 (68.4%)	0.01[c]
	Family planning	55 (48.2%)	32 (42.1%)	23 (60.5%)	0.06[c]
	Therapy adjustment	37 (32.5%)	19 (25%)	18 (47.4%)	0.02[c]
	Other	1 (0.9%)	0 (0%)	1 (2.6%)	0.33[c]
Type of genetic testing, n (%)	Fragile X	2 (1.8%)	n/a	2 (5.3%)	n/a
	CMA	16 (14%)	n/a	16 (42.1%)	n/a
	Exome sequencing	1 (0.9%)	n/a	1 (2.61%)	n/a
	Not known	21 (18.4%)	n/a	21 (55.3%)	n/a
Objects to genetic testing, n (%)		3 (2.6%)	3 (3.9%)	0 (0%)	0.55[c]
Reason for objecting to genetic testing, n (%)	Religious	3 (2.6%)	3 (3.9%)	0 (0%)	0.55[c]
	Culture	1 (0.9%)	1 (1.3%)	0 (0%)	1[c]
	Stigmatization	0 (0%)	0 (0%)	0 (0%)	n/a
	Privacy concerns	0 (0%)	0 (0%)	0 (0%)	n/a
	Other	0 (0%)	0 (0%)	0 (0%)	n/a
Difficulties in the testing process, n (%)	No difficulties	21 (18.4%)	n/a	21 (55.3%)	n/a
	Arrival	0 (0%)	n/a	0 (0%)	n/a
	Setting a meeting	3 (2.6%)	n/a	3 (9.1%)	n/a
	Child cooperation	9 (6.1%)	n/a	7 (21.2%)	n/a
	Other	0 (0%)	n/a	0 (0%)	n/a
If tests were not performed, what would you say was the reason?	Objection in principle to tests	3 (2.6%)	3 (3.9%)	n/a	n/a
	Irrelevancy	42 (36.8%)	42 (55.3%)	n/a	n/a
	Not recommended by a doctor	27 (23.7%)	27 (35.5%)	n/a	n/a
	Difficulties in working with medical system	2 (1.8%)	2 (2.6%)	n/a	n/a
	Non-cooperative child	6 (5.3%)	6 (7.9%)	n/a	n/a
	Could not find the time	6 (5.3%)	6 (7.9%)	n/a	n/a
	Other	4 (3.5%)	4 (5.3%)	n/a	n/a
Genetic knowledge score Median (IQR[a])		6 (5–8)	6 (5–8)	6 (5–8)	0.85[b]

Families' responses to study questionnaire

[a]Interquartile range

[b]Mann–Whitney test

[c]Chi square test

[d]Fisher-exact test

our sample further highlights the importance of performing other genetic tests to identify other types of ASD susceptibility genetic variants.

The main factors that affected families' compliance with the recommendation for genetic testing were the doctor's recommendation to do the test and the explanation of the test. The same factors were also reported to affect parent compliance with genetic testing in other countries (Zhao et al. 2019). Interestingly, only two-thirds of the families in our study reported that their doctor had recommended a genetic test. We suspect that these rates are an underestimation due to a recall bias resulting from the time that has passed since the diagnosis and from the anxiety and stress that usually accompany the diagnosis meeting with

Table 4 Factors affecting compliance with genetic testing

Variable	OR[a]	95% CI for OR	p value
Doctor recommended genetic testing (Q: #2)	11.58	3.16–42.44	< 0.001
Reason for running the test—Research (Q: #4a)	1.53	0.53–4.47	0.43
Reason for running the test—Therapy adjustment (Q: #4d)	2.42	0.83–7.1	0.11

The odds ratios (OR) and their 95% confidence interval (CI) of having a post-diagnosis genetic test for ASD are presented for different items in the telephone survey

[a]Odds ratios are adjusted for all other variables in the table

the doctor, which can influence the perception of such recommendation (Kessels 2003). We note that there are various techniques and recommendations as to how to convey difficult medical news to patients and how to provide the necessary information (Baile et al. 2000). More specific guidelines for ASD are also available; these suggest that recommendations for genetic testing should be provided in written form with the aim to allow families to review them later (Ministry of Health, Israel 2013; Renty and Roeyers 2006). Implementation of these recommendations may ease, to some degree, the difficulty of the parents to process the information and may improve compliance with the recommendations.

"Family planning" was mentioned as a reason to conduct postnatal genetic testing of ASD by approximately half of the families in the study. It was therefore not surprising that families that did not plan to have more children were less likely to comply with the recommendation for genetic testing. While family planning is indeed a major reason for the genetic testing (Bauer and Msall 2011), it is certainly not the only one. Many families also mentioned "research" and "understanding the cause" as important reasons for conducting postnatal genetic testing of ASD. However, it is not clear whether these families understand the clinical benefit of such scientific understanding. For example, in some cases, identifying the genetic cause of ASD can help to adjust the medical management for the child. Therefore, we recommend that, when discussing the value of genetic testing with parents, doctors should emphasize these reasons and elaborate on their potential benefit for both the family and for ASD research in general.

Our study has several limitations. First, this is a retrospective study with questionnaire items about the child's diagnosis several years previously, which may lead to a recall bias. This is best demonstrated by the fact that in most families that reported of "no recommendation of test by the doctor," such recommendations were actually noted in the child's medical file. Furthermore, parents' subjective perceptions and feelings about genetic testing may change over the years and do not necessarily represent their beliefs at the time of diagnosis. Second, only ~ 30% of the families in the NARCIS database complied with our phone questionnaire. Nevertheless, these families comprised an adequate representation of the NARCIS cohort as depicted in Table 1. Third, the fact that the survey was conducted in Hebrew might have created a bias in our sample against families that do not speak the language or those for whom Hebrew is not their mother tongue and that do not feel comfortable using it. Indeed, a few families for which both parents did not have sufficient grasp of Hebrew were excluded from the study. However, we made every effort to overcome with this language barrier by choosing the parent with the better Hebrew and confirming that s/he understood each of the questions. Indeed, there was no indication for a bias in our sample compared to other families that did not participate in this survey.

Conclusions

Our findings highlight the importance of providing clear recommendations and explanations regarding the benefits and relevance of post-diagnosis genetic testing for children with ASD. Guiding doctors as to how to inform families about such genetic testing may improve the compliance with these government-funded tests.

Acknowledgments This study was conducted as part of the requirements for MD degree from the Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev. We thank Yotam Lior for helping in statistical guidance, Rotem Saban for helping with data retrieval, and Inez Mureinik for critical reviewing and editing of the manuscript. Special thanks are for the families who participated in the study.

Author Contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by Yonah Hendel, and Gal Meiri. Data analysis was performed by Yonah Hendel and Idan Menashe. The first draft of the manuscript was written by Yonah Hendel, Gal Meiri and Idan Menashe and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest to disclose.

References

Abrahams, B. S., et al. (2013). SFARI Gene 2.0: A community-driven knowledgebase for the autism spectrum disorders (ASDs). *Molecular Autism, 4,* 36. https://doi.org/10.1186/2040-2392-4-36.

Bagni, C., & Zukin, R. S. (2019). A synaptic perspective of fragile X syndrome and autism spectrum disorders. *Neuron, 101,* 1070–1088. https://doi.org/10.1016/j.neuron.2019.02.041.

Bai, D., et al. (2019). Association of genetic and environmental factors with autism in a 5-country cohort. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2019.1411.

Baile, W. F., Buckman, R., Lenzi, R., Glober, G., Beale, E. A., & Kudelka, A. P. (2000). SPIKES—A six-step protocol for delivering bad news: Application to the patient with cancer. *The Oncologist, 5,* 302–311. https://doi.org/10.1634/theoncologist.5-4-302.

Baio, J., et al. (2018). Prevalence of autism spectrum disorder among children aged 8 years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *Morbidity and Mortality Weekly Report Surveillance Summaries (Washington, DC: 2002), 67,* 1–23. https://doi.org/10.15585/mmwr.ss6706a1.

Basu, S. N., Kollu, R., & Banerjee-Basu, S. (2009). AutDB: A gene reference resource for autism research. *Nucleic Acids Research, 37,* D832–D836. https://doi.org/10.1093/nar/gkn835.

Bauer, S. C., & Msall, M. E. (2011). Genetic testing for autism spectrum disorders. *Developmental Disabilities Research Reviews, 17,* 3–8. https://doi.org/10.1002/ddrr.131.

Chong, W. W., et al. (2014). Performance of chromosomal microarray for patients with intellectual disabilities/developmental delay, autism, and multiple congenital anomalies in a Chinese cohort. *Molecular Cytogenetics, 7,* 34. https://doi.org/10.1186/1755-8166-7-34.

Colvert, E., et al. (2015). Heritability of autism spectrum disorder in a UK population-based twin sample. *JAMA Psychiatry, 72,* 415–423. https://doi.org/10.1001/jamapsychiatry.2014.3028.

Curatolo, P., Napolioni, V., & Moavero, R. (2010). Autism spectrum disorders in tuberous sclerosis: Pathogenetic pathways and implications for treatment. *Journal of Child Neurology, 25,* 873–880. https://doi.org/10.1177/0883073810361789.

Davit, C. J., Hundley, R. J., Bacic, J. D., & Hanson, E. M. (2011). A pilot study to improve venipuncture compliance in children and adolescents with autism spectrum disorders. *Journal of Developmental and Behavioral Pediatrics: JDBP, 32,* 521–525. https://doi.org/10.1097/DBP.0b013e3182245b09.

de la Torre-Ubieta, L., Won, H., Stein, J. L., & Geschwind, D. H. (2016). Advancing the understanding of autism disease mechanisms through genetics. *Nature Medicine, 22,* 345–361. https://doi.org/10.1038/nm.4071.

Devlin, B., & Scherer, S. W. (2012). Genetic architecture in autism spectrum disorder. *Current Opinion in Genetics & Development, 22,* 229–237. https://doi.org/10.1016/j.gde.2012.03.002.

Elsabbagh, M., et al. (2012). Global prevalence of autism and other pervasive developmental disorders. *Autism Research: Official Journal of the International Society for Autism Research, 5,* 160–179. https://doi.org/10.1002/aur.239.

Fitzgerald-Butt, S. M., et al. (2016). Measuring genetic knowledge: A brief survey instrument for adolescents and adults. *Clinical Genetics, 89,* 235–243. https://doi.org/10.1111/cge.12618.

Geschwind, D. H. (2011). Genetics of autism spectrum disorders. *Trends in Cognitive Sciences, 15,* 409–416. https://doi.org/10.1016/j.tics.2011.07.003.

Girirajan, S., et al. (2013). Global increases in both common and rare copy number load associated with autism. *Human Molecular Genetics, 22,* 2870–2880. https://doi.org/10.1093/hmg/ddt136.

Goldstein, J., Ross, D. A., & Moreno De Luca, D. (2019). Found in translation: Autism genetics and the quest for its Rosetta Stone. *Biological Psychiatry, 85,* e29–e30. https://doi.org/10.1016/j.biopsych.2019.02.001.

Guideline, A.N.C. *SIGN 145—Assessment, diagnosis and interventions for autism spectrum disorders*. Healthcare Improvement Scotland.

Hallmayer, J., et al. (2011). Genetic heritability and shared environmental factors among twin pairs with autism. *Archives of General Psychiatry, 68,* 1095–1102. https://doi.org/10.1001/archgenpsychiatry.2011.76.

Hansen, S. N., et al. (2019). Recurrence risk of autism in siblings and cousins: A multi-national, population-based study. *Journal of the American Academy of Child and Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2018.11.017.

Huguet, G., Ey, E., & Bourgeron, T. (2013). The genetic landscapes of autism spectrum disorders. *Annual Review of Genomics and Human Genetics, 14,* 191–213. https://doi.org/10.1146/annurev-genom-091212-153431.

Israel, Central Bureau of Statistics of Israel. (2008). *Characterization and classification of geographical units by the socio-economic level of the population*. Environment and Region.

Israel, Ministry of Health. (1995). National Health Insurance Law.

Israel, Ministry of Health. (2013). *Children on the autism spectrum diagnosis*. Director General Circular.

Kearney, H. M., South, S. T., Wolff, D. J., Lamb, A., Hamosh, A., & Rao, K. W. (2011). American College of Medical Genetics recommendations for the design and performance expectations for clinical genomic copy number microarrays intended for use in the postnatal setting for detection of constitutional abnormalities. *Genetics in Medicine, 13,* 676–679. https://doi.org/10.1097/GIM.0b013e31822272ac.

Kessels, R. P. C. (2003). Patients' memory for medical information. *Journal of the Royal Society of Medicine, 96,* 219–222. https://doi.org/10.1177/014107680309600504.

Kogan, M. D., et al. (2018). The prevalence of parent-reported autism spectrum disorder among US children. *Pediatrics, 142,* e20174161.

Lord, C., et al. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders, 30,* 205–223.

Marshall, C. R., & Scherer, S. W. (2012). Detection and characterization of copy number variation in autism spectrum disorder. *Methods in Molecular Biology, 838,* 115–135. https://doi.org/10.1007/978-1-61779-507-7_5.

May, M. E., Brandt, R. C., & Bohannan, J. K. (2012). Moderating effects of autism on parent views of genetic screening for aggression. *Intellectual and developmental disabilities, 50,* 415–425. https://doi.org/10.1352/1934-9556-50.5.415.

Meiri, G., et al. (2017). Brief report: The Negev Hospital-University-Based (HUB) Autism Database. *Journal of Autism and Developmental Disorders, 47,* 2918–2926. https://doi.org/10.1007/s10803-017-3207-0.

Menashe, I., Larsen, E. C., & Banerjee-Basu, S. (2013). Prioritization of copy number variation loci associated with autism from AutDB-an integrative multi-study genetic database. *PLoS ONE, 8,* e66707. https://doi.org/10.1371/journal.pone.0066707.

Miller, D. T., et al. (2010). Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *American Journal of Human Genetics, 86,* 749–764. https://doi.org/10.1016/j.ajhg.2010.04.006.

Moss, J., & Howlin, P. (2009). Autism spectrum disorders in genetic syndromes: Implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. *Journal of Intellectual Disability Research, 53,* 852–873. https://doi.org/10.1111/j.1365-2788.2009.01197.x.

Muers, M. (2012). Human genetics: Fruits of exome sequencing for autism. *Nature Reviews Genetics, 13,* 377. https://doi.org/10.1038/nrg3248.

O'Roak, B. J., et al. (2011). Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. *Nature Genetics, 43,* 585–589. https://doi.org/10.1038/ng.835.

Pinto, D., et al. (2010). Functional impact of global rare copy number variation in autism spectrum disorders. *Nature, 466,* 368–372. https://doi.org/10.1038/nature09146.

Renty, J., & Roeyers, H. (2006). Satisfaction with formal support and education for children with autism spectrum disorder: The voices of the parents. *Child: Care, Health and Development, 32,* 371–385. https://doi.org/10.1111/j.1365-2214.2006.00584.x.

Sanders, S. J., et al. (2012). De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature, 485,* 237–241. https://doi.org/10.1038/nature10945.

Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Larsson, H., Hultman, C. M., & Reichenberg, A. (2014). The familial risk of autism. *JAMA, 311,* 1770–1777. https://doi.org/10.1001/jama.2014.4144.

Satterstrom, F. K., et al. (2020). Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell*. https://doi.org/10.1016/j.cell.2019.12.036.

Tammimies, K., et al. (2015). Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. *JAMA, 314,* 895–903. https://doi.org/10.1001/jama.2015.10078.

Tchaconas, A., & Adesman, A. (2017). Diagnostic evaluation of children with autism spectrum disorders: Clinician compliance with published guidelines. *Journal of Developmental and Behavioral Pediatrics: JDBP, 38,* 29–38. https://doi.org/10.1097/dbp.0000000000000349.

Tick, B., Bolton, P., Happe, F., Rutter, M., & Rijsdijk, F. (2016). Heritability of autism spectrum disorders: A meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry, 57,* 585–595. https://doi.org/10.1111/jcpp.12499.

Yip, B. H. K., et al. (2018). Heritable variation, with little or no maternal effect, accounts for recurrence risk to autism spectrum disorder in Sweden. *Biological Psychiatry, 83,* 589–597. https://doi.org/10.1016/j.biopsych.2017.09.007.

Zamora, I., Williams, M., Higareda, M., Wheeler, B., & Levitt, P. (2016). Brief report: Recruitment and retention of minority children for autism research. *Journal of Autism and Developmental Disorders, 46,* 698–703. https://doi.org/10.1007/s10803-015-2603-6.

Zhao, S., Chen, W. J., Dhar, S. U., Eble, T. N., Kwok, O. M., & Chen, L. S. (2019). Genetic testing experiences among parents of children with autism spectrum disorder in the United States. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-019-04200-z.