Broader autism phenotype in mothers predicts social responsiveness in young children with autism spectrum disorders

（　母親の自閉症広域表現型が自閉症スペクトラム児の対人応答性を予測する　）

大阪大学大学院
大阪大学・金沢大学・浜松医科大学
連合小児発達学研究科
小児発達学専攻

長谷川 千秋

２０１５年２月　博士学位論文

 doi:10.1111/pcn.12210

Regular Article

Broader autism phenotype in mothers predicts social responsiveness in young children with autism spectrum disorders

Chiaki Hasegawa, MA,[1] Mitsuru Kikuchi, MD, PhD,[1,2]* Yuko Yoshimura, PhD,[1] Hirotoshi Hiraishi, MED,[1] Toshio Munesue, MD, PhD,[1,2] Hideo Nakatani, MD, PhD,[2] Haruhiro Higashida, MD, PhD,[1] Minoru Asada, PhD,[3] Manabu Oi, PhD[1] and Yoshio Minabe, MD, PhD[1,2]

[1]*Research Center for Child Mental Development,* [2]*Department of Psychiatry and Neurobiology, Graduate School of Medical Science, Kanazawa University, Kanazawa, and* [3]*Department of Adaptive Machine Systems, Graduate School of Engineering, Osaka University, Suita, Japan*

Aims: The aim of this study was to identify phenotypes in mothers and fathers that are specifically associated with disturbances in reciprocal social interactions and communication in their young children with autism spectrum disorder (ASD) in a Japanese sample.

Methods: Autistic traits in parents were evaluated using the Autism-spectrum Quotient (AQ), the Empathy Quotient (EQ) and the Systemizing Quotient (SQ) in 88 parents (44 mothers and corresponding fathers) of children with ASD and in 60 parents (30 mothers and corresponding fathers) of typically developing (TD) children. For the measurement of autistic traits in children, we employed the Social Responsiveness Scale (SRS).

Results: In two of the five AQ subscales (social skills and communication), the parents of ASD children scored significantly higher than did the parents of TD children, regardless of whether the parent was a mother or a father. In addition, in mothers of ASD children, there were significant positive correlations between two of the five AQ subscales (attention-switching and communication) and the SRS *T*-score in their children.

Conclusions: This is the first study to demonstrate that the social skills and communication subscales in the AQ are more sensitive as autism traits in a Japanese sample and to demonstrate that some autistic traits in mothers are specifically associated with disturbances in the social ability of their young children with ASD, as measured by the SRS score. Further study is necessary to determine whether these results were caused by genetic or environmental factors.

Key words: autism spectrum disorder, Autism-spectrum Quotient, Empathy Quotient, parents, Social Responsiveness Scale.

AUTISM SPECTRUM DISORDERS (ASD) appear in early childhood, causing delays or impairments in social interactions and communication, as well as a restricted range of interests.[1] Initially, the evidence for the genetic basis of ASD was provided by twin studies of classic autism[2,3] and, more recently, twin studies of autistic traits.[4–6] A strong genetic component was indicated by a concordance of 60% versus 3–5% in monozygotic and dizygotic twins, respectively,[2] and by many molecular genetic associations.[7] However, identifying specific DNA sequence variations that cause ASD has been difficult; replicating the results has been hampered by methodological issues, such as limited power and varying designs,

Correspondence: Mitsuru Kikuchi, MD, PhD, Research Center for Child Mental Development, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan. Email: mitsuru@zc4.so-net.ne.jp
Received 6 January 2014; revised 16 April 2014; accepted 2 June 2014.

along with imprecise phenotypic definitions.[8] ASD seems to be both genetically and phenotypically heterogeneous. The behavioral traits of ASD suggest a continuous distribution across the population;[9] therefore, a categorical approach to identifying causative factors may not be the best approach to identifying the specific DNA sequence and/or neurophysiological variations that cause ASD.

In first-degree relatives of individuals with ASD, a phenotype that is milder but echoes a similar profile to the defining features of ASD is often observed[10–13] and is referred to as the broader autism phenotype (BAP). The BAP refers to heritable, sub-threshold autism-related traits and may be related to different genetic loading in families with autism.[14] The BAP is generally considered to be a subclinical set of characteristics or traits that index familiarity and/or genetic liability to autism. This conception holds that the BAP is milder but qualitatively similar to the diagnosed autism phenotype. Therefore, the importance of measuring the BAP is sharply rising not only in genetic studies but also across autism research (for example, in neuroimaging and cognitive studies).[15,16]

For adults, there are instruments available for the assessment of the BAP. One of the instruments used extensively is the Autism-spectrum Quotient (AQ).[17] The AQ was developed to assess where an individual lies on the autism spectrum (that is, how many autistic traits an individual exhibits). The AQ for adults has the format of a self-report, forced-choice questionnaire and is at the reading level of a typical 10-year-old. It can be used by adults with an IQ in the average range, who can read and understand at least at this level. There are 50 items assessing behaviors across five domains: communication, social skills, attention-switching, imagination, and attention to detail. In addition to the AQ, the traits of ASD in adults have been characterized using the following two dimensions: the Empathy Quotient (EQ)[18] and the Systemizing Quotient (SQ).[19] These three dimensions can be used to assess milder variants of autistic-like traits (i.e., high AQ, low EQ, and high SQ) in typically developing individuals.[6,20,21] Empathy is an essential part of normal social functioning that allows us to understand the intentions of others, predict their behavior, and experience an emotion triggered by their emotions. The EQ is a self-report questionnaire for use with adults of normal intelligence that focuses purely on this domain.[18] Systemizing is the drive to analyze the variables in a system and derives the underlying rules that govern the behavior of a system. The SQ is a self-report questionnaire for use with adults of normal intelligence that focuses purely on this domain across the range of different system classes.[19]

For children, one instrument available for the assessment of the BAP in Japan is the Social Responsiveness Scale (SRS).[22] The SRS is a 65-item questionnaire that is completed by an adult informant. It focuses on the ability of the subject of the questionnaire to engage in emotionally appropriate reciprocal social interactions and communication. Using the SRS, a higher number of autistic traits have been observed in the siblings of children with autism.[23]

The aims of this study were to determine the specific subtypes of the BAP in parents (i.e., the AQ, EQ and SQ scores) that are specifically associated with disturbances in reciprocal social interactions and communication in their young children with ASD (i.e., the SRS score) in a Japanese sample. Viewing the effects of the BAP on their offspring in this way sheds new light on existing and emerging data and has crucial implications for genetically identifying the BAP in adults.

METHODS

Participants

All participants were recruited from public nursery schools in Kanazawa city, Kanazawa University's Hospital and prefectural hospitals in Toyama. At first, 96 children and their parents voluntarily participated in this study. Clinically recruited children were diagnosed by a clinical psychiatrist and a clinical psychologist with more than 5 years of experience in ASD using the Autism Diagnostic Observational Schedule–Generic (ADOS),[24] the Diagnostic Interview for Social and Communication Disorders (DISCO),[25] and the DSM-IV[1] criteria at the time that they participated in this study. ASD children were included in this study when they fulfilled the diagnosis of childhood autism, atypical autism or Asperger's syndrome with DISCO, or the ADOS criteria for the autism spectrum. Exclusion criteria for children included known hearing loss or a central nervous system involvement other than autism. The final clinical group consisted of 44 children with ASD (35 boys, nine girls) aged 38–93 months and their parents (44 mothers and the corresponding fathers) (Table 1). The controls were 30 typically developing (TD) children (23 boys, seven girls) aged 37–95

Table 1. Demographic characteristics of the study participants

	TD children	ASD children	t	*P*
Number of subjects	30	44		
Sex (male/female)	23/7	35/9		
Chronological age (months)	66.4 (37–95)	65.4 (38–93)	0.29	NS
SRS total *T*-score	48.2 (5.9)	72.8 (10.4)	12.9	$P < 0.01$
K-ABC Mental Processing Scale	99.2 (11.5)	94.7 (24.3)	−1.1	NS
K-ABC Achievement Scale	100.5 (13.7)	96.4 (20.9)	−1.0	NS
Parents				
Age of mother (years)	36.3 (22–47)	36.6 (26–48)	0.26	NS
Age of father (years)	39.0 (24–54)	37.7 (25–48)	−0.98	NS

Values are mean (range or SD) for chronological age, father's age, mother's age and scales on the K-ABC and the SRS. ASD, autism spectrum disorder; K-ABC, Kaufman Assessment Battery for Children; NS, not significant; SRS, Social Responsiveness Scale; TD, typically developing.

months and their parents (30 mothers and the corresponding fathers) (Table 1). All TD children and their parents had no prior or current developmental, learning, or behavioral problems, as reported on a questionnaire completed by their parents. If the parents reported difficulties in daily life because of their intelligence level, we excluded them from this experiment. The parents agreed to their child's participation in the study with full knowledge of the experimental nature of the research. Written informed consent was obtained prior to participation. The Ethics Committee of Kanazawa University Hospital approved the methods, and all procedures were performed in accordance with the Declaration of Helsinki.

Psychological tasks for autistic traits

Quantitative autistic traits in children were assessed by parents using the Japanese version[22] of the SRS.[26] Higher scores on the SRS indicate a higher degree of social impairment. The raw scores of the SRS were converted to *T*-scores (with a mean of 50 and a standard deviation of 10) for sex. All *T*-scores in the SRS were significantly higher in the ASD group compared to the controls (Table 1). The Kaufman Assessment Battery for Children (K-ABC)[27] was employed to estimate the intelligence level in the children.

Traits of ASD in parents were assessed by the AQ,[17] EQ[18] and SQ scores,[19] which consisted of self-report measures of autistic traits. These three dimensions can be used to assess milder variants of autistic-like traits (i.e., low EQ, high AQ and high SQ) in typically developing individuals.[6,20,21]

Statistical analysis

For the AQ, the EQ and the SQ total scores, a two-way ANOVA was performed (parent × diagnosis). The within-subjects factor was the parent effect (mother vs father), whereas the between-subjects factor was the diagnosis effect (ASD vs TD).

For the AQ subscales (i.e. social skills, attention-switching, attention to detail, communication and imagination), a two-way ANOVA was performed (parent × diagnosis) in the same manner.

In the present study, our main concern was to evaluate how autistic traits in young children are constrained by autistic traits in their mothers and fathers. We performed multiple linear regressions to predict the autistic traits in young children measured by the SRS *T*-score using the AQ, EQ, and SQ total scores in their mothers and fathers as predictors (i.e., six independent variables) in the ASD ($n = 44$), TD ($n = 30$) and mixed groups ($n = 74$).

Because a multiple regression analysis demonstrated that the AQ total score in the mother was the significant predictor for the SRS score in their children in the ASD group, a Pearson's correlation was used to find significant correlations between the AQ subscales in mothers (i.e., social skills, attention-switching, attention to detail, communication and imagination) and the SRS subscales in their children (i.e., awareness, cognition, communication, motivation and mannerisms).

The significance level was set at $P < 0.05$ for all statistical analyses.

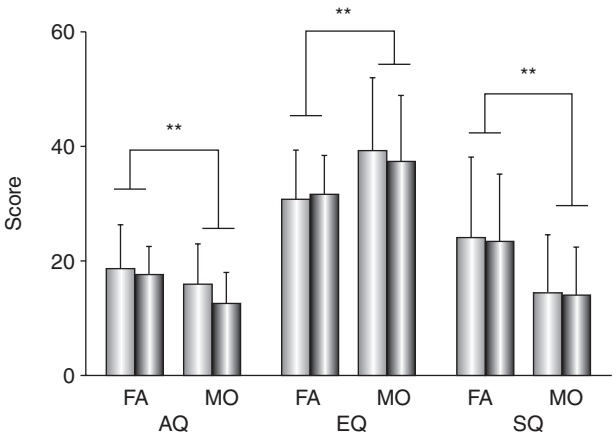

Figure 1. Parents' scores on the Autism-spectrum Quotient (AQ), the Empathy Quotient (EQ) and the Systemizing Quotient (SQ). (▯) Parents who have autism spectrum disorder children ($n = 44$). (▮) Parents who have typically developing children ($n = 30$). A two-way ANOVA revealed a significant effect between the father (FA) and the mother (MO) on the AQ, the EQ and the SQ. The values indicate the mean. Error bars represent the SD. $^{**}P < 0.01$.

RESULTS

As shown in Table 1, 74 trios satisfied the inclusion criteria for the present study. There were no significant differences in the children's chronological age (months), scores on the K-ABC or parents' ages (father and mother) between the TD and ASD groups.

For the AQ, EQ and SQ scores, two-way ANOVA failed to demonstrate a significant main effect of group (i.e. ASD vs TD) or a significant interaction (i.e. group × sex in parent). As shown in Figure 1, significant main effects of sex in parents were observed in the total AQ ($F = 12.72$, $P < 0.01$), the EQ ($F = 17.39$, $P < 0.01$) and the SQ ($F = 25.50$, $P < 0.01$).

For the AQ subscales, two-way ANOVA revealed significant main effects of the group, with the ASD parents scoring higher than the TD parents on two of the five AQ subscales: social skills ($F = 5.87$, $P < 0.05$) and communication ($F = 5.27$, $P < 0.05$) (Fig. 2). There were significant main effects of sex in parents on two of the five AQ subscales: social skills ($F = 8.73$, $P < 0.01$) and imagination ($F = 9.19$, $P < 0.01$). There were no significant interactions (group × sex in parent) in any AQ subscales (Fig. 2).

We performed multiple liner regressions separately for the ASD ($n = 44$), TD ($n = 30$) and mixed groups

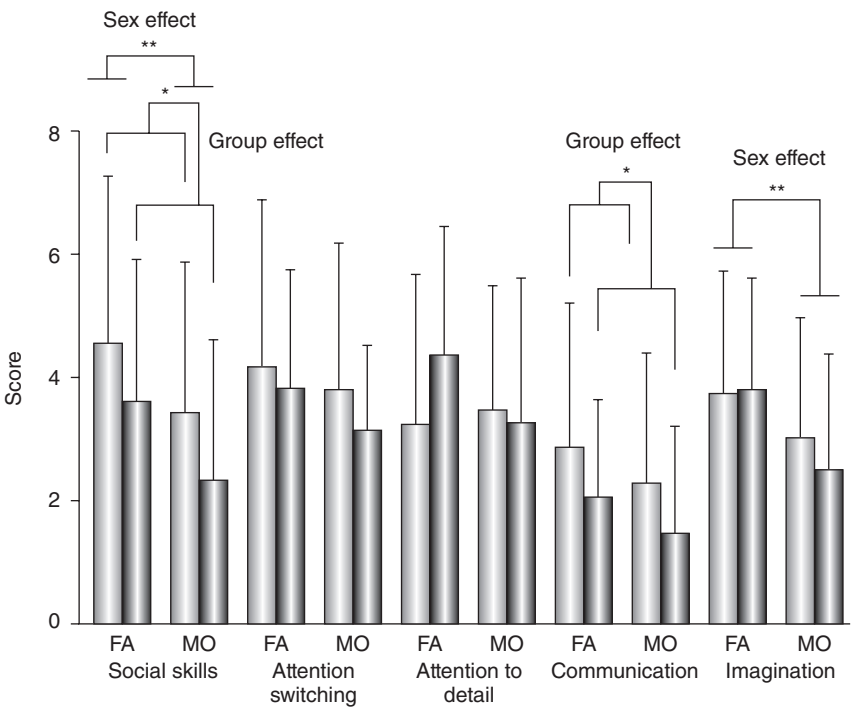

Figure 2. Subscales of the Autism-spectrum Quotient in parents. (▯) Parents who have autism spectrum disorder (ASD) children ($n = 44$). (▮) Parents who have typically developing (TD) children ($n = 30$). Two-way ANOVA revealed significant group (ASD vs TD) effects in the subscales of social skills ($P < 0.05$) and communication ($P < 0.05$). Significant effects between the father (FA) and mother (MO) were also observed in the subscales of social skills ($P < 0.01$) and imagination ($P < 0.01$). The values indicate the mean. Error bars represent the SD. $^{*}P < 0.05$ and $^{**}P < 0.01$.

Table 2. Standardized regression coefficient β and t values for the multiple regression models with the SRS total score in ASD children as the dependent variable. AQ, EQ, and SQ scores in their fathers and mothers were utilized as the independent variables

	β	t
AQ in FA	−0.213	−1.322
AQ in MO	0.567	2.805**
EQ in FA	0.226	1.239
EQ in MO	0.080	0.405
SQ in FA	−0.175	−1.072
SQ in MO	−0.113	−0.735

** $P < 0.01$.
Number of subjects = 44, $R^2 = 0.304$ ($P < 0.05$).
AQ, Autism Quotient; ASD, autism spectrum disorder; EQ, Empathy Quotient; FA, father; MO, mother; SQ, Systemizing Quotient; SRS, Social Responsiveness Scale.

($n = 74$). In the parents of the ASD children (Table 2), the coefficient of multiple determination for multiple regression (i.e., $R^2 = 0.304$) reached significance ($P < 0.05$), and this model revealed that only the AQ total score in the mother was a significant predictor of the SRS score in children (correlation coefficients: $n = 44$, $\beta = 0.567$, $P < 0.01$); the EQ and SQ of the mother and the AQ, EQ and SQ of the father did not reach statistical significance. In the TD parents, the coefficient of multiple determinations for multiple regressions did not reach statistical significance. In the parents of all the children (i.e., TD and ASD) (Table 3), the coefficient of multiple determination for multiple regression (i.e., $R^2 = 0.179$) reached significance ($P < 0.05$), and this model revealed that only the AQ total score in the mother was a significant predictor of the SRS score in children (correlation coefficients: $n = 74$, $\beta = 0.520$, $P < 0.01$); the EQ and SQ of the mother and the AQ, EQ and SQ of the father did not reach statistical significance.

As a complementary analysis, for relationships in which significance was observed in the multiple linear regression analysis, Pearson's correlation coefficients (i.e., simple liner regressions) were calculated between the SRS total score of the children and the AQ total score of their mothers. As shown in Figure 3, a significant positive correlation was observed in the mothers who had ASD children ($r = 0.394$, $P < 0.01$), whereas no significant correlation was found in the mothers who had TD children.

Because there was a significant correlation between the SRS total score and the AQ total score in the ASD group, we added a complementary analysis, that is, a simple correlation analysis using a Pearson correlation coefficient between the five AQ subscales (and total scale) in the mother and the five SRS subscales (and total scale) in their children. As shown in Table 4, there were significant positive correlations in 10 of the 36 correlations.

DISCUSSION

The main aim of this study was to identify phenotypes in mothers and fathers that are specifically associated with the disturbance of social interactions in their young children with ASD in a Japanese sample. This study in a Japanese sample replicates previous findings reported in other countries and provides new evidence. The cross-cultural stability of the AQ and SRS as a measure of the BAP or ASD symptom is the main strength of the study.

This case–control study demonstrated that in two of the five AQ subscales (social skills and communication), the parents of ASD children scored significantly higher than did the parents of TD children, regardless of whether the parent was the mother or the father. The present study replicated four of the five previous studies examining AQ scores in other countries. Bishop *et al*. demonstrated that AQ scores

Table 3. Standardized regression coefficient β and t values for the multiple regression models with the SRS total score in all children (TD and ASD) as the dependent variable. AQ, EQ, and SQ scores in their fathers and mothers were utilized as the independent variables

	β	t
AQ in FA	−0.036	−0.273
AQ in MO	0.520	3.686**
EQ in FA	0.171	1.186
EQ in MO	0.200	1.469
SQ in FA	−0.074	−0.602
SQ in MO	−0.119	−1.026

** $P < 0.01$.
Number of subjects = 74, $R^2 = 0.179$ ($P < 0.05$).
AQ, Autism Quotient; ASD, autism spectrum disorder; EQ, Empathy Quotient; FA, father; MO, mother; SQ, Systemizing Quotient; SRS, Social Responsiveness Scale; TD, typically developing.

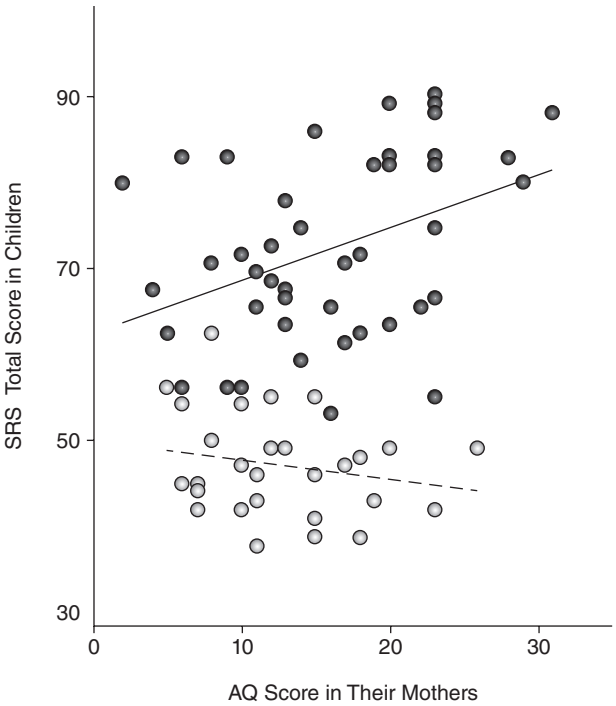

Figure 3. Scatter plot of the Social Responsiveness Scale (SRS) total *T*-score in children and the Autism-spectrum Quotient (AQ) score of their mothers in the (●) autism spectrum disorder (ASD) and (○) typically developing (TD) groups. In the ASD group, the SRS score in children was significantly correlated with the AQ score of their mother ($P < 0.01$). Solid line, regression line for the children with ASD; broken line, regression line for the TD. ASD ($P < 0.01$, $r = 0.394$, $n = 44$); TD ($P = 0.284$, $r = -0.202$, $n = 30$).

differentiate parents of children with an ASD from control parents on the social skills and communication subscales.[11] Ruta *et al.* obtained similar results: the total score and the communication, imagination and social skills subscales of the Italian version of the AQ were higher in ASD parents.[12] Kose *et al.* reported similar results: there were group differences in the AQ total score and in two of the five subscales (i.e. social skills and communication) in the Turkish version of the AQ.[13] In a larger sample size, Wheelwright *et al.* reported that ASD parents scored higher than did the control parents on the total scale and on four of the five AQ subscales (i.e., except the attention to details subscale).[10] Only one study failed to demonstrate differences in the total or AQ subscale scores.[28] Intriguingly, in two of the five studies, a significant group × sex interaction for some AQ subscales was demonstrated with a relatively large sample design.[10,12] Ruta *et al.* reported that the higher scores in parents of ASD children in the imagination subscale were driven by mothers.[12] Wheelwright *et al.* also reported a similar finding for the AQ total score and the imagination and attention-switching subscales.[10] In the present study, as shown in Figure 2, we found the same trend (i.e., higher scores in mothers of ASD children on the imagination and attention-switching subscales); however, we failed to find a significant group × sex interaction. This could be due to the smaller sample size in the present study (i.e., limitation of the statistical power).

For the main aim of this study, as shown in Table 4, we performed a correlation study and provided the first evidence that two of the five autistic traits measured by the AQ subscales (attention-switching and communication) in mothers were

Table 4. Correlation coefficients between AQ subscales in mothers and SRS subscales in their children with ASD

	SRS total	SRS AWA	SRS COG	SRS COM	SRS MOT	SRS MAN
AQ total	0.394**	−0.075	0.383*	0.346*	0.370*	0.375*
AQ: social skill	0.245	0.010	0.179	0.233	0.235	0.205
AQ: attention-switching	0.355*	0.010	0.353*	0.370*	0.262	0.284
AQ: attention to detail	0.089	−0.152	0.199	0.002	0.166	0.118
AQ: communication	0.341*	0.028	0.297	0.292	0.289	0.310*
AQ: imagination	0.212	−0.168	0.188	0.178	0.228	0.284

*$P < 0.05$ and **$P < 0.01$. $n = 44$.
AQ, Autism Quotient; ASD, autism spectrum disorder; AWA, awareness; COG, cognition; COM, communication; MAN, mannerisms; MOT, motivation; SRS, Social Responsiveness Scale.

specifically associated with a disturbance in social ability, as measured by the SRS score, in their young children with ASD. In addition, significant positive correlations in 10 of the 36 correlations were revealed by a Pearson correlation coefficient between the five AQ subscales (and total scale) in the mother and the five SRS subscales (and total scale) in their children. To our knowledge, no previous quantitative study has demonstrated the correlation between the BAP in mothers and the autism phenotype in their children with ASD. However, two case–control studies reported that the higher scores on the imagination[10,12] or attention-switching[10] subscales in parents of ASD children were driven by mothers. Therefore, these findings suggested that the BAP that indexes genetic liability to autism tends to be observed in specific AQ subscales, especially in the case of female subjects.

In the present study, autistic traits measured by the AQ, the EQ and the SQ in fathers were not significantly correlated with disturbances in social ability, measured by the SRS score, in their young children with ASD. Consistent with our results, no previous study has demonstrated a significant correlation between the BAP in the father measured by a self-report questionnaire and severity in their children with ASD. Conversely, many case–control studies have demonstrated that performance in cognitive tasks was lower among the fathers of ASD children than among fathers of TD children.[28–31] We cannot draw a definitive conclusion from our study because we did not measure cognitive function in parents; however, the findings from previous studies suggest that the BAP that indexes genetic liability to autism tends to be observed in cognitive impairment (e.g. executive function or central coherence), but not in the AQ score, especially in male subjects.

This study has some limitations. The first limitation is that the AQ for adults has the format of a self-report questionnaire. Therefore, we need to consider the possibility that the self-report from the parents of ASD children could, in part, reflect their familiarity with the symptoms of ASD. To help rule out a role for response bias on the AQ, future studies are needed to assess how the self-reported traits identified by the AQ relate to behaviors identified using other means of assessment. However, it seems unlikely that such bias could explain the findings that we observed in the present study because the AQ was designed to minimize such biased responding by having test items that ask about an individual's preferences, rather than one's ability or disability.[17] In addition, an individual who has been over-sensitized to autistic behaviors might be expected to score high on all five subscales of the AQ, rather than selectively on two subscales. A second limitation is that we did not measure the intelligence level or the socioeconomic status of the parents; therefore, we could not control for these potential confounds. However, all parents had no prior or current developmental, learning, or behavioral problems, and they were at or above the reading level required to understand these questionnaires. A third limitation is that with our study design, we could not draw a definitive conclusion whether the observed phenotypic correlations between mothers and ASD children were caused by hereditary or environmental factors. Future studies could also include families that have a non-biological child with ASD, to test whether there are effects of environmental factors that contribute to phenotypic correlations between parents and ASD.

Conclusions

In summary, autistic traits in parents were evaluated using the AQ, the EQ and the SQ in 88 parents of children with ASD and in 60 parents of TD children. For the measurement of autistic traits in children, we employed the SRS. In the AQ subscales, the parents of ASD children scored significantly higher than the parents of TD children on two of the five subscale scores, social skills and communication, regardless of whether the parent was a mother or a father. This is the first study in a Japanese sample to demonstrate that the social skills and communication subscales are more sensitive as autism traits. A multiple regression analysis revealed that a higher AQ total score in the mother was only one significant predictor of higher autistic traits (i.e., the SRS total score) in their children, whereas the other total scores in mothers (i.e., the EQ and SQ) and fathers (i.e., the EQ, SQ and AQ) were not significant predictors. A simple linear correlation analysis revealed that two of the five autistic traits measured by the SRS subscales (attention-switching and communication) in mothers were specifically associated with a disturbance in the social ability, measured by the SRS score, in their young children with ASD. Viewing the effects of the BAP on their offspring in this way sheds new light on existing and emerging data and has crucial implications for genetically identifying the BAP in adults.

ACKNOWLEDGMENTS

This study was supported by a Grant-in-Aid for Specially Promoted Research (Number 24000012) from MEXT, and was partially supported by the Center of Innovation Program from Japan Science and Technology Agency, JST, Japan. The authors declare that they have no conflicts of interest.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association, Washington, DC, 1994.
2. Bailey A, Le Couteur A, Gottesman I *et al*. Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychol. Med.* 1995; **25**: 63–77.
3. Folstein S, Rutter M. Infantile autism: A genetic study of 21 twin pairs. *J. Child Psychol. Psychiatry* 1977; **18**: 297–321.
4. Constantino JN, Todd RD. Intergenerational transmission of subthreshold autistic traits in the general population. *Biol. Psychiatry* 2005; **57**: 655–660.
5. Ronald A, Happe F, Bolton P *et al*. Genetic heterogeneity between the three components of the autism spectrum: A twin study. *J. Am. Acad. Child Adolesc. Psychiatry* 2006; **45**: 691–699.
6. Hoekstra RA, Bartels M, Verweij CJ, Boomsma DI. Heritability of autistic traits in the general population. *Arch. Pediatr. Adolesc. Med.* 2007; **161**: 372–377.
7. Abrahams BS, Geschwind DH. Advances in autism genetics: On the threshold of a new neurobiology. *Nat. Rev. Genet.* 2008; **9**: 341–355.
8. Losh M, Sullivan PF, Trembath D, Piven J. Current developments in the genetics of autism: From phenome to genome. *J. Neuropathol. Exp. Neurol.* 2008; **67**: 829–837.
9. Constantino JN, Todd RD. Autistic traits in the general population: A twin study. *Arch. Gen. Psychiatry* 2003; **60**: 524–530.
10. Wheelwright S, Auyeung B, Allison C, Baron-Cohen S. Defining the broader, medium and narrow autism phenotype among parents using the Autism Spectrum Quotient (AQ). *Mol. Autism* 2010; **1**: 10.
11. Bishop DV, Maybery M, Maley A, Wong D, Hill W, Hallmayer J. Using self-report to identify the broad phenotype in parents of children with autistic spectrum disorders: A study using the Autism-Spectrum Quotient. *J. Child Psychol. Psychiatry* 2004; **45**: 1431–1436.
12. Ruta L, Mazzone D, Mazzone L, Wheelwright S, Baron-Cohen S. The Autism-Spectrum Quotient – Italian version: A cross-cultural confirmation of the broader autism phenotype. *J. Autism Dev. Disord.* 2012; **42**: 625–633.
13. Kose S, Bora E, Erermis S, Ozbaran B, Bildik T, Aydin C. Broader autistic phenotype in parents of children with autism: Autism Spectrum Quotient-Turkish version. *Psychiatry Clin. Neurosci.* 2013; **67**: 20–27.
14. Virkud YV, Todd RD, Abbacchi AM, Zhang Y, Constantino JN. Familial aggregation of quantitative autistic traits in multiplex versus simplex autism. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2009; **150B**: 328–334.
15. Yoshimura Y, Kikuchi M, Ueno S *et al*. The brain's response to the human voice depends on the incidence of autistic traits in the general population. *PLoS ONE* 2013; **8**: e80126.
16. Hirosawa T, Kikuchi M, Higashida H *et al*. Oxytocin attenuates feelings of hostility depending on emotional context and individuals' characteristics. *Sci. Rep.* 2012; **2**: 384.
17. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J. Autism Dev. Disord.* 2001; **31**: 5–17.
18. Baron-Cohen S, Wheelwright S. The empathy quotient: An investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *J. Autism Dev. Disord.* 2004; **34**: 163–175.
19. Baron-Cohen S, Richler J, Bisarya D, Gurunathan N, Wheelwright S. The systemizing quotient: An investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. *Philos. Trans. R. Soc. Lond. B. Biol Sci.* 2003; **358**: 361–374.
20. Dawson G, Webb S, Schellenberg GD *et al*. Defining the broader phenotype of autism: Genetic, brain, and behavioral perspectives. *Dev. Psychopathol.* 2002; **14**: 581–611.
21. Valla JM, Ganzel BL, Yoder KJ *et al*. More than maths and mindreading: Sex differences in empathizing/systemizing covariance. *Autism Res.* 2010; **3**: 174–184.
22. Kamio Y, Inada N, Moriwaki A *et al*. Quantitative autistic traits ascertained in a national survey of 22 529 Japanese schoolchildren. *Acta Psychiatr. Scand.* 2013; **128**: 45–53.
23. Constantino JN, Lajonchere C, Lutz M *et al*. Autistic social impairment in the siblings of children with pervasive developmental disorders. *Am. J. Psychiatry* 2006; **163**: 294–296.
24. Lord C, Rutter M, DiLavore P, Risi S. *Autism Diagnostic Observation Schedule*. Western Psychological Services, Los Angeles, CA, 1999.
25. Wing L, Leekam SR, Libby SJ, Gould J, Larcombe M. The Diagnostic Interview for Social and Communication Disorders: Background, inter-rater reliability and clinical use. *J. Child Psychol. Psychiatry* 2002; **43**: 307–325.
26. Constantino JN. *The Social Responsiveness Scale*. Western Psychological Services, Los Angeles, CA, 2002.
27. Kaufman A, Kaufman N. *Kaufman Assessment Battery for Children: Administration and Scoring Manual*. American Guidance Service, Circle Pines, MN, 1983.

28. Scheeren AM, Stauder JE. Broader autism phenotype in parents of autistic children: Reality or myth? *J. Autism Dev. Disord.* 2008; **38**: 276–287.
29. Hughes C, Leboyer M, Bouvard M. Executive function in parents of children with autism. *Psychol. Med.* 1997; **27**: 209–220.
30. Happe F, Briskman J, Frith U. Exploring the cognitive phenotype of autism: Weak 'central coherence' in parents and siblings of children with autism: I. Experimental tests. *J. Child Psychol. Psychiatry* 2001; **42**: 299–307.
31. Wong D, Maybery M, Bishop DV, Maley A, Hallmayer J. Profiles of executive function in parents and siblings of individuals with autism spectrum disorders. *Genes Brain Behav.* 2006; **5**: 561–576.