Genetic syndromes in the family : child characteristics and parenting stress in Angelman, CHARGE, Cornelia de Lange, Prader-Willi, and Rett syndrome

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2 Autistic disorder symptoms in Rett syndrome

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ABSTRACT

According to the major classification systems it is not possible to diagnose a comorbid autistic disorder in persons with Rett syndrome. However, this is a controversial issue, and given the level of functioning of persons with Rett syndrome, the autistic disorder is expected to be present in a comparable proportion as in people with the same level of functioning. To investigate, parents of 52 females with classical and atypical Rett syndrome (2.4 – 49.3 years) completed the Developmental Behavior Checklist (DBC), the Diagnostic Interview for Social and Communication Disorders (DISCO) and the Dutch Vineland Screener 0-6 (VS 0-6). All participants had a severe to profound intellectual disability according to the VS 0-6. Behavior indicated an autistic disorder in 42% (DBC) to 58% (DISCO) of the Rett cases. Autistic behavior had decreased in 19% such that they no longer met the criteria for autistic disorder. Some participants were suspected of having a comorbid autistic disorder, though not more often than can be expected at their level of functioning. Clinicians should be aware of the possibility of a comorbid autistic disorder as much as they should be in other people with this level of functioning.

INTRODUCTION

Rett syndrome (RS) is a neurodevelopmental disorder with a particular course: a seemingly normal early development is disturbed by a loss of acquired developmental skills, but is followed afterwards by a so-called 'wake up period'. The RS phenotype consists of a classical and certain atypical variants. In classical RS the physical and developmental characteristics fall in four stages, i.e. stagnation (I), regression (II), a pseudostationary period (III) followed by late motor deterioration (IV). The course and features differ for the atypical variants (Hagberg, 2002). According to an overview study, people with RS have a severe but mostly profound intellectual disability (ID), with occasionally higher abilities in the atypical variants (Demeter, 2000). Although RS almost exclusively affects females, some cases of males with RS are known. Mutations in the *MECP2* gene were identified as a cause of RS and now can be detected in most individuals with RS (Percy, 2008). Our knowledge of the genetics and medical aspects of RS has increased dramatically over the last couple of years and was recently reviewed by Percy (2008). The behavior of people with RS however, has received far less attention in

recent years. In this study we focus on the behaviors in relation to the classification of the autistic disorder (AD).

Soon after Rett syndrome became internationally known, one of the diagnostic pitfalls mentioned was to diagnose infantile autism in persons with RS by overestimating the autistic behaviors seen in stages I and II (Hagberg & Witt-Engerström, 1986). It has been observed that the autistic behaviors usually improve or become less prominent when the persons grow older (Gillberg, 1986; Hagberg & Witt-Engerström, 1986). Research into the features of AD, qualitative impairments in social interaction and communication, and restricted, stereotyped patterns of behavior, interests and activities (American Psychiatric Association [APA], 2000), has been carried out in RS. Qualitative differences between people with RS and those with AD with regard to social interaction have been stressed by various authors. In several studies, some to all of the participants with RS were socially orientated and enjoyed social interaction (Dahlgren Sandberg, Ehlers, Hagberg, & Gillberg, 2000; Kerr, Archer, Evans, Prescott, Gibbon, 2006; Olsson & Rett, 1987). Not all authors found this social orientation, but they still clearly distinguished the behavior of people with RS from that of people with AD. In contrast to people with AD, people with RS did not exhibit resistance or a defense reaction when approached (Gillberg, 1987; Olsson & Rett, 1990). On the other hand, Woodyatt and Ozanne (1992) concluded that the six girls in their study made poor eye contact and showed almost no awareness of the people around them.

Research into the other two domains which are impaired in people with AD, namely qualitative impairments in communication and stereotyped patterns of behavior, has shown mixed results for people with RS. Most of them function at the pre-intentional level of communication (Dahlgren Sandberg et al., 2000; Woodyatt & Ozanne, 1992); according to Woodyatt and Ozanne (1997), communicative functions were impaired in persons with RS, even compared to persons with profound ID. Hagberg (2002) however, stressed the importance of intense eye communication as an alternative mode to interact for these severely disabled persons. In a study with 30 participants with the preserved speech variant of the syndrome, all showed echolalia (Zapella, Gillberg, & Ehlers, 1998). Stereotypic hand movements like washing and wringing have been mentioned as the core feature of RS (Hagberg, 2002) and these could be clearly differentiated from the stereotypic behavior seen in AD (Olsson & Rett, 1987).

In two more recent studies with standardized instruments, autism symptoms have been compared between children with RS and children with comparable levels of ID (Mount, Charman, Hastings, Reilly, & Cass, 2003; Mount, Hastings, Reilly, Cass, & Charman, 2003). Mount, Hastings et al. (2003) found that children with RS (all were under 18 years) showed more autistic behavior than children with severe to profound ID. However, compared to the behavior of children with the same level and comorbid AD, girls with RS showed a different behavioral profile. The AD group displayed more 'truly autistic' behavior (e.g. avoiding eye contact, not responding to others' feelings), whereas girls with RS showed more related symptoms (e.g. underactive, unhappy). In a different study, girls with classical RS (aged 11 to 18 years) were compared with children with severe and profound ID whereby the authors controlled for differences in developmental level and motor skills. Participants with RS scored in the range people with AD obtain, but with a slightly different pattern. The children with classical RS may show some but not the full range of autistic behavior (Mount, Charman, et al., 2003).

Although differences in behavior between people with RS and those with AD have been reported, the behavior of some people with RS fulfilled all criteria for AD. Two out of eight participants with RS (11 to 36 years) met the criteria for AD of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV: APA, 1994) (Dahlgren Sandberg et al., 2000). Eight out of 12 females (3 to 24 years) met DSM-III-R criteria (APA, 1987) for AD (Mazzocco et al., 1998). Of 30 persons with the RS preserved speech variant (5 to 28 years) 97% met DSM-IV criteria for AD (Zapella et al., 1998). People with ID have a higher risk of a comorbid diagnosis of AD. Exact prevalence rates are difficult to compare between publications, for instance because of different levels of functioning in the sample, and the definitions and instruments used. In a sample of children with severe to profound ID, at which level almost all persons with RS function, 37% also had AD (Deb & Prasad, 1994). Keeping this high prevalence of AD in people with severe to profound ID in mind, it is expected that a substantial percentage of people with RS have a comorbid AD, whereas others have not.

However, this is a highly controversial point in relation to the major classification systems, i.e. the DSM-IV-TR and the International Statistical Classification of Diseases 10 (ICD-10). There, RS is classified under the pervasive developmental disorders (PDDs) and a diagnosis of RS excludes a diagnosis of autistic disorder or childhood autism (CA) (APA, 2000; World Health Organization [WHO], 1993). Debate about this topic is

ongoing. Opponents of this view wondered why RS was placed in the PDD section when not all RS girls show autistic symptoms. The fact that other genetic syndromes with as high or even higher risk for autistic symptoms were not included in this particular section seemed to argue against this decision as well (Gillberg & Billstedt, 2000; Wing, 2005). Others stated that the clinical picture of RS is different from AD and therefore a subcategory in the PDD section is justified (Rutter, 1994) or placement in that section seemed most relevant at that time (Tsai, 1992). Gillberg (1992) strongly underlined the possibility of diagnosing both RS and AD in an individual.

In this study, in addition to Gillberg's opinion, we want to test the hypothesis that AD symptoms will be present in people with RS in proportions comparable to those in the population of people with a severe to profound ID. We therefore investigated the presence of AD symptoms in children and adults with classical or atypical RS in the Netherlands. We decided to take a broad age range to explore whether autistic symptoms are similar in different age groups, since such a comparison is currently lacking. Apart from this we also want to determine whether autistic symptoms change in some individuals, as this has not been investigated with a semi-structured instrument before. We expect AD symptoms in some individuals to become less prominent as they grow older, as suggested in earlier research.

METHOD

Participants

Participants were 52 families with a daughter with RS; the youngest person was 2.4 years old, the oldest participant 49.3 years. Mean age was 16.5 years (*SD* = 11.8 years). Children (0 to 18 years) accounted for 63% of the sample. Of the 52 participants, 41 had classical RS and 10 atypical RS. For one person the RS type was unknown; this person had an *MECP2* mutation. Of the 41 participants with classical RS, 35 appeared to have *MECP2* mutations; only two females did not have an *MECP2* mutation. For four persons the presence or absence of *MECP2* mutations was unknown, either because genetic screening had not been carried out, or because genetic screening was carried out before the discovery of the *MECP2* gene as a cause of RS. Of the 10 participants with atypical RS, 8 had *MECP2* mutations and 2 did not.

Procedure

The participating families were members of the Dutch Rett Parent Support Group. By letter from the parent support group, all 190 families were asked to take part in the current study. Initially parents of 52 daughters with RS joined the project, but for 3 females it was unclear whether they really had RS; for 1 female no questionnaire was returned. These four persons were excluded from further analyses. After preliminary results were presented at the national family day 2007 of the Dutch Rett Parent Support Group, six other parents expressed willingness to participate. For two of these six children it was unclear whether they really had RS. Data on these two females were also excluded, which left data on 52 persons available for analyses. The participating parents were asked whether their child had classical or atypical RS and whether an *MECP2* mutation was present. Some parents did not know the answers to these questions. In that case written permission to contact the relevant medical specialist was obtained from all but one parent and all specialists approached provided genetic records.

After giving written consent to participate, parents were contacted by phone to schedule an interview with the research assistants. Subsequently the questionnaires were sent out. Parents were asked to send them back in the return envelope before the interview, but the option existed to discuss uncertainties with the interviewers and return the questionnaires afterwards. Parents who did not return the questionnaires were called and encouraged to send it back. If items of the questionnaires were unanswered, the research assistants tried to contact parents by phone and then asked them to complete the blank items verbally. There was limited time to call the parents afterwards as the interval between the original completion of the questionnaires and the completion of items by phone was set to a month. There remained 21 participants for whom one or more items of the questionnaires were unanswered.

Research instruments

The *Developmental Behavior Checklist–Primary Carer* (DBC-P) assesses the emotional and behavioral problems of children with ID over the past six months (Einfeld & Tonge, 2002; Dutch version: Koot & Dekker, 2001). Parents rate 95 items on a three-point scale: score 0 if the item is ‘not true as far as you know’, score 1 if ‘somewhat or sometimes true’, and score 2 if ‘very true or often true’. A total behavior problem score and five subscale scores can be computed. Inter-rater and retest reliability, internal

consistency, and construct and criterion validity are all satisfactory (Koot & Dekker, 2001). The DBC-P has an autism screening algorithm (DBC-ASA), consisting of 29 items of the questionnaire, which screens for autistic disorder as defined by DSM-IV (APA, 1994). The DBC-ASA has good validity to detect children with AD. A cutoff score of 17 had a sensitivity of .86 and specificity of .69. Internal consistency is .94 (Brereton, Tonge, Mackinnon, & Einfeld, 2002).

The *Diagnostic Interview for Social and Communication Disorder–10th revision* (DISCO-10) is a semi-structured interview to support clinicians in diagnosing autism and related disorders in people of all ages and levels of functioning for past and present behavior (Wing, 1999). For research purposes, different algorithms exist (Wing, Leekam, Libby, Gould, & Larcombe, 2002). In DISCO-10 there are, among others, algorithms based on the PDD classifications in ICD-10 and DSM-III-R. We decided to take the ICD-10 criteria for CA as the DSM-III-R criteria are outdated. Good inter-rater reliability has been obtained with the Swedish DISCO-10 translation (Nygren et al., 2009). Good correspondence between a clinical diagnosis of autistic disorder or childhood autism and DISCO-10 CA classification is demonstrated in several studies (Billstedt, 2007; Hoekstra, 2007). In our study the research assistants who took the interview always worked in pairs and received DISCO-10 training by officially registered instructors.

The *Vineland Screener 0-6* (VS 0-6: Scholte, Van Duijn, Dijkxhoorn, Noens, & Van Berckelaer-Onnes, 2008) is a Dutch screening instrument adapted from the Vineland Screener as developed by Sparrow, Carter, and Cicchetti (1993). The VS 0-6 measures the level of adaptive functioning by 72 items on the domains of communication, daily living skills, socialization, and motor skills. Parents indicate on a four-point scale whether the person exhibits the behavior in daily life: score 0 for ‘no, never’, score 1 for ‘sometimes or partly’, and score 2 for ‘yes, usually’. A fourth possible score is ‘unknown’ if the parent is unsure. The VS 0-6 is developed to measure the adaptive developmental level of children up to age six or older people with comparable levels of functioning. It shows good reliability and validity. Inter-rater reliability (intra-class correlation .90 - .97), test-retest reliability (intra-class correlation .97 - .99), and internal consistency (Cronbach’s alpha .95 - .99) have coefficients of .90 or higher for the total score and the four domains. The content validity, construct validity, and criterion validity have all proven to be sufficiently adequate (Scholte et al., 2008).

The first 20 participating parents did not fill out the VS 0-6, but were interviewed with the expanded form of the Vineland Adaptive Behavior Scales (VABS; Sparrow, Balla, & Cicchetti, 1984). The research assistants received the official training for this interview. As the combination of the DISCO-10 and VABS interview appeared to be time-consuming for the parents, it was decided to replace the VABS with the VS 0-6 questionnaire. The relevant items from the VABS interview were used to complete the VS 0-6 for the first 20 participants.

Statistics

The DBC-P and VS 0-6 manuals give rules for the maximum number of missing items per individual to keep the measurement reliable. For the DBC-P no more than 10% of the items per subscale or total scale can be missed; in the VS 0-6 a maximum of three missing items or scores 'unknown' is allowed. Inspection of data revealed this limit was not exceeded for any individual on the instruments and that there were no patterns of missing data. For the DBC-P, mean values for the relevant item were computed and rounded off to 0, 1 or 2. For the VS 0-6, in accordance with the manual, missing items were replaced with a score of 1. If the data showed no serious deviations from a normal distribution, *t*-tests were used. For DBC-P item analysis we wanted to determine which behaviors were present in persons with RS. Therefore we added scores 1 and 2 since both indicate behavior exhibited by a person, as opposed to score 0 when the behavior is not present. To study differences in items between groups, chi-square tests for association were used because after the aforementioned transformation the DBC-P items were dichotomous. If the expected count in one or more of the cells was less than 5, Fisher's exact test was used for that item. For the DISCO-10 the specifically designed computer program was used to calculate the current and past classifications of CA.

RESULTS

Level of functioning

The level of adaptive functioning of the 52 participants was measured with the VS 0-6. Transformation of the raw scores with the Dutch norms yielded a mean age of adaptive functioning of 7.6 months (*SD* = 4.4 months). Only four persons (8%) had a level higher than 12 months (13, 16, 18 and 28 months). Although the course of development

for the younger participants is not totally clear yet, it can be concluded that in line with most other research all participating persons with RS have a profound to severe ID.

Autistic symptoms in Rett syndrome

The DBC-ASA shows whether further assessment of the presence of AD is indicated. The DBC-ASA score was above the cutoff for 22 persons (42%), which means they exhibited behavior which is related to AD; 30 persons (58%) had a score below the cutoff point. The algorithm yielded a higher percentage of persons with RS who did not score in the AD range compared to those who did. The items forming the DBC-ASA were selected based on their discriminative power between persons with AD and without AD and were not selected on their relationship with DSM-IV criteria for AD (only three items were added to the DBC-ASA because of the relationship with DSM-IV AD criteria). Thus, this implies that the screening algorithm describes behavior which can be categorized under the criteria of the classification systems, and as such can be regarded as 'truly autistic', and behavior which statistically turned out to predict whether a person has the autistic disorder but does not fall under the classification system criteria for AD. To acquire further insight into the presumably autistic behavior of the participants with RS, item analysis of the DBC-ASA was used. Table 2.1 shows how many females with RS obtained a score 1 or 2, which implies the behavior described is exhibited by the person, for all DBC-ASA items. This results in a percentage per item which indicates how often the item is true, listed in descending order, of 'truly autistic' behavior separated into three domains and more general or associated behavior.

The prevalence of behaviors rated on the DBC-ASA varied widely. Unfortunately no published research on DBC-ASA item analysis in persons with AD is present and as such a comparison of the symptom profile of the RS participants with other groups is not possible. Most types of 'truly autistic' behavior, as listed in Table 2.1, appeared in less than 50% of the persons. The participants showed more associated behaviors, which can be seen in both people with AD and people with ID. Some of the items had a low score because of the nature of development in RS: only six participants were able to speak some words, so the item about repeating words over and over was not likely to get a high score. This behavior, however, was present in four of the six verbal participants. Low scores on items such as lighting fires or running away should be seen in the light of the physical disabilities of the participants; most of them simply did not have enough motor skills to

Table 2.1 *Item analysis of the DBC-ASA for persons with Rett syndrome*

DBC-ASA item	**Rett syndrome (%)** (N=52)
Abnormalities in social interaction	
Aloof, in her own world	73
Doesn't respond to others' feelings	52
Avoids eye contact	50
Resists being cuddled, touched or held	27
Prefers to do things on her own	25
Abnormalities in communication	
Repeats the same word or phrase over and over	8
Restricted, repetitive and stereotyped behavior/interests/activities	
Repeated movements of hands, body, head or face	92
Stares at lights or spinning objects	52
Preoccupied with only one or two particular interests	29
Likes holding or playing with unusual object	29
Smells, tastes, or licks objects	29
Upset over small changes in routine/environment	27
Flicks, taps, twirls objects repeatedly	25
Arranges objects or routine in strict order	17
Gets obsessed with idea or activity	12
Associated behavior	
Poor attention span	87
Laughs or giggles for no obvious reason	81
Makes non-speech noises	79
Mood changes rapidly for no apparent reason	62
Screams a lot	50
Unrealistically happy	50
Poor sense of danger	42
Impatient	39
Overactive, restless, unable to sit still	27
Throws or breaks objects	19
Wanders aimlessly	14
Has temper tantrums	14
Deliberately runs away	6
Lights fires	0

Note. DBC-ASA = Developmental Behavior Checklist-Autism Screening Algorithm.

perform these actions. On the other hand, 92% of the females scored on the item 'repeated movements of hands, body, head or face', which was not unexpected as repeated hand movements are the hallmark of RS (Hagberg, 2002).

Autistic symptoms compared between younger and older persons with Rett syndrome

To study possible differences between people with RS of different ages, the sample was divided into children up to 10 years of age (n = 24) and older individuals (n = 28). Participants older than 10 years are all post-regression, so if autistic behavior decreases with age it is expected that a lower percentage of these individuals will score above the DBC-ASA cutoff. Nine (37.5%) of the girls younger than 11 years scored below the cutoff, 15 girls (62.5%) scored above. Of the persons aged 11 years or older, 21 (75%) scored below the cutoff, 7 (25%) scored above. The older participants were less likely to need screening for AD. For the total DBC-ASA, younger persons scored significantly higher (M = 18.8, SD = 9.3) compared to older persons (M = 13.7, SD = 6.4) as shown by a t-test for unequal variances, $t(40) = 2.3$, $p = .03$.

Item analysis with chi-square tests showed that differences in the percentage of items being 'true' were significant at the .01 level for only one item. The item 'smells, tastes, or licks objects' occurred more often in younger persons. Four other items were more prevalent for younger participants at the .05 level, namely preoccupied with only one or two particular interests, impatient, overactive/restless/unable to sit still, and wanders aimlessly. Older participants scored less often above the cutoff; most of them showed some autistic behavior but not the whole range of behavior.

The course of autistic behavior in people with Rett syndrome

In addition to the DBC-ASA percentage of participants who were suspected of AD, the DISCO-10 was also used. According to the DISCO interview, 30 persons (58%) currently have a classification of CA, whereas 22 persons (42%) do not have this classification. The DISCO algorithm gave an identical classification for 77% of the participants with RS as the DBC-ASA. The DISCO can be used to determine whether the CA classification changed with age in some individuals. Of the 40 participants who received a CA classification in the past, 10 (25%) no longer met criteria for the

classification for their present behavior (Table 2.2). Eight of these participants were older than 10 years, which means post-regression.

Thus, the behavior of some persons with RS (19%) changed in such a way that they first could be classified as having childhood autism, whereas currently they no longer meet criteria for this classification.

Table 2.2 *DISCO current and past classification of CA*

	DISCO 'current'		**Total**
	No CA	CA	
DISCO behavior 'ever'			
No CA	12	-[a]	12
CA	10	30	40
Total	22	30	52

Note. DISCO = Diagnostic Interview for Social and Communication Disorders; CA = Childhood Autism.
[a] DISCO behavior 'ever' includes 'current' behavior. Therefore it is not possible to get a CA classification on 'current behavior' and not on 'behavior ever'.

DISCUSSION

The current study is the first to describe autistic disorder symptoms in a sample of females with RS with a broad age range and to track changes in autistic behavior in individuals with (semi)standardized instruments. In line with our hypothesis, further assessment of the presence of AD is necessary in a substantial, but still minor, part of the sample according to the DBC-ASA. The percentage for this (42%) is in agreement with percentages found for people with profound and severe ID (Deb & Prasad, 1994), the level at which almost all persons with RS, and also in this sample, function. On the DISCO-10 interview a somewhat higher percentage of CA is found (58%).

The decrease in autistic behavior in some persons, as observed in earlier research (Gillberg, 1986; Hagberg & Witt-Engerström, 1986), is supported by the results of the DBC-ASA and the DISCO-10. According to the DBC-ASA autistic behavior is present in both younger and older participants, but the younger persons fall within the AD range more often. These girls show more symptoms, whereas most older, post-regression persons display some autistic characteristics but not enough to indicate AD. In one-quarter of the persons with RS with a CA classification in the past, based on the DISCO-10,

autistic symptoms decreased in such a way that they do not fulfill ICD-10 CA criteria anymore. Most of these participants are post-regression.

Our findings support the view of Gillberg (1992) that a diagnosis of comorbid AD in RS, if applicable, should be possible since this will be the case for some persons with RS. The need to keep individual differences between persons with RS in mind had already been stressed by Rett (1986) and turns out to be true for the presence of AD in females with RS. Thus, it is important to make a clear distinction between persons with RS and persons with RS *and* AD in the classification process. The presence of a comorbid AD will have implications for the approach and care of a person with RS, as it has in people without RS. Clinicians should be aware of the heightened possibility of AD as much as they should be in people with a severe to profound ID without RS. The diagnostic process, which is already difficult in people functioning at these low levels, can take several years in RS because of the need to follow the development of the child due to possible changes over time in RS.

However, another important issue concerning RS in the DSM-IV-TR and ICD-10 is the placement of RS under the PDD section. According to our data there are many persons with RS who are not suspected of AD because of a lack of AD symptoms. In the current project no measure of the category pervasive developmental disorder not otherwise specified (PDD-NOS) or atypical autism was used. This classification is, however, not strongly validated in people with severe and profound ID. The boundaries of the PDD-NOS or atypical autism classification, which are already unclear in the general population, become even more unstable at the lowest levels of functioning (Mahoney et al., 1998; Njardvik, Matson, & Cherry, 1999; Towbin, 2005). Keeping these considerations in mind, we hold the view that our data might be supportive of the opinion of Gillberg and Billstedt (2000) and Wing (2005) that it is inappropriate to classify RS under the section for PDD. AD/CA in RS does not seem to be present more often (DBC-ASA), or is present only slightly more often (DISCO-10), than in people without the syndrome but with the same level of functioning (Deb & Prasad, 1994). In addition, other genetically identified syndromes associated with autism (e.g. Zafeiriou, Ververi, & Vargiami, 2007) are also not included in this section. Therefore, a reconsideration of the placement of RS under the PDD section might be needed.

A limitation in the current study is the lack of observational data in addition to the use of a questionnaire and semi-structured interview to establish a diagnosis of AD/CA. It

would be an important step in RS research to use clinical diagnoses of AD in future studies with large samples. Furthermore, the decrease in AD symptoms in a substantial proportion of the participants is measured in retrospect by the DISCO-10 interview. This will have a negative effect on the reliability of the information. The best direction in research seems to be to follow the persons with RS from the moment the syndrome is identified to get more objective measures of behavior over the lifespan.

The autism screening instruments obtained a 77% agreement on AD/CA classification for our sample, which may be seen as a satisfactory amount in the population of people with a severe to profound ID. However, it would be interesting to compare these often used instruments in depth to gain more insight into the usefulness of these instruments and their similarities and differences in people with ID. For this particular purpose a much larger sample, not restricted only to RS, should be used.

The use of standardized instruments is a strength but at the same time can be a limitation. The DBC-ASA was developed for a diverse population, namely people with different levels of ID. It is likely that very few people with RS were included in the standardization sample, given the relatively low incidence of the syndrome. Unique behavior in RS will therefore probably not be accounted for in the instrument. On the other hand, some DBC-ASA items are almost always present in the RS group, such as repeated hand movements. A few other types of behavior presumably cannot be performed by most persons with RS because of their limited physical abilities, like running away. The question arises of whether cutoff scores developed for the general ID population should be the same for such a specific population. To answer this requires an extensive study. To date, using standardized instruments with well-known psychometric properties seems the best option we have to obtain objective and reliable information. The Rett Syndrome Behavior Questionnaire is a useful instrument for obtaining specific RS information (Mount, Charman, Hastings, Reilly, & Cass, 2002), but seemed less suitable for our focus on autism in RS.

A last limitation is the composition of the sample. By gathering data via the Dutch Rett Parent Support Group, and it is possible the parents concerned had certain characteristics, such as relatively high socio-economic status, which could influence the results. In addition, not all members of the parent support group participated in our study. Apart from that, obtaining a well-balanced sample with respect to age also turned out to be difficult. These limitations may have put constraints on the generalization of our results.

An interesting next step in research would be the worldwide linking of the genetic information to the behavioral phenotype. Several projects have already shown the influence of the type of *MECP2* mutations for the phenotype including some behavioral aspects (Percy, 2008). A much larger sample than ours is needed to search for the possible link between the type of gene mutation and autistic behavior. This may be done in an international database with much used standardized and translated behavioral instruments such as the DBC, VABS and Rett Syndrome Behavior Questionnaire. In this way our knowledge on the link between behavior and genetics in Rett syndrome could be expanded, with new possibilities for diagnostics and treatment.