

The diagnosis of autism in a female: could it be Rett syndrome?

Deidra J. Young · Ami Bebbington · Alison Anderson · David Ravine · Carolyn Ellaway · Alpana Kulkarni · Nick de Klerk · Walter E. Kaufmann · Helen Leonard

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Abstract The overlap between autism and Rett syndrome clinical features has led to many cases of Rett syndrome being initially diagnosed with infantile autism or as having some autistic features. Both conditions seriously disrupt social and language development and are often accompanied by repetitive, nonpurposeful stereotypic hand movements. The aims of this study were to compare the early and subsequent clinical courses of female subjects with Rett syndrome categorised by whether or not a diagnosis of autism had been proposed before Rett syndrome had been diagnosed and compare the spectrum of methyl-CpG binding protein 2 (*MECP2*) mutations identified among the two groups. This study made use of a total of 313 cases recorded in two databases: the Australian Rett Syndrome Database (ARSD) and the International Rett Syndrome

Phenotype Database (InterRett). Cases with an initial diagnosis of autism had significantly milder Rett syndrome symptoms and were more likely to remain ambulant, to have some functional hand use and not to have developed a scoliosis. Females with the p.R306C or p.T158M mutations in the *MECP2* gene were more likely to have an initial diagnosis of autism, and the specific Rett syndrome symptoms were noted at a later age. We recommend that females who are initially considered to have autism be carefully monitored for the evolution of the signs and symptoms of Rett syndrome.

Keywords *MECP2* · Rett syndrome · Autistic spectrum disorders · Autism

D. J. Young · A. Bebbington · A. Anderson · N. de Klerk · H. Leonard
Centre for Child Health Research, Telethon Institute for Child Health Research, University of Western Australia, Perth, WA, Australia

D. Ravine
Western Australian Institute for Medical Research, Centre for Medical Research, University of Western Australia, Perth, WA, Australia

D. Ravine
School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia

C. Ellaway
School of Paediatrics and Child Health, University of Sydney, Sydney, NSW, Australia

C. Ellaway
The Children's Hospital at Westmead, Sydney, NSW, Australia

A. Kulkarni
Princess Margaret Hospital for Children, Perth, WA, Australia

W. E. Kaufmann
Kennedy Krieger Institute, Baltimore, MD, USA

W. E. Kaufmann
School of Medicine, Johns Hopkins University, Baltimore, MD, USA

D. J. Young (✉)
Telethon Institute for Child Health Research, P.O. Box 855, West Perth, WA 6872, Australia
e-mail: Deidray@ichr.uwa.edu.au

Introduction

The onset of symptoms after a period of apparently normal growth and development is a feature of both autism and Rett syndrome. Both conditions are included in a group of conditions known as pervasive developmental disorders (PDD), which are characterised by severe impairment in communication, language, social interaction, play and behaviour and language development and are often accompanied by repetitive stereotypic movements. In contrast to Rett syndrome, which affects mostly females and is caused in the majority by mutations in the X-linked *MECP2* gene [13], autism has a male predominance, and only a small number of autism-associated genes have been characterised to date despite an estimated heritability of more than 90% [12].

The aims of this study were to (1) compare the early and subsequent clinical course of female subjects with Rett syndrome categorised by whether or not a diagnosis of autism was proposed before Rett syndrome was diagnosed and (2) compare the spectrum of *MECP2* mutations identified among the two groups.

Historical background

In the early 1980s, Rett syndrome was described by Hagberg as a “progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls” [14]. The overlap with autism was first studied through a comparison of clinical observations in patients with both conditions ($n=49$) [33]. The sentinel characteristics of Rett syndrome appeared to be a restricted repertoire of movement, occurrence of motor stereotypies, severe motor retardation with ataxia and apraxia, and lack of rudimentary speech. Chewing difficulties and respiratory pattern abnormalities were often evident. In contrast, although those with Kanner-type autism had a striking disregard of objects and people with associated rejection of social approaches, their level of cortical function was higher and there was preservation of precise and coordinated movements.

Subsequently, Percy and colleagues explored the relationship of Rett syndrome to PDD [34] and concluded that Rett syndrome, along with fragile X syndrome, phenylketonuria and tuberous sclerosis, comprised an aetiologically defined subgroup of autistic disorders. Later, Tsai reconsidered whether Rett syndrome should continue to be categorised as a subtype of PDD in the *Diagnostic Statistical Manual of the Mental Disorders, IV* (DSM-IV) [46]. In general, it was recognised that many of the early manifestations of Rett syndrome were compatible with a diagnosis of PDD. However, the issue of whether their natural history followed the same path needed further longitudinal research.

More recently, Mount and colleagues attempted to assess more quantitatively the presence of autistic symptomatology in Rett syndrome [31]. Despite the small sample size, they found that a Rett syndrome group ($n=15$) scored significantly higher than a comparison group with severe intellectual disability ($n=14$) on the total Autism Behaviour Checklist score and on two of the subscales, confirming their higher frequency of autism features.

Mutations in the *MECP2* gene

In 1999, mutations in the methyl-CpG binding protein 2 (*MECP2*) gene were first found to be associated with Rett syndrome, and molecular genetic testing has since become a valuable diagnostic test, particularly for confirming the diagnosis in suspected cases [1]. There are eight common pathogenic mutations accounting for about two thirds of *MECP2*-positive cases and, among these, there appears to be considerable clinical variability [5, 8, 16, 17, 20, 25, 38, 39]. *MECP2* mutations have been found infrequently in female patients diagnosed with autism [3, 4, 23, 27, 48] and also in females with Angelman syndrome [49]. Therefore, these findings point to a possible overlapping pathway of gene dysregulation in Rett syndrome, Angelman syndrome and other autism spectrum disorders [26, 36, 37, 43].

The phenotypic overlap between Rett syndrome and autism has led to autism being one of the most common misdiagnoses in Rett syndrome, especially between 1 and 3 years of age [32, 35, 45, 51]. Witt-Engerström and Gillberg reported that an initial diagnosis of autism or “autistic features” was made in more than three quarters of their series of 50 Rett syndrome patients [51]. Zappella and colleagues reported that milder cases of Rett syndrome, such as the preserved speech variant (PSV), appear to be more likely to be associated with autistic behaviours [52, 53, 55]. Screening of 19 girls with autism found two cases with PSV and pathogenic mutations (p.R133C and p.R453X) in the *MECP2* gene who eventually lost their autistic symptoms (at 12 and 13 years of age) [54]. It was therefore concluded that *MECP2* mutations were less likely to be found in subjects in whom autism remains stable over time.

Methods

Data sources

This study made use of information recorded in two databases: the Australian Rett Syndrome Database (ARSD) and the International Rett Syndrome Phenotype Database (InterRett). The ARSD is a population-based register that

has been in operation since 1993. It contains information regarding all Australian Rett syndrome cases born since 1976. In addition to the questionnaires administered on enrolment to families and clinicians [24], follow-up questionnaires have been administered to study families every 2 years since 2000 [19]. *MECP2* testing was initiated for the cohort in 2000 and, for the last 3–4 years, most other cases have been tested around recruitment. At the time of the last follow-up study in 2004, there were 288 cases in the database, 254 of whom had molecular testing, with a pathogenic mutation identified in 186 (73.2%). The families of 149/186 (80.1%) cases with a known *MECP2* mutation have completed at least one follow-up questionnaire and were eligible for this study. InterRett is an international database (<http://www.ichr.uwa.edu.au/rett/irsa>) that collects similar information to that in the ARSD but is not an age-defined cohort and, at the present time, does not have a follow-up component [30]. Information was collected from families and clinicians through online and paper-based questionnaires. At the time of data extraction for this study, excluding ARSD cases there were 637 cases from 31 countries, 544 of whom had had genetic testing. Disease-causing mutations were identified in 346 (63.6%) of those tested. Family questionnaires, in which the question about the initial diagnosis had been included, were not available for the majority of Spanish and Israeli cases, whose data had been provided directly from clinical centres in the format of a clinical questionnaire. Therefore, this study was restricted to the remaining 164 cases with a completed family questionnaire and, thus, the necessary information for this study.

A total of 313 cases were included in this study from the two datasets on the basis of the following inclusion criteria:

1. A questionnaire had been completed by the family of each subject
2. A pathogenic *MECP2* mutation had been identified in the subject
3. The case was female

An initial diagnosis of autism

Families in the ARSD and InterRett studies were asked to report the initial diagnosis given to their child. In this study, 55 of 313 cases (17.6%) had an initial diagnosis of autism (Table 1).

Age group

The females in this study were aged 1.5–45 years. Age groups were categorised as follows: 0–7 years, 8–12 years, 13–17 years, 18–34 years and 35 years and older (Table 1).

Table 1 Initial diagnosis of autism by age group and data source

Age group	No autism diagnosis	No autism diagnosis	Autism diagnosis	Autism diagnosis	Total
	<i>n</i>	%	<i>n</i>	%	
0–7 years	100	85.47	17	14.53	117
8–12 years	44	72.13	17	27.87	61
13–17 years	44	83.02	9	16.98	53
18–34 years	64	86.49	10	13.51	74
35+ Years	4	66.67	2	33.33	6
Missing	2	100.00	0	0.00	2
Total	258	82.32	55	17.68	313
Data source	No.	%	No.	%	No.
InterRett	137	83.54	27	16.46	164
AussieRett	121	81.21	28	18.79	149
Total	258	82.43	55	17.57	313

Mutation type

In the Australian cohort, information on *MECP2* genotype was available either as a result of our own studies [50] or from the clinician at recruitment or subsequently with parental permission. In the InterRett cohort, mutation details were provided by the family or the clinician or both. The pathogenicity of the less frequently encountered mutations was verified by checking the details of the nucleotide/amino acid changes involved, with the aid of the *MECP2* gene locus-specific database (RettBASE) [6, 9]. The genotypes were categorised as follows: p.R106W, p.R133C, p.T158M, p.R168X, p.R255X, p.R270X, p.R294X, p.R306C, C-terminal deletions, early truncating mutations, large exon 3 and 4 deletions, and a final group that included “other” pathogenic mutations in the *MECP2* gene.

Measures of Rett syndrome symptoms

Clinical features of Rett syndrome were categorised either as early features, which could have influenced whether or not the child was diagnosed with autism, or later-onset features, which were age related and reflected the phenotype or functional status at the time of data collection. Early developmental progress up to 12 months, as reported by families, was categorised with a three-point scale: no or virtually no progress; suboptimal progress; normal progress [21]. Mobility at 10 months was defined as poor, normal or above average.

Ages at diagnosis, loss of hand function, loss of communication skills and onset of hand stereotypies were compared between subjects with and without the initial diagnosis of autism, as were whether the loss of hand use and deterioration of speech was sudden or gradual. Patterns of early development and mobility at 10 months were similarly compared, as were functional aspects, including

Table 2 Likelihood of an initial diagnosis of autism by mutation type

Mutation type	Total <i>n</i>	No autism diagnosis <i>n</i> (%)	Autism diagnosis <i>n</i> (%)	Odds ratio (OR) for autism	<i>P</i> value for OR for Autism	95% confidence interval (CI)	
						LCI	UCI
p.R106W	16	13 (81.3)	3 (18.8)	2.02	0.40	0.40	10.27
p.R133C	26	21 (80.8)	5 (19.2)	2.08	0.31	0.50	8.63
p.T158M	37	28 (75.7)	9 (24.3)	2.81	0.11	0.78	10.10
p.R168X	39	35 (89.7)	4 (10.3)	–	–	–	–
p.R255X	31	28 (90.3)	3 (9.7)	0.94	0.94	0.19	4.54
p.R270X	26	21 (80.8)	5 (19.2)	2.08	0.31	0.50	8.63
p.R294X	26	22 (84.6)	4 (15.4)	1.59	0.54	0.36	7.02
p.R306C	20	14 (70.0)	6 (30.0)	3.75	0.06	0.92	15.34
C terminal	36	28 (77.8)	8 (22.2)	2.50	0.17	0.68	9.16
Early truncating	15	14 (93.3)	1 (6.7)	0.63	0.69	0.06	6.09
Large deletion	9	7 (77.8)	2 (22.2)	2.50	0.34	0.38	16.41
Other	32	27 (84.4)	5 (15.6)	1.62	0.50	0.40	6.62
Total	313	258 (82.4)	55 (17.6)	–	–	–	–

Mutation type was not significantly different for cases with an initial diagnosis of autism (LR=8.56; $p=0.66$).

whether the child had ever walked, talked, had functional hand use or developed hand stereotypies and whether or not there was slowing of head growth.

Clinical severity at the time of data collection in each group was compared between the two groups using Kerr [21], Percy [38] and Pineda [29] scales and by individual items (used in the composite scales), adjusted for age where appropriate. Severity of breathing problems, oromotor difficulties and presence of epilepsy and scoliosis were categorised broadly from the items defined by Kerr; mobility, hand use and self-feeding from the items defined by Percy; and language on an item from the Pineda scale.

Missing data

As the severity scores (referred to as the Kerr, Percy and Pineda scales) are additive systems, it was essential that the total possible score was the same for each case to ensure comparability (as proportions of the maximum severity). Where missing data existed (many subjects had one or two missing responses), the total possible score for that case was less than the total score in a complete case, because the score for the missing item was unknown, so these missing

data were imputed using the STATA routine MICE (multiple imputation using chained equations) [47].

Analyses

Logistic regression was used to examine the relationship between mutation type and autism diagnosis, the impact of early characteristics on the likelihood of autism diagnosis and, after adjustment for age, the clinical outcomes (categorical) in those who did or did not have a diagnosis of autism. Linear regression was used to compare age differences at development of early features for those with and without an autism diagnosis and, after age adjustment, to compare current severity and growth parameters. The statistical package STATA was used for all analyses [42].

Results

Fifty-five (17.6%) cases had an early diagnosis of autism. These cases were distributed across the age groups relatively evenly, with the largest proportion in the 8- to 12-year-old age group (Table 1). The two mutations most likely to have an initial diagnosis of autism were p.R306C and p.T158M (Table 2). Cases with a p.R255X mutation or

Table 3 Comparison of early clinical features (continuous variables) in those who were and were not initially diagnosed with autism

Early clinical symptoms	No autism diagnosis mean score	Autism diagnosis mean score	<i>P</i> value for autism diagnosis	Odds ratio (OR) for autism diagnosis	95% confidence interval (CI)	
					LCI	UCI
Age at diagnosis of Rett syndrome in years	4.72	6.08	0.09	1.05	0.99	1.10
Age at loss of hand function in months	23.25	29.74	0.02	1.02	1.00	1.04
Age at loss of communication in months	20.25	25.69	0.04	1.02	1.00	1.04
Age at onset of hand stereotypies in months	26.02	31.83	0.05	1.02	1.00	1.03

Table 4 Comparison of early clinical features (categorical variables) in those who were and were not initially diagnosed with autism

Clinical feature	Level of severity	No autism diagnosis n (%)	Autism diagnosis n (%)	Odds ratio (OR) for autism	P value for OR for autism	95% confidence interval (CI)	
						LCI	UCI
Early development	Normal	74 (73.3)	27 (26.7)	1.31	0.73	0.29	6.02
	Mild	162 (86.6)	25 (13.4)	3.10	0.15	0.67	14.32
	Severe	17 (89.5)	2 (10.5)	1.00	–	–	–
Mobility at 10 Months	Above average	26 (81.3)	6 (18.8)	5.28	0.00	2.57	10.82
	Normal	74 (69.2)	33 (30.8)	2.73	0.06	0.94	7.93
Functional hand use	Poor	142 (92.2)	12 (7.8)	1.00	–	–	–
	Had functional hand use	248 (82.1)	54 (17.9)	2.18	0.46	0.27	17.37
Learned to talk	Never had functional hand use	10 (90.9)	1 (9.1)	1.00	–	–	–
	Learned to talk	236 (81.9)	52 (18.1)	1.62	0.45	0.47	5.60
Hand use	Never learned to talk	22 (88.0)	3 (12.0)	1.00	–	–	–
	Maintained hand use	25 (80.7)	6 (19.4)	1.14	0.78	0.44	2.93
Speech	Lost hand use	233 (82.6)	49 (17.4)	1.00	–	–	–
	Maintained speech	29 (85.3)	5 (14.7)	0.79	0.64	0.29	2.14
Learned to walk	Lost speech	229 (82.1)	50 (17.9)	1.00	–	–	–
	Learned to walk	161 (75.9)	51 (24.1)	10.24	0.00	3.11	33.71
Hand stereotypy	Never learned to walk	97 (97.0)	3 (3.0)	1.00	–	–	–
	Never had hand stereotypies	14 (93.3)	1 (6.7)	0.32	0.28	0.04	2.51
Total	Hand stereotypies present	244 (81.9)	54 (18.1)	1.00	–	–	–
		258 (82.4)	55 (17.6)	–	–	–	–

an early truncating mutation were least likely to have an initial diagnosis of autism odds ratio (OR)=0.94, 0.63, respectively].

The odds of having had an autism diagnosis increased by 1.02 for every increase in month of age at which loss of hand function, loss of communication abilities and development of hand stereotypies were reported to occur. However, sudden as opposed to gradual deterioration of speech and hand skills occurred in similar proportions for those without (36.6% and 25.5%, respectively) and with (34.1% and 26.5%, respectively) an initial diagnosis of autism ($p=0.75$ and $p=0.88$). The odds of having a diagnosis of autism increased by 1.05 for every increase in year of age at Rett syndrome diagnosis (Table 3). In addition, these girls were more likely to have above-average mobility at 10 months (OR=5.28) and to have learned to walk (OR=10.24) (Table 4).

With respect to the clinical severity of Rett symptoms at the time of data collection, females who were originally diagnosed with autism had significantly lower (better) Kerr ($b=-2.34$), Percy ($b=-4.76$) and Pineda ($b=-3.35$) scores, after adjustment for age. In addition, this group was more likely to have a higher z score for weight ($b=1.17$) (Table 5), still to be ambulant (OR=13.49), to finger feed themselves (OR=2.43), to have some functional hand use (OR=2.46) and not to have developed scoliosis (OR=3.09) (Table 6). There were no significant differences for current head circumference or current height.

Two of the *MECP2* mutations, p.R306C and p.T158M, were investigated for within-group differences in severity of symptoms according to whether there was an initial autism diagnosis. For p.R306C, the Kerr score was 5.48 points lower ($t=3.31$; $p=0.004$), the Percy score 7.77 points lower ($t=3.01$; $p=0.008$) and the Pineda score 3.62 points lower

Table 5 Comparison of current severity scores and z scores for weight, height and head circumference in those who were and were not initially diagnosed with autism (adjusted for age)

Severity and anthropometric scores	No autism diagnosis mean score	Autism diagnosis mean score	P value for significance of autism	Regression coefficient for autism	95% confidence interval (CI)	
					LCI	UCI
Kerr score	20.35	18.01	0.00	-2.34	-3.62	-1.06
Percy score	22.66	17.78	0.00	-4.76	-6.62	-2.89
Pineda score	15.98	12.55	0.00	-3.35	-4.62	-2.08
Z score for present head circumference	-1.44	-1.32	0.50	0.18	-0.36	0.72
Z score for present height	-2.04	-1.92	0.74	0.14	-0.70	0.98
Z score for present weight	-2.00	-1.01	0.01	1.17	0.29	2.05

Table 6 Comparison of current clinical severity (categorical variables) in those who were and were not initially diagnosed with autism (adjusted for age)

Clinical feature	Level of severity	No autism	Autism	Odds ratio (OR) for autism	<i>P</i> value for OR for autism	95% confidence interval (CI)	
		diagnosis <i>n</i> (%)	diagnosis <i>n</i> (%)			LCI	UCI
Disturbed awake breathing rhythm	Normal	75 (87.2)	11 (12.8)	0.74	0.51	0.30	1.81
	Mild	109 (79.0)	29 (21.0)	1.28	0.50	0.63	2.59
	Severe	74 (83.5)	15 (16.5)	1.00	—	—	—
Epilepsy	No epilepsy	97 (84.4)	18 (15.7)	0.85	0.64	0.43	1.68
	Epilepsy present	156 (81.7)	35 (18.3)	1.00	—	—	—
Oromotor difficulty	Normal	34 (79.1)	9 (20.9)	2.88	0.09	0.85	9.76
	Mild	121 (81.2)	28 (18.8)	2.15	0.14	0.77	6.01
	Severe	45 (90.0)	5 (10.0)	1.00	—	—	—
Ambulation	Still walking	143 (73.7)	51 (26.3)	13.49	0.00	4.07	44.69
	Not walking	115 (97.5)	3 (2.5)	1.00	—	—	—
Ability to feed self	Feeds self with spoon	10 (83.3)	2 (16.7)	1.16	0.86	0.23	5.81
	Finger feeds self	46 (74.2)	16 (25.8)	2.43	0.02	1.17	5.05
	Feeds self with assistance	35 (77.8)	10 (22.2)	1.93	0.13	0.83	4.51
	Not able to feed self	167 (86.5)	26 (13.5)	1.00	—	—	—
Hand use	Hand use acquired/conserved	54 (79.4)	14 (20.6)	1.99	0.09	0.89	4.44
	Hand use partially conserved	70 (75.3)	23 (24.7)	2.46	0.01	1.20	5.03
	No normal hand use	116 (87.9)	16 (12.1)	1.00	—	—	—
Language	Can use phrases	7 (87.5)	1 (12.5)	0.54	0.57	0.06	4.69
	Use single words	21 (75.0)	7 (25.0)	1.44	0.44	0.57	3.65
	No normal speech	230 (83.0)	47 (17.0)	1.00	—	—	—
Scoliosis	No scoliosis	96 (75.6)	31 (24.4)	3.09	0.00	1.53	6.23
	Scoliosis present	157 (87.2)	23 (12.8)	1.00	—	—	—
Frequency of Hand Stereotypy	Occasional/never	38 (86.4)	6 (13.6)	0.57	0.26	0.22	1.50
	Frequent	76 (86.4)	12 (13.6)	0.57	0.13	0.27	1.18
	Constant	129 (78.7)	35 (21.3)	1.00	—	—	—
Total		258 (82.4)	55 (17.6)	—	—	—	—

Some cases had missing data for some items.

($t=1.99$; $p=0.062$) in those with an autism diagnosis. For p.T158M, the Kerr score was 3.97 ($t=1.92$; $p=0.064$), the Percy score 6.89 ($t=2.75$; $p=0.010$) and the Pineda score 4.45 points lower ($t=3.04$; $p=0.005$).

Discussion

In our study, which represented cases from Australia and other countries (predominantly the USA and the UK), an initial diagnosis of autism had been proposed in almost one fifth of subjects. Those children were more likely to develop symptoms later, had significantly milder Rett syndrome symptoms, were more likely to remain ambulant, to have some functional hand use and not to have developed scoliosis. Females with the p.R306C or p.T158M mutations in the *MECP2* gene were more likely to have an initial diagnosis of autism. The p.R306C mutation has been previously been shown to be associated with a milder clinical course [38]. On the other hand, although the likelihood for an initial autism diagnosis was also higher for other mild mutations—p.

R133C [25], p.R294X [8] and C terminal deletions [40]—these results did not approach statistical significance. Whereas features of Rett syndrome are clearly different from autism, our data show that there continues to be a significant probability of Rett syndrome cases being categorised early as autism. The concern is that in some cases, the diagnosis of autism might persist unaltered, despite the presence or later emergence of other clinical features more suggestive of Rett syndrome—in particular, the development of hand stereotypies, noted to be reported later in our group with an initial diagnosis of autism.

One of the strengths of this study is the number of Rett syndrome cases ($n=313$) with a pathogenic *MECP2* mutation and the detailed clinical data available for analysis. We were able to source Australian cases from the ARSD and non-Australian cases from InterRett. The main weaknesses in the comparative analyses were the small numbers in each mutation subgroup for the cases with an initial autism diagnosis. Nevertheless, the number of cases with individual mutations was considerably larger than in any other previously published studies. For some

common mutations, we had almost as many cases in our study as in the three previous major studies from Germany, USA and UK combined [5, 17, 18, 22, 38].

Methods for autism diagnosis have changed over the last 20 years, and this may have had some impact on our study. Each family reported the diagnosis given to them by the child's clinician at the time. However, there could be considerable variability amongst clinicians' method of diagnosis, including the use of DSM criteria [2]. It is generally now accepted that some of the secular increase in incidence of autism diagnosis has been associated with changing criteria and clinical diagnostic practices, along with increased awareness [11]. The fact that the prevalence of an earlier autism diagnosis was highest in Rett syndrome subjects born between 1994 and 1998 could relate to these secular changes.

The prevalence of autism diagnosis in females with Rett syndrome in our study (17.5%) was significantly lower than previous research (78%) published in the 1980s [10, 15, 51]. However, the Swedish research was based on a series of some of the earliest cases of Rett syndrome identified and, therefore, many of these children would probably have first presented prior to 1983, before the time that Rett syndrome was described [11]. Although we had a small proportion of older cases, the majority were diagnosed after the publication of the initial clinical guidelines [44]. With the development of clinical diagnostic guidelines in 1988 [44] and availability of *MECP2* gene testing since 2000 [1], Rett syndrome has become easier to diagnose at a younger age [7]. Therefore, our study adds a new perspective to the issue of early differential diagnosis in an era much better informed with clinical and molecular information.

It is likely that a proportion of females with an initial diagnosis of autism may have received behavioural management interventions, possibly quite intensively (clinical observation HL). What we do not know is whether such interventions may have had any beneficial effects on these children's long-term outcome or whether their more favourable outcomes are simply associated with their better early potential, as indicated by their early clinical status or genotype. Further investigation of the impact of intensive early interventions in females with Rett syndrome is needed [41].

In Australia, the rate of autism diagnosis in females aged 0–16 years is 11.1/10,000 [28] compared with an incidence of diagnosis of Rett syndrome of 1.2/10,000 by the age of 15 years. Our research shows that a small proportion of those diagnosed with autism may have Rett syndrome, but identifying their true diagnosis is important for their ongoing management and support. We recommend that females who are initially considered to have autism be carefully monitored clinically for the evolution of the signs and symptoms of Rett syndrome, including head growth deceleration. If specific Rett syndrome features are seen to develop, then *MECP2* mutation testing may be indicated.

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Ethics Statement All data collected for the purposes of the Australian Rett Syndrome Register and the International Rett Syndrome Study Register have been monitored and approved by the Princess Margaret Hospital for Children Human Ethics Committee and performed in accordance with the ethical standards laid down by the Declaration of Helsinki, Fifth Revision, <http://www.bmj.com/cgi/content/full/321/7266/913>.

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