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The Behavioral Phenotype of Mowat–Wilson Syndrome

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Mowat–Wilson syndrome (MWS) is caused by a heterozygous mutation or deletion of the *ZEB2* gene. It is characterized by a distinctive facial appearance in association with intellectual disability (ID) and variable other features including agenesis of the corpus callosum, seizures, congenital heart defects, microcephaly, short stature, hypotonia, and Hirschsprung disease. The current study investigated the behavioral phenotype of MWS. Parents and carers of 61 individuals with MWS completed the Developmental Behavior Checklist. Data were compared with those for individuals selected from an epidemiological sample of people with ID from other causes. The behaviors associated with MWS included a high rate of oral behaviors, an increased rate of repetitive behaviors, and an under-reaction to pain. Other aspects of the MWS behavioral phenotype are suggestive of a happy affect and sociable demeanor. Despite this, those with MWS displayed similarly high levels of behavioral problems as those with intellectual disabilities from other causes, with over 30% showing clinically significant levels of behavioral or emotional disturbance. These findings have the potential to expand our knowledge of the role of the *ZEB2* gene during neurodevelopment. Furthermore, they are a foundation for informing interventions and management options to enhance the independence and quality of life for persons with MWS.

Key words: Mowat–Wilson syndrome; *ZEB2* protein; human genetics; behavioral; mental retardation; intellectual disability

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INTRODUCTION

Mowat–Wilson syndrome (MWS) is a multiple congenital anomaly syndrome associated with intellectual disability (ID) and a distinct facial appearance [Mowat et al., 2003; Zweier et al., 2005]. It is caused by heterozygous mutation or deletion of the Zinc Finger E-box-binding homeobox 2 gene (*ZEB2*), previously known as the Zinc Finger Homeobox 1 B gene (*ZFHX1B*), or *SIP1* [Wakamatsu et al., 2001; Wilson et al., 2003]. The syndrome was first delineated by Mowat et al. [1998].

The prevalence of MWS has been estimated in the range of 1 per 50,000–70,000 live births [Mowat and Wilson, 2010], though several authors have suggested it is more common than originally thought [Mowat et al., 2003; Adam et al., 2006; Garavelli and Cerruti Mainardi, 2007; Engenheiro et al., 2008]. So far, over 190 mutation proven cases of MWS have been reported, arising from over 100 different mutations to the *ZEB2* gene [Zweier et al., 2005; Dastot-Le Moal et al., 2007; Garavelli and Cerruti Mainardi, 2007; Sasongko et al., 2007; Adam et al., 2008; Engenheiro et al., 2008;

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Ohtsuka et al., 2008; Rauch, 2008; Verstappen et al., 2008; Garavelli et al., 2009].

Early publications on MWS tended to show a higher number of males than females, though recent reports suggest that MWS affects males and females equally [Zweier et al., 2005; Garavelli and Cerruti Mainardi, 2007]. This ascertainment bias may be explained by the increased frequency of Hirschsprung disease in males and the presence of hypospadias suggesting a syndromal diagnosis.

At present, the published literature on MWS consists of individual case reports [e.g., Adam et al., 2008; Sasso et al., 2008], case reports in series [e.g., Mowat et al., 1998; Amiel et al., 2001; Garavelli et al., 2005], and reviews of the phenotype [e.g., Mowat et al., 2003; Zweier et al., 2005; Garavelli and Cerruti Mainardi, 2007; Garavelli et al., 2009].

Motor milestones in infancy and early childhood are generally very delayed [Garavelli and Cerruti Mainardi, 2007]. Intelligence quotients (IQ) have not been reported for MWS. However, from the published case reports it appears that the syndrome leads to ID which is reported to be at least moderate and more often severe [Mowat et al., 2003; Adam et al., 2006; Garavelli and Cerruti Mainardi, 2007].

Case reports suggest that MWS may be associated with a happy demeanor with frequent smiling [e.g., Mowat et al., 1998; Wilson et al., 2003; Cerruti Mainardi et al., 2004], and that persons with MWS have a "generally happy, social personality" [Zweier et al., 2002] or are "socially engaging and responsive" [Mowat and Wilson, 2010, p. 522]. However, despite these reports, the behavioral phenotype of this syndrome has not yet been systematically investigated.

The aim of the current study was to investigate the behavioral phenotype of MWS. Specifically, the study aimed to determine if there was a difference in the rate and type of behavior problems in those with MWS compared with those with ID from other causes.

MATERIALS AND METHODS

Participants: The MWS Group

The MWS Group comprised 61 individuals with MWS and their carers. Recruitment occurred via an advertisement on a website dedicated to the support of families affected by MWS; this advertisement was also emailed to a listing for parents and carers of people with MWS, and to the email listing for the Australasian Association of Clinical Geneticists. Clinicians who had referred patients for genetic testing for MWS were asked to distribute information regarding the study to patients' families. Some recruitment occurred via a "snowball" process, whereby families involved in the study informed others about the research. Fourteen participants came from Australia and 14 from the USA. Nine came from Italy, 8 from Japan, 7 from the UK, 3 from Germany, 2 from each of The Netherlands and France, and 1 from each of Canada and the UAE.

Sixty percent of the sample was reported to have Hirschsprung disease, 89% seizures, and 41% congenital heart defects. Of the 80% of participants who had received brain imaging, 44% were diagnosed with agenesis of the corpus callosum. Microcephaly, defined in this study as a head circumference smaller than the 2nd standard deviation below the mean, occurred in 37.5% of the group.

For 56 participants, the diagnosis of MWS was previously confirmed by genetic testing. Photographs of the remaining five participants were reviewed by a geneticist (D.M. and M.W.) to confirm the clinical diagnosis. These five participants all displayed the classic facial phenotype of MWS.

Determining Level of ID for the MWS Group

For 32 MWS participants, the level of ID was estimated by the research team using the Vineland Adaptive Behavior Scales Interview Edition Survey Form [VABS; Sparrow et al., 1984a], the Griffiths Mental Development Scales [GMDS; Griffiths, 1984, 1986, 1996], the Matson Evaluation of Social Skills for Individuals with Severe Retardation [Matson, 1995], The Peabody Picture Vocabulary Test Third Edition [PPVT-III; Dunn and Dunn, 1997], and the matrices subtest of the Kaufman Brief Intelligence Test [K-BIT2; Kaufman and Kaufman, 2004]. All interviews and assessments were conducted by a registered psychologist (E.E.). For one case there was a marked discrepancy between scores of the VABS and those of the GMDS. Therefore, this participant was excluded from the analyses.

For a total of 42 MWS participants, results of previously administered psychometric tests were available. Those tests included the Bayley Scales of Infant Development, Second Edition [Bayley, 1993], the Wechsler Intelligence Scale for Children, 3rd and 4th Editions [Weschler, 1991, 2003], the Stanford-Binet Fourth and Fifth Editions [Thorndike et al., 1986; Roid, 2003], The Vineland Adaptive Behavior Scales, Survey Forms or Classroom edition [Sparrow et al., 1984b, 1985] and the PPVT [Dunn, 1959; Dunn and Dunn, 1981, 1997, 2007], the Kent Infant Development Scale [Schneider et al., 1990], and the Slosson Intelligence Test [Slosson, 1963; Slosson et al., 1998, 2002]. For 22 MWS participants the level of ID was determined by results of such previously administered psychometric tests.

In 20 participants, there was both data from previous formal developmental or intelligence assessments, and from the VABS administered by the researcher (E.E.). As a check of the validity of the previous assessments of level of ID, we compared the two sets of scores. A chi-squared test revealed no significant differences between classifications of level of ID according to prior developmental assessments and the VABS ($\chi^2 = 0.06$, $P > 0.05$).

For seven MWS participants, no formal test scores were available. For these seven, an estimate of developmental level was made by comparing parents' or carers' reports of developmental milestones against the norms described in the Denver Developmental Screening Test II [Frankenburg et al., 1992].

Contrast Group

Contrast participants were selected from the epidemiological sample of children and adults with ID from various etiologies that formed part of the Australian Child to Adult Development Study (ACAD) [Einfeld and Tonge, 1996a,b; Tonge and Einfeld, 2000; Einfeld et al., 2006]. The ACAD sample was derived by recruiting all children with ID in seven census districts in two states of Australia. Analysis of the obtained sample suggested that it provided near complete ascertainment of those with ID in the moderate, severe, and profound ranges, while those with mild ID were under ascertained.

A complete evaluation of causes of ID of the ACAD cohort was undertaken and over 60 causes were identified. At the time of

publication of that evaluation, a diagnosis could not be identified in 40% of cases. Since that time, using newer genetic technologies, a further 14 of 67 of these undiagnosed cases were found to have submicroscopic pathogenic copy number variant. One person was identified as having MWS. This person was excluded from the potential sample from which to select appropriate contrasts.

The process of establishing level of ID in the ACAD sample has been described by Einfeld and Tonge [1996a]. Briefly, IQ tests were conducted by psychologists, or results from previous tests obtained from clinic or Department of Education records, and the level of ID determined according to Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised [DSM-III-R; American Psychiatric Association, 1987] criteria. Where more than one previous test result was obtained for a participant, the best result was selected based on a combination of the psychometric properties of the test used, and the experience and qualifications of the psychologist conducting the test [Einfeld and Tonge, 1996a].

Two contrast participants were selected for each MWS participant to yield a sample with an age range and level of ID that matched the MWS sample as closely as possible.

Characteristic of both groups are displayed in Table I. A *t*-test revealed no significant difference between the groups for age, and chi-squared tests revealed no differences between groups for either gender or level of ID ($P > 0.05$ for all tests).

Measure: The Developmental Behaviour Checklist [DBC]

The DBC [Einfeld and Tonge, 1995] is a questionnaire measuring behavioral and emotional problems in persons with ID. Items were derived by extracting all descriptions of behavior disturbance from medical records of 7,000 assessments of children with developmental disabilities. In this study, both the 96-item parent-report version (DBC-P) and the 107 item version for adults over 19 years (DBC-A) were used. However, because the DBC-A was collected for only a small proportion of participants in both the MWS (N = 6) and contrast groups (N = 11), DBC-A data were converted to DBC-P using the 95 items that are common to both the DBC-A and DBC-P [Mohr et al., 2004]. Parents or carers complete the DBC by rating each item on a 3-point scale: 0 (“not true as far as you know”), 1 (“somewhat true or sometimes true”), and 2 (“very true or often true”). Items can be summed to yield 5 subscale scores (Disruptive/Antisocial, Self-absorbed, Communication Disturbance, Anxiety and Social Relating) and a Total Behaviour Problem Score (TBPS). A TBPS score above 46 is indicative of psychiatric disorder. The DBC Autism Screening Algorithm (DBC-ASA) measures behaviors associated with autism [Brereton et al., 2002]. The DBC-P has good psychometric properties [Einfeld and Tonge, 2002] and is available in 21 languages.

TABLE I. Demographics of MWS and Contrast Participants

Demographic		MWS (n = 60)	Contrast (n = 122)
Age	Min	3.57	3.72
	Max	50.35	33.20
	Mean	12.16	12.39
	Median	8.87	9.67
	SD	9.35	7.77
Gender	Male	33 (55%)	73 (60%)
	Female	27 (45%)	49 (40%)
Level of ID	Moderate	6 (10%)	14 (11.48%)
	Severe–profound	54 (90%)	108 (88.52%)

Procedures

For the MWS group, the DBC was sent via mail as part of a larger questionnaire pack to parents and carers of people with MWS. For the contrast group, the DBC had previously been collected as part of a larger questionnaire pack which was mailed to parents or carers of people with ID.

Data Analysis

Data were analyzed using Intercooled Stata 8.2 for Windows [Statacorp, 2003]. DBC item scores were converted to 0–1 indicator variables reflecting whether or not respondents had endorsed the item (i.e., scored it 1 or 2). The probability of an individual DBC item being endorsed was modeled via logistic regression as a function of MWS status, age, gender, and level of ID.

To examine possible interactions between MWS and either age, gender, or severity of ID on item scores, logistic regressions were repeated separately for the MWS and contrast groups, using independent variables gender, age, and severity of ID and the 95% confidence intervals for the odds ratios obtained for each variable compared between the MWS and contrast groups.

Subscale scores and the TBPS were calculated as the Mean Item Scores across all items comprising the subscale [Taffe et al., 2008]. Mean item scores for the DBC subscales were then modeled via linear regression as a function of MWS status, age, gender, and level of ID, both with and without terms for interactions between MWS status and other explanatory variables.

Chi-squared tests were used to examine associations between MWS status and a classification above or below the clinical cut-off of the TBPS or DBC-ASA.

To examine the potential impact of agenesis of the corpus callosum on behaviors within the MWS group, the probability of a DBC item being endorsed was modeled using logistic regression as a function of agenesis of the corpus callosum, age, gender, and level of ID, in the sample with MWS.

RESULTS

DBC-P Items

Table II displays the DBC-P items which were endorsed as 1 or 2 more or less often in the MWS group than the contrast group and for which *P*-values were low (<0.05).

Total Behavior Problem Score (TBPS) and Subscales of the DBC

Table III shows the means and standard deviations for the Mean Item Scores of the subscales and Total Behaviour Problem Score for

TABLE II. DBC-P Items Endorsed (Scored as 1 or 2) More or Less Often in the MWS Group Than the Contrast Group, With Low *P*-Values

DBC-P item	Description	% of Sample endorsed: MWS	% of Sample endorsed: Contrast	Odds ratio for IV MWS[a] for item endorsed (rated 1 or 2)	95% Confidence interval of odds ratio
Items endorsed more often in the MWS group than Contrast group					
10	Chews or mouths objects or body parts	95.00	57.38	15.13***	4.36–52.54
21	Eats non-food items (e.g., dirt, grass, soap)	41.67	27.05	1.99*	1.02–3.87
25	Flicks, taps, twirls objects	58.33	35.85	2.65**	1.37–5.16
29	Grinds teeth	86.67	51.64	6.74***	2.86–15.88
72	Switches lights on and off or other repetitive activity	49.15	29.51	2.44**	1.26–4.70
78	Stands too close to others	30.00	11.88	3.49**	1.50–8.14
88	Under-reacts to pain	60.00	41.80	2.20*	1.15–4.21
89	Unrealistically happy or elated	30.51	17.21	2.17*	1.04–4.57
Items endorsed less often in the MWS group than Contrast group					
1	Appears depressed, downcast, or unhappy	15.25	35.25	0.31**	0.13–0.73
11	Cries easily for no reason, or over small upsets	20.00	39.34	0.35**	0.16–0.74
17	Doesn't show affection	16.67	35.25	0.33**	0.15–0.74
42	Mood changes rapidly for no apparent reason	40.00	55.73	0.52*	0.27–0.98
47	Laughs or giggles for no obvious reason	20.00	36.07	0.44*	0.21–0.92
57	Prefers to do things on his or her own. Tends to be a loner	26.67	51.64	0.34**	0.17–0.67
95	Whines or complains a lot	13.33	27.05	0.41*	0.17–0.96

[a]Odds ratio of independent variable MWS, adjusted for age, gender, and severity of ID.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

TABLE III. Mean Item Scores and Regression Results for the DBC-P Subscales and Total Behaviour Problem Score

DBC-P subscale	N: MWS	N: Contrast	Mean subscale score SD: MWS	Mean subscale score SD: Contrast	β Coefficient for independent variable MWS[a]	95% CI of coefficient
Total Behaviour Problem Score	60	122	0.44 0.27	0.42 0.24	0.02	−0.06 to 0.10
Disruptive/Antisocial	60	122	0.32 0.31	0.33 0.27	−0.004	−0.09 to 0.09
Self-absorbed	60	122	0.68 0.35	0.60 0.37	0.08	−0.04 to 0.18
Communication Disturbance	60	122	0.32 0.35	0.27 0.30	0.05	−0.05 to 0.15
Anxiety	60	122	0.40 0.33	0.41 0.30	−0.01	−0.11 to 0.08
Social Relating	60	122	0.37 0.33	0.51 0.36	−0.14*	−0.25 to −0.03

[a]Coefficient of MWS, adjusted for age, gender, and severity of ID.
*$P < 0.05$.

the MWS and contrast participants, along with the results of the multivariable regressions comparing the two groups. Compared with the contrast group, the MWS group scored lower on the Social Relating subscale ($P = 0.011$). No other differences were found between the groups for the Total Behavior Problem Score, the DBC subscales, the clinical subscales, nor the ASA.

Interactions Between MWS, Age, and ID on DBC Scores

No interaction effects between MWS and age, between MWS and gender, or between MWS and severity of ID were found for DBC items, nor for the DBC subscales or Total Behavior Problem Score.

TBPS Clinical Cut-Off

In total, 33.33% of the MWS group and 40.16% of the contrast group were above the clinical cut-off score for the TBPS. The difference between the proportion of each group scoring above the cut-off was non-significant ($\chi^2_{(1)} = 0.80$, $P = 0.37$).

Scores for the DBC-Autism Screening Algorithm (DBC-ASA)

In total, 40% of the MWS participants, and 42.62% of contrast participants scored above the cut-off score for the DBC-ASA. A chi-squared test examining the proportion of each group above or below the cut-off revealed no significant differences between the MWS and contrast groups on the DBC-ASA ($\chi^2_{(1)} = 0.11$, $P = 0.73$).

Agenesis of the Corpus Callosum

Data regarding agenesis of the corpus callosum was available for 45 participants. No significant associations were found between agenesis of the corpus callosum and either DBC items or DBC subscale or TBPS scores.

Reanalyzing Excluding 5 MWS Participants Without Genetic Confirmation of MWS, and Excluding 7 MWS Participants for Whom No Formal Developmental Assessment Results Were Available

As a precaution, results were reanalyzed excluding the 5 MWS participants with only a clinical diagnosis, and again excluding the 7 participants for whom neither a VABS nor a report of a prior developmental assessment was available. In both cases, all results followed the same direction as those presented here and *P*-values changed only minimally.

DISCUSSION

The study aimed to investigate the behavioral phenotype of MWS. There was a set of behaviors found to be more common in individuals with MWS than others of similar ages and with similar levels of ID.

Affect and Sociability

Regarding affect, people with MWS were less likely to "appear depressed, downcast or unhappy" (DBC item 1), to "cry easily for no reason" (DBC item 11), or to show mood that "changes rapidly for no apparent reason" (DBC item 42). Although more likely to appear "unrealistically happy or elated" (DBC item 89), they were less likely to "laugh or giggle for no obvious reason" (DBC item 47).

Regarding sociability, those with MWS were more likely to "stand too close to others" (DBC item 78) and were less likely to "not show affection" (DBC item 17), or to "prefer to do things on his/her own, tends to be a loner" (DBC item 57). The MWS group also had lower scores for the Social Relating subscale compared with the contrast group. Lower scores on this subscale represent fewer problems of social interaction.

The findings regarding affect and sociability are consistent with previous reports in the genetic literature suggesting that individuals with MWS typically display a happy affect, with frequent smiling and a sociable demeanor [Mowat et al., 1998; Wilson et al., 2003; Cerruti Mainardi et al., 2004; Garavelli and Cerruti Mainardi, 2007].

Oral Behaviors

The MWS group was more likely to endorse the items "grinds teeth" (DBC item 29) and "Chews or mouths objects or body parts" (DBC item 10).

There was a very high rate of oral behaviors in the MWS group, with 95% endorsing the item "Chews or mouths objects or body parts," and over 86% endorsing the item "Grinds teeth." Excessive mouthing can increase the risk of choking or accidental ingestion of objects, as well as increasing exposure to pathogens [Fessler and Abrams, 2004]. Several studies have demonstrated the efficacy of interventions to reduce sensory-maintained hand-mouthing in people with severe or profound disabilities through strategies, such as differential reinforcement of other behaviors [e.g., Luiselli, 1998] or through a prompt towards a preferred leisure activity incompatible with hand-mouthing [e.g., Turner et al., 1996]. Such approaches could also prove useful in addressing the types of mouthing behavior seen in MWS.

Whether the high rate of teeth grinding and other oral behaviors seen in the MWS group is influenced by other factors (e.g., other genes, seizures, changes to oral-facial structures, or other medical conditions associated with MWS) remains unclear. Recent research suggests that bruxism may be genetically determined, though the genes responsible and the genetic mechanisms involved are yet to be discovered [Hublin et al., 1998; Lobbezoo et al., 2006]. However, at this point, further investigation is required to determine whether *ZEB2* (and other genes in the same pathway) may be candidate genes involved in bruxism, which affects approximately 10% of the population and is considered responsible for tooth wear, loss of dental implants, and temporomandibular pain [Lobbezoo et al., 2006].

Stereotyped Behaviors

The MWS group scored higher for the items "flicks taps twirls objects" (DBC item 25) and "switches lights on and off or similar repetitive activity" (DBC item 72). Stereotyped behaviors are relatively common in people with severe-to-profound ID. However, the results for this study suggest that such behaviors are even higher in those with MWS. Behavioral interventions based on differential reinforcement may be helpful in reducing other forms of repetitive behaviors where intervention is necessary (e.g., due to risk of injury or if the behavior interferes with educational progress).

Given the high rate of stereotyped behaviors in the MWS group, it is possible that some individuals with MWS could meet criteria for Stereotyped Movement Disorder [DSM-IV 307.3; American Psychiatric Association, 2000]. Investigating the clinical severity of such behaviors was beyond the scope of the present study. However, this could be an interesting avenue for future research.

Under-Reaction to Pain

"Under-reacts to pain" (DBC item 88) was more often endorsed for the MWS group compared with the contrast group. An abnormal reaction to pain has been reported in people with ID from varying etiologies [e.g., Biersdorff, 1994; Foley and McCutcheon, 2004] and has been documented in Prader–Willi syndrome [Udwin and Dennis, 1995; Cassidy et al., 1997] and Down syndrome [Hennequin et al., 2000]. Abnormal reactions to pain are also reported in children with autism, and some authors theorize that this may relate to abnormal endogenous opioid regulation [see Muhle et al., 2004, for a review]. Nagasako et al. [2003] distinguish between *insensitivity* to pain, which can reflect either peripheral neuropathy and/or lesions or abnormalities of one or more of the specific regions of the brain involved in the pathways of pain sensation (which include the thalamic nuclei, somatosensory cortex, and anterior cingulate cortex), and pain *indifference*, which does not require peripheral nerve anomalies. Thus, particularly in persons with severe cognitive impairments, an under-reaction to pain may not reflect an inability to perceive pain but rather "an inability to communicate their experience, observers' inability to recognize their pain signals, or uncertainty of pain behaviors seen" [Breau et al., 2001, p. 721]. From the current study, it is not possible to determine whether the participants with MWS for whom an under-reaction to pain was reported would be classified as being "indifferent" or "insensitive" to pain. Either way, the finding that 60% of the MWS group showed under-reaction to pain suggests it is important that carers and doctors of individuals with MWS are made aware of the potential for abnormal or subdued reactions to painful stimuli in people with MWS.

Overall Behavior Problems

Importantly, there was no difference between the MWS and contrast groups on the Total Behaviour Problem Score. Thus, although there may be some support for the reports that many people with MWS have a happy, affectionate demeanor, it is certainly not true that they are always placid or easy-going. Those with MWS are just as likely to show behavioral problems as others with comparable ages and levels of ID, and over 30% of the MWS group was above the clinical cut-off on the TBPS, suggesting that over 30% of people with MWS may have clinically significant levels of psychopathology and/or behavioral and emotional difficulties.

Levels of behavior and emotional disturbance are known be much higher in individuals with ID than the general population [Einfeld and Tonge, 1996; Dekker et al., 2002; Einfeld et al., 2006], and the results for those with MWS are consistent with this. Managing behavior problems in individuals with MWS is therefore just as important as in any person with ID and behavior problems.

Developmental Level in MWS

It was not possible to provide a single type of IQ assessment for all subjects conducted by a single well-qualified assessor. Consequently, a range of sources of IQ estimates were used. Nevertheless, the results were highly consistent. Ninety percent scored in the severe to profound range of ID, so it is reasonable to regard this as a reflection of the typical cognitive attainments of this group. However, it is possible that there is some imprecision in the estimates obtained.

Comparison to Angelman Syndrome

There are similarities between the overall gestalt of the MWS behavioral phenotype and that of Angelman syndrome. Individuals with Angelman syndrome also typically display ID in the severe range [Cassidy et al., 2000], and are commonly described as happy [Horsler and Oliver, 2006]. As in MWS, over 80% of people with Angelman syndrome suffer seizures [Williams et al., 2006], and both sleep disturbance and feeding disorders are also common in Angelman syndrome [Pelc et al., 2008]. Indeed, the smiling, happy, sociable affect seen in many individuals with MWS, combined with some of its physical features (e.g., microcephaly, seizures, and a wide-based gait) has initially led to some individuals erroneously being suggested to have Angelman syndrome [Mowat et al., 2003; Garavelli and Cerruti Mainardi, 2007].

However, while there are similarities between the behavioral phenotype of MWS described in this study, and features commonly reported as part of the behavioral phenotype of Angelman syndrome, there are also notable differences. Firstly, individuals with Angelman syndrome are often said to show an attraction to water [Barry et al., 2005; see also Horsler and Oliver, 2006 for a review; Didden et al., 2008] and this did not emerge from the current study on MWS. Secondly, Angelman syndrome is reportedly associated with bouts of laughter [Horsler and Oliver, 2006]. However, the current study found that inappropriate laughter is no more common MWS than those of similar age and level of ID, and, indeed, results indicated it may be less common in those with MWS.

Should future research confirm a generally elevated mood in MWS then this may suggest that the *ZEB2* gene has a role to play in mood, though at this point such a potential association is only speculative. One previous study has suggested a potential link between the rat homolog of *ZEB2* and antidepressant function, however, 576 other genes were also found to be expressed differently following the administration of the drugs [Takahashi et al., 2008].

Limitations of the Study

The results of the current study must be interpreted with several caveats in mind. One limitation of the study was the small size of the MWS sample. MWS is a rare condition, and in this study, participants were recruited via multiple sources, and questionnaires and consent forms were made available in five languages (including English) to enhance recruitment.

As described above, it was not possible to obtain a single type of IQ or developmental assessment result for all MWS participants, and so a range of sources of IQ estimates were used. Despite the fact that a wide range of assessments was used, the results were quite consistent. However, the possibility exists that there is some imprecision in the estimates obtained.

Only one behavioral checklist was used in this study. It is possible, but unlikely, that some behavior was missed, given the extensive source of DBC items [Einfeld and Tonge, 2002, p. 33].

The study was predominately of children and adolescents with MWS. Although there were some adults aged over 19 years (N = 10) in the MWS group, the numbers were too small to determine if the pattern of behavioral disturbance alters in adulthood.

Despite these limitations, the current findings offer information which may form part of the picture regarding gene-behavior pathways in MWS. Neuroanatomical studies using imaging technologies such as magnetic resonance imaging are now needed to enable the elucidation of gene-brain-behavior pathways. Future research could also extend the current findings by investigating the longitudinal course of behaviors in MWS and documenting the natural history of the syndrome.

CONCLUSION

As far as we are aware, this is the first investigation of the behavioral phenotype of MWS. Results support previous suggestions from the genetic literature that people with MWS typically display a happy, sociable demeanor. Other behaviors found to be associated with MWS include repetitive or stereotyped behaviors, oral behaviors, such as mouthing and teeth grinding, and an under-reaction to pain. One-third of the MWS group showed clinically significant levels of behavioral and emotional problems as measured by the DBC. This points to the importance of managing behavior problems in this group and providing appropriate interventions for those with MWS.

ETHICS

The MWS Study was approved by the Human Research Ethics Committees for South Eastern Sydney Illawarra Health Service—Northern Section, The University of New South Wales, and The University of Sydney. The ACAD Study was approved by the above Committees and the Human Research Ethics Committee of Monash University.

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