

Autism spectrum disorders in Prader-Willi and Angelman syndromes: a systematic review

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Autism spectrum disorders (ASDs) have been linked with maternally derived duplications/triplications of chromosome 15q11–13 and therefore might occur more frequently in people with Prader-Willi syndrome (PWS) when due to uniparental disomy (UPD), than in other forms of chromosomal abnormality involving this region [i.e. deletion (DEL) forms of PWS and DEL + UPD forms of Angelman's syndrome –(AS)]. Twelve studies regarding ASD in PWS and AS were reviewed. It was noteworthy that among the genetically confirmed UPD and DEL cases of PWS and AS, the rate of ASD was 25.3% (38/150; range 0–36.5%) in PWS and 1.9% in AS (2/104; range 0–100%) (Fisher's exact $P < 0.0001$). Among the subset of cases with confirmed UPD or DEL, the rate of ASD in the UPD cases of PWS was significantly higher (20/53) than in the remaining combined samples (i.e. DEL PWS + UPD AS + DEL AS cases; 20/201) (Fisher's exact $P < 0.0001$). ASD in UPD PWS cases (20/53) compared with DEL PWS cases (18/97) was also statistically significant (Fisher's exact $P = 0.0176$). Thus, the limited available evidence supported the predic-

tion that overexpression of maternally imprinted genes in 15q11–13 confers a risk for ASD. Further research will be required to confirm these findings. *Psychiatr Genet* 15:243–254 © 2005 Lippincott Williams & Wilkins.

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Introduction

Autism is a neurodevelopmental disorder affecting communication and reciprocal social interactions, accompanied by stereotyped, repetitive behaviors. It is highly heritable and thought to be the result of multiple, interacting genes (Wassink and Piven, 2000) with the genetic liability to autism conferring a risk for a broader range of impairments in social communication and play. The term autism spectrum disorder (ASD) is used to refer to individuals with pervasive developmental disorders among this broader range of manifestations. Occasionally, single gene disorders like tuberous sclerosis and various chromosomal abnormalities are implicated in pathogenesis. More specifically, according to some authors, 'chromosome 15 is the most frequent site of autosomal abnormalities in autism' (Wassink and Piven, 2000, p. 173; see also Schroer *et al.*, 1998). The most often reported abnormality has involved inversion duplications of chromosome 15 and this has led to speculation that genes on chromosome 15 may confer a susceptibility to autism. Further support for this idea has come from findings of positive linkage signals in the 15q11–13 region in studies of families multiplex for idiopathic autism, as well as the evidence for allelic association with polymorphisms in UBE3A and other genes within 15q11–13. The linkage and linkage disequilibrium findings, however, are not consis-

tent across studies, leaving some uncertainty over their significance. Accordingly, it would be informative if there were other lines of evidence that might throw light on the issue. Recent reports of ASD, in association with maternally derived interstitial duplications of 15q11–13, have led to the suggestion that overexpression of maternally imprinted 15q11–13 genes may confer an increased risk for ASD (e.g. Kerbeshian *et al.*, 1990; Hotopf and Bolton, 1995; Battaglia *et al.*, 1997; Browne *et al.*, 1997; Cook *et al.*, 1997; Cook, 1998; Repetto *et al.*, 1998; Schroer *et al.*, 1998; Martin *et al.*, 2000; Wolpert *et al.*, 2000; Bolton *et al.*, 2001). If overexpression of maternally imprinted genes in the 15q11–13 region is involved in creating a susceptibility to ASD, the rate of disorder in individuals with Prader-Willi syndrome (PWS) due to uniparental disomy (UPD) (where there is overexpression of maternally imprinted genes) should be higher than the rate observed in individuals with deletion (DEL) forms of PWS and possibly also the rate in individuals with Angelman's syndrome (AS) (where there is a reduced expression of maternally imprinted genes). To test this prediction, the initial objective was to systematically review the available literature, examine the rate of ASD in published studies of PWS and compare the rate of ASD in cases due to UPD with the rate in DEL forms of PWS as well as the rate in AS.

Prader-Willi syndrome

PWS (Prader *et al.*, 1956) is a rare disorder characterized by mild to moderate intellectual disability, obesity associated with hyperphagia, hypogonadism, and, in the neo-natal period, feeding difficulties and hypotonia. Short stature, small hands and feet, hypopigmentation, and a characteristic narrow face have also been noted (Cassidy, 1984; Butler, 1990; Thompson *et al.*, 1996; Cassidy *et al.*, 1997). PWS may also be associated with a variety of behavioral disturbances, including obsessive-compulsive disorder and autism (Roof *et al.*, 2000), temper tantrums, impulsiveness, repetitive speech, obsessive rituals, self-injury (such as skin-picking), mood fluctuations (Clarke *et al.*, 1996; Dykens *et al.*, 1996; Einfeld *et al.*, 1999), as well as emotional and psychological problems, such as depression and excessive unhappiness (Beardsmore *et al.*, 1998; Boer and Clarke, 1999). It has been suggested that many of the symptoms may be due to hypothalamic deficiency (Cassidy, 1997; Swaab, 1997).

PWS has been estimated to occur in 1 child in 10 000–15 000 births (Cassidy, 1997). The four genetic classes of PWS are (Chamberlain and Brannan, 2001) (1) maternal uniparental disomy for chromosome 15 (UPD), (2) 3–4 MB deletion of the paternally inherited 15q11–13 region (DEL), (3) paternally inherited balanced translocations involving this region, and (4) imprinting mutations or deletions of the Prader-Willi syndrome Imprinting Center (PWS-IC). Approximately 25–30% of patients with PWS present with UPD for maternal chromosome 15 and 60–70% of patients have DEL of 15q11–13 on the paternal chromosome (Ledbetter *et al.*, 1981; Butler *et al.*, 1986; Mascari *et al.*, 1992; Cassidy *et al.*, 1997; Nicholls *et al.*, 1998). Only a small proportion of cases (approximately 5%) are due to mutations/deletions of the PWS-IC (Sutcliffe *et al.*, 1994; Buiting *et al.*, 1995). Although 15q11–13 deletions on the paternally inherited chromosome and UPD for the maternal chromosome both result in loss of expression of paternally imprinted genes, and hence PWS, the two forms of chromosomal abnormality give rise to some important differences in the expression of other genes in the 15q11–13 region. Thus, DEL forms of PWS result in monosomy for non-imprinted genes in the deleted region, whereas UPD PWS cases are disomic for non-imprinted and maternally imprinted genes, by virtue of there being two copies of the maternally inherited chromosome. Accordingly, expression of maternally imprinted genes in the UPD cases is increased in comparison with the level of expression seen in DEL cases and normal individuals.

It is noteworthy, therefore, that several phenotypic differences have been reported between the UPD and DEL groups. In general, it has been found that maternal UPD is associated with increased parental age (Webb, 1994; Gillissen Kaesbach *et al.*, 1995) and it has been

suggested that UPD patients are less severely affected than those with deletions. For example, UPD patients have fewer of the facial characteristics, a lower pain threshold, and less tendency to skin-pick than the DEL patients (Cassidy *et al.*, 1997; Dykens *et al.*, 1999). UPD patients have also been reported to have a higher IQ, with verbal IQ being higher than performance IQ. Interestingly, DEL patients are reported to have relative strength in specific visual perceptual skills, which may account for reports that some PWS patients have a peculiar ability in putting together jigsaw puzzles (Roof *et al.*, 2000). A recent finding from a population-based study indicated that older UPD patients were more prone than DEL patients to severe affective disorder with psychotic features (Boer *et al.*, 2002).

Angelman syndrome

AS (Angelman, 1965) is a neurodevelopmental disorder caused by abnormalities in the expression of a maternally imprinted gene, UBE3A, which plays a role in the ubiquitin pathway and synaptogenesis. The disorder is characterized by severe developmental delay, intellectual disabilities, a partial or complete lack of speech, ataxia, and dysmorphic facial features. Electroencephalogram (EEG) abnormalities and seizures occur in up to 80–90% of cases (Angelman, 1965; Boyd *et al.*, 1988; Clayton-Smith and Pembrey, 1992; Zori *et al.*, 1992; Clayton-Smith, 1993; Williams *et al.*, 1995a,b). Patients have frequently been described as happy and sociable, with a tendency to burst out laughing. Case studies and parental questionnaires have indicated that hyperactivity, attentional difficulties, aggression, temper-tantrums, non-compliance, eating and sleeping difficulties, a lack of social responsiveness, and repetitive and stereotypic behavior can be problematic (Hersh *et al.*, 1981; Zori *et al.*, 1992; Summers *et al.*, 1995). Facial features associated with AS include deep-set eyes, a broad, smiling mouth, and a prominent chin (Watson *et al.*, 2001). Thirty percent of patients are microcephalic (Zori *et al.*, 1992; Clayton-Smith, 1993).

The prevalence rate of AS is estimated to be 1 child in 10 000–20 000 births (Ruggieri and McShane, 1998). Molecular analyses have identified four genetic types of AS. Approximately 2–7% are due to a paternal UPD, 68–75% result from maternally-derived DEL in the 15q11–13 region (including rare families with unique translocations and smaller deletions within 15q11–13), a further 2–5% or so are due to imprinting center mutations, and 8–11% are caused by mutations in UBE3A (Williams *et al.*, 2001).

Once again, phenotypic differences between the UPD and DEL cases have been reported. On the whole, UPD patients tend to present with a milder phenotype than those with deletions. UPD patients have a lower

incidence and later onset of seizures, less severe ataxia, are able to walk at an earlier age, are more able to use symbolic communication, and may have fewer/less defined facial characteristics (Bottani *et al.*, 1994; Smith *et al.*, 1997, 1998; Moncla *et al.*, 1999b; Fridman *et al.*, 2000). Patients with imprinting and UBe3A mutations have also been found to exhibit a milder phenotype (Moncla *et al.*, 1999a; Otha *et al.*, 1999).

Aims

Literature regarding chromosome 15 abnormalities and ASD indicates that maternal duplication in 15q11–13 carries an increased risk for ASD (Browne *et al.*, 1997; Cook *et al.*, 1997). ASD and their associated behaviors have been reported in relationship to PWS and AS (e.g. Kerbeshian *et al.*, 1990; Summers *et al.*, 1995; Roof *et al.*, 2000). At this time, however, it is not clear how prevalent ASDs are in relationship to PWS and AS. Therefore, the aim of this systematic review was to identify all published studies, including case studies, adhering to given inclusion and exclusion criteria, linking ASD to PWS and AS. Furthermore, examination of the frequency of ASD in cytogenetically verified PWS maternal UPD and PWS DEL probands, as well as that in PWS maternal UPD and AS probands, tested the notion that maternally imprinted genes increase susceptibility for ASD.

Method

Studies were considered for inclusion according to predetermined criteria. Thus, studies were selected using the search terms Prader-Willi, PWS, and Angelman found anywhere in the text in combination with any of the search terms autism, autistic, ASD, Asperger, pervasive developmental disorder, and PDD. Any study that did not link PWS or AS to these latter terms was excluded. Literature reviews and articles that did not include original data were also excluded. Owing to the broad nature of the review all study designs were included, although case studies were included only for descriptive purposes. Case studies were not included in the calculation of the rate of ASD in PWS or AS. Studies considered were written in English, German, or Dutch. All retrieved abstracts were scanned and only full papers/theses/books meeting the inclusion criteria were obtained.

The electronic databases searched were Medline (1966–2002/07), Cinahl (1982–2002/06), and PsychInfo (1887–2002/05) (all via <http://www.silverplatter.com/erl/web-spirs4.htm>). Papers and studies known to the authors already in the project's possession were also 'hand-searched' for any relevant studies, as not all of these may have been cited in the electronic databases used. This combination of electronic-search and hand-search strategies was employed in order to optimize the likelihood of unbiased and more complete identification

of relevant studies as the problem of identifying non-Medline/Cinahl/PsychInfo published studies is a real concern. Studies found by each search strategy are marked in the tables so as to ease replication of the findings presented here. When further information was required, the original authors were contacted with a request to elaborate on the details provided in their papers.

Data analysis

In order to test the hypothesis, this review's focus was on comparing the rates of ASD in confirmed UPD and DEL cases. In particular, cases were excluded if there were possible imprinting center deletions/mutations or UBe3A mutation, as the effect of these abnormalities on the expression of maternally imprinted genes in the region is unclear. The analyses were concerned with three key comparisons. First, the hypothesis predicts that the rate of ASD should be higher in PWS than in AS cases, as long as UPD PWS cases are included in the PWS samples. Second, it predicts that the rate of ASD should be higher in UPD PWS cases than in PWS DEL cases and AS DEL and UPD cases. As the number of cases was small, it was not meaningful to compare the rates of each subgroup with the PWS UPD cases. Therefore, the PWS UPD cases were compared with the combined sample of other cases (to maximize power) and also with the DEL PWS cases as a within-syndrome analysis. Exact tests were used and significance levels are for two-tailed tests.

Results

The electronic databases produced a total of 73 references, which, together with the project's bibliographic search and the application of the inclusion and exclusion criteria, resulted in the identification of eight relevant case-series investigations (see Tables 1, 2a and 3a) and four descriptive case studies, giving a total of 12 papers meeting the inclusion criteria. Ten authors were contacted with requests for further information; eight replied, one of whom provided new and updated information, as well as permission for the additional information to be included in this review (Tables 2b and 3b) (Hou, 27 September 2002; personal communication).

Of the studies identified and included in the systematic review, four studies were carried out in the UK, three in Sweden, two in the USA, and one each in Spain, Belgium, The Netherlands, and Taiwan. Seven of the 12 studies concerned PWS, three looked at AS, and one at both PWS and AS. The 12 studies included four case studies (PWS = 3, AS = 1), four within-syndrome studies (PWS = 4, AS = 1), two case-control studies (PWS = 2), and two epidemiological studies (PWS/AS = 1, AS = 1). One of the excluded PWS studies (Akefeldt *et al.*, 1991) should be mentioned. This 1991 Swedish study was excluded because it did not specifically mention ASD.

Table 1 Electronic databases and 'hand-search' results

| Literature search | Search terms | Number of references retrieved | Number of papers included |
|--|----------------------------------|--------------------------------|---------------------------|
| Electronic database search | | | |
| #1 | Autism | 14 065 | |
| #2 | Autistic | 13 966 | |
| #3 | ASD | 1495 | |
| #4 | Asperger | 709 | |
| #5 | Pervasive developmental disorder | 861 | |
| #6 | PDD | 1009 | |
| #7 | Prader-Willi | 1779 | |
| #8 | PWS | 933 | |
| #9 | Angelman | 661 | |
| #10 | #1 or #2 or #3 or #4 or #5 or #6 | 21 170 | |
| #11 | #7 or #8 or #9 | 2467 | |
| #12 | #10 and #11 | 73 | 6 |
| Hand-search | | | |
| Papers previously collected by the project team concerning studies on PWS and AS and not found through the electronic databases searched | As above #1-9 | 79 | 6 |
| Total number of papers considered | | 152 | 12 |

Nevertheless, in a later study, concerning AS the authors stated that no cases of ASD had been found in the study by Akefeldt and colleagues (Steffenburg *et al.*, 1996). Fortunately, not all of the PWS cases from the excluded 1991 study were lost to the review as a later study (Akefeldt and Gillberg, 1999) included four of the cases cited in the 1991 study; the other cases from the 1991 were not included in the 1999 study.

Prader-Willi syndrome

Three descriptive case studies were identified. Of the four cases that these three studies described, there was one female study participant, with a translocation between chromosomes 5 and 15 and a partial deletion from 15pter to the Angelman region, who was found to have ASD (Arrieta *et al.*, 1994). Two male participants were diagnosed with PDD-NOS (Not otherwise specified) (Demb and Papola, 1995; Eikelenboom and Berckelaer-Onnes, 2000) and one further female participant was reported not to have ASD (Eikelenboom and Berckelaer-Onnes, 2000).

The six case-series reports identified were of varying relevance in fulfilling the aims of this review (see Table 2a). Akefeldt and Gillberg's (1999) study intended to determine whether children with PWS had behaviors that were not specifically related to mental retardation or obesity, whether these behaviors were age-related, and whether treated and untreated PWS cases differed with respect to behavior. They ascertained PWS cases from a variety of sources and included a comparison group of individuals matched group-wise on the basis of age, IQ, body mass index, and appetite. Forty of the 44

participants underwent molecular genetic screening, though apart from two cases, they were not systematically examined for UPD or DEL status. One 10-year-old boy with a deletion (probably a mosaic form) was diagnosed by a neuropediatrician as having DSM-IV autistic disorder (Akefeldt, 12 August 2003; personal communication).

Beardsmore *et al.*'s (1998) study attempted to gain a better understanding of psychopathology in PWS. All adults with PWS ($n = 23$) identified in one UK county were assessed on measures of adaptive and maladaptive behaviors. Medical records and psychiatric case-notes were examined. None of the patients had any communication from any specialists in the notes suggesting that they had ASD in childhood only. ASD was also excluded at the time of the adult assessment for the work published in the paper (Beardsmore *et al.*, 1998). Not all of the individuals had living parents in contact with them; therefore, a parent history was not available for everyone. The general practitioner notes, however, were reviewed in all cases. ASD diagnosis in childhood was ruled out on this information. This, of course, does not exclude the possibility that ASD in childhood was present but not diagnosed (Cooper, 22 October 2002; personal communication). Although all the cases in this study had a clinical diagnosis of PWS, only a subset (17/23) was genetically verified and it was only possible to classify a subset of these cases as DEL or UPD cases (Beardsmore *et al.*, 1998).

A recent and ongoing study was reported by Descheemaeker *et al.* (2002). This 15-year follow-up study of 53 known genetically verified PWS clinic cases, monitored medical, cognitive, behavioral and emotional development as well as the evolution of psychiatric disorders in adolescence and adulthood. Only eight patients, aged 9-37 years old, were fully reported on. These included four cases diagnosed with acute cycloid psychosis and four cases with unspecified bipolar disorder. ASD in childhood was diagnosed by independent psychiatrists. The cases are currently being followed up by the researchers using the Child Behavior Checklist (Achenbach, 1991), the Developmental Behavior Checklist (Einfeld and Tonge, 1995), the Checklist for Autism in Toddlers (CHAT; Baron-Cohen *et al.*, 1992), the Autism Spectrum Screening Questionnaire (ASSQ; Ehlers and Gillberg, 1993), and the Autisme en Verwante Stoornis-senschaal-Z-revisie (AVZ-R; Kraijer, 1999) (Descheemaeker, 17 October 2002, personal communication).

Dykens and Cassidy's (1995) study measured four features of maladaptive behavior in PWS using the Reiss Scales for Children's Dual Diagnosis (Reiss, 1990) for children under the age of 13 years and the Reiss Scales for Maladaptive Behavior (Reiss, 1988) for older participants. These scales included derived domains, including an

Table 2a Studies concerning ASD in PWS – information obtained from original published studies

| Author, country of study, year of publication | Ascertainment | PWS cases | | | | PWS diagnosis | ASD assessment | ASD diagnostic criteria | ASD rate in PWS | | |
|--|--|--|-----------------------------|-----|-----|---|---|-------------------------------|-----------------------------------|-----|-----|
| | | Total cases reported (% male) | Genetically confirmed cases | | | | | | Total | UPD | DEL |
| | | | Total | UPD | DEL | | | | | | |
| Akefeldt ^a and Gillberg, ^b Sweden (1999) | Referral by clinician | 44 (64%) | 40 | – | 2 | PWS criteria (Holm <i>et al.</i> , 1993) | Asperger syndrome and high functioning Autism Screening Questionnaire (Ehlers and Gillberg, 1993; Ehlers <i>et al.</i> , 1999) | DSM-IV | 2.3% (1/44; male) | – | 1 |
| | Epidemiological investigation | | | | | Molecular genetics: 40 cases had paternal deletion or maternal disomy | Clinical diagnosis by a neuro-pediatrician | | | | |
| | Through membership of national PWS assoc | | | | | Cytogenetics carried out on only a few cases Two cases refused genetic exam | | | | | |
| Beardsmore ^a <i>et al.</i> , ^c UK (1998) | Through health records of two National Health Service trusts | 23 (39%) | 17 | 1 | 10 | PWS criteria (Holm <i>et al.</i> , 1993) | The Mini Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD) (Prosser <i>et al.</i> , 1997): developmental disorder section ^a | ICD-10 | 0 | 0 | 0 |
| | Through two private care homes | | | | | 87% had genetic testing for PWS DNA analysis showed PWS in 13 cases | | DSM-IV | | | |
| Descheemaeker ^a <i>et al.</i> , ^b Belgium (2002) | Known clinic cases | 53 (57%) (with 8 cases fully described) | 8 | 2 | 6 | Genetic analysis carried out on all cases, though only eight cases with psychiatric symptomatology were reported upon | Psychiatric diagnosis ^a | Unknown | 7.5% (4/53 in childhood; 3 males) | 2 | 2 |
| Dykens and Cassidy, ^c USA (1995) | Volunteers through a PWS Association annual meeting | 86 (50%) | 32 | 6 | 26 | Parental or caregiver reports Physical phenotype Developmental history and clinical presentation Genetic testing in 32 cases | Reiss Scale for Children's Dual Diagnosis (Reiss, 1990) for 4–12 years Reiss Screen For Maladaptive Behavior (Reiss, 1988) for >13 years | n/a | – | – | – |
| Hou ^a <i>et al.</i> , ^b Taiwan (1998) | Epidemiological cytogenetic study into the causes of intellectual disability | 56 | 56 | – | – | Cytogenetic analysis | Autism Diagnostic Interview: (ADI and ADI-R) (Le Couteur <i>et al.</i> , 1989) ^a | ICD-10 ^a DSM-IV | – | – | – |
| Veltman <i>et al.</i> , ^c UK (2004b) | Volunteers ascertained through a PWS Association and previous studies | 76 (<i>n</i> =63 reported for Autism Screening Questionnaire) | 63 | 32 | 31 | Cytogenetic analysis | Autism Screening Questionnaire (ASQ) (Berument <i>et al.</i> , 1999) | ICD-10 DSM-IV | 36.5% (23/63) | 14 | 9 |

ASD, autism spectrum disorder; PWS, Prader-Willi syndrome; UPD, uniparental disomy; DEL, deletion.

^aClarifying information obtained through author's correspondence.

^bPaper found through electronic database search.

^cPaper found through hand-search.

Table 2b Studies concerning ASD in PWS – augmented data obtained through authors' correspondence

| Author, country of study, year of publication | PWS cases | | | ASD rate in PWS | | | |
|---|------------------------------|-----------------------------|-----|-----------------|---|-----|-----|
| | Total cases studied (% male) | Genetically confirmed cases | | | Total | UPD | DEL |
| | | Total | UPD | DEL | | | |
| Hou ^a <i>et al.</i> , ^b Taiwan (1998) | 66 (68%) | 66 | 18 | 48 | 15.2% (10/66; 9 males: 4 UPD, 5 Del; of whom two male UPD with high-functioning ASD in childhood) | 4 | 6 |

ASD, autism spectrum disorders; PWS, Prader–Willi syndrome; UPD, uniparental disomy; DEL, deletion.

^aAdditional, updated, as yet unpublished results obtained through author's correspondence.

^bPaper found through electronic database search.

autism/pervasive developmental disorder and autism domain, respectively. The 86 PWS cases included were identified through parents/caregivers attending a PWS Association's Annual Meeting and genetic status was derived through information provided by the parents/caregivers.

Hou *et al.* (1998) described a large nationwide (Taiwan) investigation into the etiology and prevalence of mild and serious learning disability. All children with a learning disability that were known to services or were identified by a nationwide screening program were investigated. This study included evaluations of photographs of the face, hands and feet, as well as scrutiny of family and past medical records. Chromosomal studies in selected patients were carried out and followed up by cytogenetic analysis if deemed necessary. Molecular genetic analysis for certain recognizable syndromes was also performed. The cases were evaluated using the Autism Diagnostic Interview (ADI or ADI-R), which generates ICD-10 and DSM-IV diagnoses (Le Couteur *et al.*, 1989). The operational criteria for a diagnosis of ASD used in the study have not yet been reported. Sixty-six cases of PWS were identified (this includes 10 new cases identified since the original report) and cytogenetically confirmed as having PWS (see Table 2b) (Hou, 23 May 2002; personal communication).

Finally, Veltman *et al.* (2004a) predicted that maternal UPD PWS cases would be more prone to ASD than DEL PWS cases because of their duplicated maternally expressed genes. This hypothesis was tested using postal and telephone surveys of matched, genetically verified, UPD and DEL cases using the Autism Screening Questionnaire. Cases with suspected ASD were calculated by taking the number of cases above cutoff of 15 for diagnosis of probable ASD. UPD cases were said to exhibit significantly more autistic symptomatology. These results lend support to the notion that abnormality in the expression of maternal imprinted 15q11–13 genes may confer a susceptibility to ASD.

Prader–Willi syndrome summary

Excluding the descriptive case reports, a total of 348 (including 10 new cases as yet unpublished, see

Table 2b) patients with PWS were described in the six selected case-series investigations (see Tables 2a and 2b). The rates of ASD found within PWS patients were calculated using five of the six case-series reports concerning PWS (diagnostic information was not included in the report by Dykens and Cassidy (1995), so this study was not included in these calculations). The rates ranged from 0 to 36.5%. Combining the cases reported in these five studies, including the updated data provided by one author (Hou, 27 September 2002; personal communication) (see Table 2b), gives an overall rate of 14.5% for all cases reported ($n = 38/262$) and a rate of 25.3% for the genetically confirmed UPD and DEL cases ($n = 38/150$). Six of the PWS cases diagnosed with an ASD did not have that diagnosis later in life (Descheemaeker *et al.*, 2002; Hou, 27 September 2002; both personal communications). Indeed, these transient autistic-like symptoms were also reported in eight of 12 PWS children (youngest group) at approximately age 1–4 years in the Scandinavian study (Akefeldt and Gillberg, 1999; Akefeldt, 11 October 2002, personal communication). It should be noted, however, that four cases, which were diagnosed with ASD in childhood, went on to develop psychosis in adulthood (Descheemaeker *et al.*, 2002).

One study (Dykens and Cassidy, 1995), not included in calculating the above rate, used the Reiss Screen for Maladaptive Behavior to assess psychopathology (Reiss, 1988). They found a significant difference in older patients in several domains, including the autism domain of the scale [$F(1,52) = 8.64, P < 0.01$] (specifically the social withdrawal component), but the number of patients with an autism spectrum diagnosis was not reported.

Angelman syndrome

Three case-series studies were included regarding AS. Of these, Chan *et al.* (1993) reported a survey study on the molecular genetic mechanisms in AS. Although this survey did not set out to study ASD in AS, one case was found with typical AS facial features and marked autistic behavior. No molecular deletion could be found at 15q11–13. The proband was heterozygous for one or more loci within 15q11–13. The authors concluded in the paper that the proband

would have either a point mutation or a very small deletion.

In their 1998 published study (see above), Hou *et al.* also identified AS cases. None of the AS cases was diagnosed with an ASD using the ADI, although all had marked intellectual impairments, which made assessment difficult (Hou, 23 May 2002, personal communication).

The final AS study was specifically designed to investigate the rate of ASD in children with Angelman syndrome (Steffenburg *et al.*, 1996). All children with mental retardation and active epilepsy of 5 years duration ($n = 98$) were investigated and four cases of Angelman syndrome were identified (in two there was genetic verification of the diagnosis). The other two cases were described as having mental retardation, typical speech impairment, movement/balance disorder, epilepsy, and typical EEG abnormality (Steffenburg, 11 October 2002, personal communication). All four cases were reported as meeting full behavioral criteria for the diagnosis of autistic disorder/childhood autism.

Angelman syndrome summary

Within the three AS case-series studies, the rate of ASD, in the 138 patients studied, was 3.6% for all reported cases ($n = 5/138$) (see Tables 3a and 3b). Four of the patients with a diagnosis of ASD came from one epidemiological study (Steffenburg *et al.*, 1996) and were not all genetically verified, thus, for the purposes of this review, limiting the total number of patients identified in that study with AS ($n = 4$; 2 DEL). Furthermore, as stated above, in the case of the single AS female identified with ASD in the Chan *et al.* (1993) study, no deletion could be identified. No significant distinction could be made between the UPD and DEL cases in the diagnosis of an ASD as only two DEL cases with an ASD were cytogenetically verified; the other three cases were not cytogenetically verified cases of AS. This meant a rate of 1.9% for the genetically confirmed UPD and DEL cases with a diagnosis of ASD ($n = 2/104$).

In addition to these three studies, one descriptive case study was found. The report described a male AS patient with a small maternally derived supernumerary marker chromosome 15 (see Roberts *et al.*, 2002), but there were no signs of ASD (Thompson and Bolton, 2003).

Summary of findings in genetically verified cases and according to uniparental disomy and deletion status

Only one of the studies (Veltman *et al.*, 2004a) had explicitly tested the hypothesis that maternal duplications of 15q11–13 increased the risk for an ASD, although in most studies found, autism was not the focus of the investigation. As such, methodological limitations in the assessment of psychopathology were evident in all studies

and sample sizes were usually small. Therefore, it was not possible to draw any firm conclusions. The overall rate of ASD according to clinical diagnosis and genetic abnormality is summarized in Table 4. It was noteworthy that among the genetically confirmed UPD and DEL cases of PWS, the rate of ASD was 25.3% (38/150; range 0–36.5%). This rate was significantly (Fisher's exact $P < 0.0001$) higher than the rate of ASD in all genetically confirmed UPD and DEL cases of AS (1.9%; 2/104; range 0–100%). Moreover, among the subset of cases with confirmed UPD or DEL, the rate of ASD in the UPD cases of PWS was significantly higher (20/53) than the rate of ASD in the remaining combined samples (i.e. DEL PWS + UPD AS + DEL AS cases; 20/201) (Fisher's exact $P < 0.0001$). The frequency of ASD in UPD PWS cases (20/53) compared with DEL PWS cases (18/97) was also statistically significant (Fisher's exact $P = 0.0176$). Thus, the limited available evidence was in keeping with the prediction that overexpression of maternally imprinted genes in 15q11–13 confers a risk for ASD. Further, larger scale, more robust and focused research will be required to confirm these findings.

Discussion

The rates of disorders calculated here might not be representative of the true rate of ASD found in PWS/AS, as not all the studies were population based. In terms of PWS, the rate of ASD in the Hou *et al.* (1998) study was 15%, lower than the rate found by Veltman *et al.* (2004), but using more robust ASD assessments. In the two population-based studies that reported rates of ASD in AS, the findings are quite inconsistent. One study reported no AS patients (0/40) with an ASD, although they acknowledged the challenge of diagnosing ASD in severely handicapped children (Hou *et al.*, 1998). The other found that all four patients with AS (4/4) identified in their population had an ASD (Steffenburg *et al.*, 1996). Two of these latter cases, however, were not cytogenetically verified cases of AS (Steffenburg *et al.*, 1996).

Since the publication of the Steffenburg *et al.* (1996) study, Steffenburg reports finding no further AS cases meeting the full criteria of an ASD. Aside from this, Steffenburg notes that severe intellectual disabilities in these cases make it difficult to fulfill full criteria for an ASD. She commented that 'although most AS cases seen did show some autistic traits, the majority of these children had at least some interest in social interaction'. Indeed, Steffenburg postulates that these children's behavior is more comparable to an extreme degree of hyperactivity/excitability in combination with hand flapping and very brief social interaction (Steffenburg, 11 October 2002, personal communication). Other authors have also specifically noted that 'although AS has been reported to manifest autism-like traits, AS individuals are definitely not autistic, especially in their

Table 3a Studies concerning ASD in AS – information obtained from original published studies

| Author, country of study, year of publication | Ascertainment | AS cases | | | | AS diagnosis | ASD assessment | ASD diagnostic criteria | ASD rate in AS | | |
|---|--|----------------------------------|-----------------------------|-----|-----|--|--|-------------------------------|----------------|-----|-----|
| | | Total cases reported (% male) | Genetically confirmed cases | | | | | | Total | UPD | DEL |
| | | | Total | UPD | DEL | | | | | | |
| Chan ^a <i>et al.</i> , ^b UK (1993) | Clinical referrals | 94 (\approx 50%) ^a | 79 | 3 | 63 | Molecular genetic analysis Cytogenetic analysis | Clinical history and examination; unknown whether a clinical assessment of ASD was made by a psychiatrist | Unknown | 1.3% (1/79) | 0 | 0 |
| Hou ^a <i>et al.</i> , ^c Taiwan (1998) | Epidemiological cytogenetic study into the causes of intellectual disability | 34 | 34 | – | – | Cytogenetic analysis | Autism Diagnostic Interview: ADI and ADI-R (Le Couteur <i>et al.</i> , 1989) ^a | ICD-10 ^a DSM-IV | – | – | – |
| Steffenburg ^a <i>et al.</i> , ^c Sweden (1996) | Epidemiological study | 4 (75%) | 2 | – | 2 | The clinical diagnosis was confirmed by DNA analysis in two of the four children diagnosed with AS | Handicaps, Behaviors and Skills Schedules (HBS) (Wing, 1970) Childhood Autism Rating Scale (CARS) (Schopler <i>et al.</i> , 1988) (Swedish version) Autistic Behavior Checklist (ABC) (Krug <i>et al.</i> , 1980), a DSM-III-R checklist The Global Assessment of Functioning (GAF) (DSM-IV) (APA, 1987) The Autism Diagnostic Interview (ADI) (Le Couteur <i>et al.</i> , 1989) | ICD DSM-III-R-10 DSM-IV | 100% (4/4) | – | 2 |

ASD, autism spectrum disorders; AS, Angelman syndrome; UPD, uniparental disomy; DEL, deletion.

^aClarifying information obtained through author's correspondence.

^bPaper found through hand-search.

^cPaper found through electronic database search.

Table 3b Studies concerning ASD in AS – augmented data obtained through author's correspondence

| Author, country of study, year of publication | AS cases | | | ASD rate in AS | | | |
|---|------------------------------|-----------------------------|-----|----------------|-------|-----|-----|
| | Total cases studied (% male) | Genetically confirmed cases | | | Total | UPD | DEL |
| | | Total | UPD | DEL | | | |
| Hou ^a <i>et al.</i> , ^b Taiwan (1998) | 40 (38%) | 40 | 8 | 28 | 0 | 0 | 0 |

ASD, autism spectrum disorders; AS, Angelman syndrome; UPD, uniparental disomy; DEL, deletion.

^aAdditional, updated, as yet unpublished results obtained through author's correspondence.

^bPaper found through electronic database search.

Table 4 Rate of autism spectrum disorder in genetically confirmed UPD and DEL cases according to clinical diagnosis and genetic status

| Clinical diagnosis | UPD | DEL | Total |
|-----------------------|--------------------|--------------------|---------------------|
| Prader-Willi syndrome | 20/53 ^a | 18/97 ^a | 38/150 ^a |
| Angelman syndrome | 0/11 | 2/93 | 2/104 |

UPD, uniparental disomy; DEL, deletion.

^aRates do not include cases from the Dykens and Cassidy (1995) study (see p.11 in results for clarification).

ability to engage in appropriate social reciprocity and personal interactions' (Williams *et al.*, 2001, p. 61). It is also suspected that in some cases, childhood autism may be misdiagnosed as AS, especially during the age of 2–4 years. As AS children get older, however, the pervasive features of ASD serve to differentiate these children from those with AS in that the latter are usually sociable and have good social reciprocity (Williams *et al.*, 2001). The four AS children diagnosed with ASD were older than 4 years (10–16 years old) (Steffenburg *et al.*, 1996), thus complicating the issue and indicating that other factors such as sampling and ascertainment may need to be taken into consideration [see Thompson and Bolton, (2003) for a fuller discussion of this issue]. It may therefore be concluded that the rates estimated in this review from the pooled studies appear to be in keeping with the rates reported in population-based series, although as both conditions are rare, the confidence interval around these estimates is large.

The picture concerning AS is further complicated by a newly published study concerning autism in AS (Trillingsgaard and Østergaard, 2004). This study did not meet the inclusion criteria for the systematic review presented here, as the authors were not aware of the study and it had not been published at the time of data collection, inclusion, and synthesis. This recent, carefully conducted study found that 13 of 16 children with AS received an Autism Diagnostic Observation Schedule – Generic (ADOS-G) algorithm classification of ASD. This study based the ASD diagnoses solely on the ADOS-G scores. Furthermore, the mean mental age for the children with an autism diagnosis and AS was 9.5 months (SD = 2.4 months) and the validity of using the ADOS-G with children whose mental age is below 12 months old is

questionable, as the authors themselves point out. Therefore, this draws into question the appropriateness of using the ADOS-G as the sole diagnostic instrument for this particular group of children. The authors speculated that the impairments in AS may be better understood in terms of developmental delay, compared with autism where the impairments are considered to signify developmental deviance. They also concluded that the rate of ASD in AS in their study might have been overestimated because of the extremely low mental age of the children with AS. Their findings and those of Peters *et al.*, (2004) further underscore the uncertainties regarding the rate of autism and autistic symptomatology in AS. Both these studies suggest that the estimate derived from the studies summarized in the present systematic review is an underestimate and that perhaps reduced expression of maternally expressed genes may also constitute a risk factor for ASD (Peters *et al.*, 2004; Trillingsgaard and Østergaard, 2004). The issue is worthy of further investigation in order to determine whether perturbations in the level of expression of UBE3a (up and/or downregulation) may increase the risk for an ASD.

Not all studies had the PWS/AS status of their participants confirmed by genetic testing; indeed, one study relied on parental reports of genetic status (Dykens and Cassidy, 1995). Reliance upon parental information regarding genetic status may be problematic as it has been found that this may not always be a reliable method of deciding upon genetic subgroup (see Veltman *et al.*, 2004). Furthermore, molecular genetics is now able to identify different classes within each syndrome (e.g. UPD or DEL) that are linked with differences in phenotype associated with each syndrome. Therefore, this review examined rates in genetically verified cases and the clinically diagnosed samples.

Another consideration is the possibility that other studies concerning this topic were missed in this systematic review. In order to minimize this possibility, the present review adhered to standard systematic review procedures and employed both electronic-search and hand-search strategies. Although some authors advocate not making the effort to identify the 'gray literature' identified through hand-searching as not all of it may have undergone peer-review (Chalmers *et al.*, 1987), excluding

data from studies thus identified may lead to a loss in precision of the estimate of an effect size (Dickersin *et al.*, 1994).

Studies, however, have included individuals with PWS/AS in testing hypotheses relating to the cognitive deficits comprising autism, although these did not look at ASD specifically and as such were not included in the current review. For example, Tager-Flusberg *et al.* (1998) used a matched PWS contrast group to Williams syndrome (WS) and 'normal' cases in a study examining social cognition or more specifically the domain of understanding other people's minds, otherwise termed 'mentalizing'. Weaknesses in this domain have been shown to be associated with ASD (Baron-Cohen *et al.*, 1985; Baron-Cohen and Howlin, 1993). Interestingly, the finding showed that the PWS group performed significantly worse than the WS group and the 'normal' groups in this domain and indeed they performed about as poorly as participants with autism who were tested by Baron-Cohen *et al.* in 1997. This latter finding was, at least partially, explained by the difference in intellectual ability as the PWS group tested was intellectually disabled whereas the participants with autism tested by Baron-Cohen *et al.* were of normal intelligence (Tager-Flusberg *et al.*, 1998).

It is also necessary to consider the possibility of publication and reporting bias further, as it is quite possible that some studies examined the issue addressed here, but because no differences were observed, the findings have not been reported or published. Although this remains a possibility, this is deemed unlikely, as the importance and rationale for undertaking a study of ASD in PWS/AS has only recently become apparent and that most studies identified here did not focus on the prevalence of ASD in their sample. This is perhaps one of the most significant shortcomings in the extant literature. The fact that very few of the studies have focused on evaluating the rate of ASD in their sample, using standardized procedures, is a real limitation in the current literature. Taken together, the methodological limitations identified in the reported studies preclude any firm conclusions being drawn. Despite this, it is noteworthy and of interest that the pooled rate of ASD in the UPD PWS cases was significantly higher than the rate in other forms of 15q11–13 abnormality and that there was a similar significant tendency for the rate of ASD in UPD PWS cases to be higher than in the DEL PWS cases. Further indications that these findings may reflect a true difference is provided by the two studies that examined the frequency of autistic behaviors/social impairments in PWS, as both showed a higher rate in the UPD group (Dykens and Cassidy, 1995; Veltman *et al.*, 2004a). It should be noted that although Veltman *et al.* found that the total symptom score of the Autism Screening Questionnaire was significantly elevated for the UPD PWS cases compared with the DEL PWS cases, the

difference in rate of ASD was not statistically significant. Also, as discussed, the study reported by Tager-Flusberg *et al.* above is also in keeping with the findings reported here. It seems clear, therefore, that there is a case for investigating ASD and autistic-like behaviors further in PWS and, to a lesser extent, in AS. Studies in the future will need to investigate sufficiently large numbers of cases to ensure adequate power and they will have to employ state of the art diagnostic measures for ASD. It is also evident that there will have to be careful attention to the developmental course of the disorder as the current findings raise the possibility that autistic-like behaviors may be most prominent in early childhood. Of course, one should not forget that a number of other reasons exist for studying phenotypic manifestations of individuals with 15q11–13 abnormalities, quite apart from the desire to investigate the prevalence of autistic-like impairments and social dysfunction. The current evidence suggests interesting differences in the pattern of cognitive strengths and difficulties in subgroups and further clarification of these patterns may throw light on the nature of genetic influences on cognitive development. Also of great potential interest are the reports suggesting an association between genetic subtype and the development of psychosis in PWS, especially as some cases were reported to have ASD-like problems prior to the onset of the psychosis (e.g. Clarke, 1998; Clarke *et al.*, 1998; Verhoeven *et al.*, 1998; Boer *et al.*, 2002).

As such, this should be an encouragement to research groups to pursue these topics of enquiry in more detail.

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