Prevalence of Angelman Syndrome and Prader–Willi Syndrome in Estonian Children: Sister Syndromes Not Equally Represented

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In 2000–2004, we performed a focused search for individuals with Angelman syndrome (AS) and Prader–Willi syndrome (PWS) aiming to establish the prevalence data for the individuals born between 1984 and 2004 in Estonia. All persons with probable AS or PWS (n = 184) were studied using the DNA methylation test. Individuals with abnormal methylation were all further tested by chromosomal and FISH analysis, and if necessary for uniparental disomy and UBE3A gene mutation. Nineteen cases with abnormal methylation test result were identified. Seven of them had AS, including six (85.7%) due to 15q11-13 deletion and one paternal UPD15. Twelve subjects had PWS: 4 (33%) 15q11-13 deletions, 6 (50%) maternal UPD15, 1 unbalanced chromosome 14:15 translocation resulting in a chromosome 15pter-q13 deletion, and 1 Robertsonian 15q:15q translocation. The minimum livebirth prevalence in 1984–2004 for AS was 1:52,181 (95% CI 1:25,326–1:1,29,785) and for PWS 1:30,439 (95% CI 1:17,425–1:1,32,908). The livebirth prevalence of AS and PWS increased within this period, but the change was statistically significant only for PWS (P = 0.032), from expected 1:88,495 (95% CI 1:24,390–1:3,22,580) to expected 1:12,547 (95% CI 1:540–1:29,154). Six individuals with AS and 11 with PWS were alive on the prevalence day (January 1, 2005), indicating the point prevalence proportion of 1:56,112 (95% CI 1:25,780–1:1,52,899) and 1:30,606 (95% CI 1:17,105–1:61,311), respectively. Our results showing the birth prevalence of AS 1.7 times less than PWS challenge the opinion that both syndromes are equally represented, and are in line with the view that mutations in sperm and oocytes occur at different frequencies. © 2006 Wiley-Liss, Inc.

Key words: Angelman syndrome; Prader–Willi syndrome; population prevalence; livebirth prevalence


INTRODUCTION

Angelman syndrome (AS) and Prader–Willi syndrome (PWS) are two clinically distinct disorders that result from the loss of expression of imprinted genes in the maternal and paternal chromosome region 15q11-13, respectively. The most common cause for both syndromes is deletion 15q11-13 accounting for ~70% of AS and PWS cases, whereas maternal uniparental disomy (UPD) has been reported in ~25% of PWS patients and paternal UPD in 2–5% of AS patients. Defective imprinting causes ~5% of AS and PWS, chromosomal translocations <1% of AS and PWS, and for AS, 4–20% of diagnoses are suspected to arise from mutations in the UBE3A gene [Nicholls et al., 1998; Jiang et al., 1999]. However, there is a group of patients (10–15%) with a clinical diagnosis of AS who have no identifiable molecular
abnormality indicating either yet undetected lesions in 15q11-13 affecting function of the UBE3A gene, novel genetic lesions mapping elsewhere but affecting the expression of UBE3A, mutations in other genes with regulating effects [Jiang et al., 1999; Lossie et al., 2001], or a misdiagnosis of AS [Williams et al., 2001].

The main clinical criteria for AS are severe developmental delay, absent speech or profound speech impairment, movement or balance disorder, and behavioral uniqueness including outbursts of inappropriate laughter [Williams et al., 1995, 2006]. PWS is characterized by neonatal and infantile central hypotonia, feeding problems in infancy, developmental delay, excessive or rapid weight gain in early childhood, hypogonadism, characteristic minor facial anomalies, and food-related behavior problems [Holm et al., 1993].

Occurrence of both syndromes has been considered similar with an approximate frequency of 1 in 15,000 [Nicholls et al., 1998]. However, these frequencies have been deduced from a few studies of either PWS or AS only, and any direct comparison between these surveys are weakened by differences in study populations and methods (Table I). Additionally, there have been some population-based studies looking for causes of mental retardation with results leading to a different outcome—these syndromes are not equally prevalent [Hou et al., 1998; Stroemme and Hagberg, 2000]. Two recent publications from Western Australia summarized the long-term (50 years) population-based observations on AS and PWS with a birth prevalence of AS 1:40,000 and PWS 1:29,500 [Thomson et al., 2006a,b]. Unfortunately, more than 50% of AS and at least 25% of PWS persons who were taken into account did not have a genetic proof of diagnosis.

Here we report on an Estonian epidemiological study on AS and PWS aiming to establish the livebirth prevalence and population prevalence among individuals who were born during the years 1984–2004.

**METHODS**

### Patients and Samples

The population-based descriptive epidemiological study was performed involving the whole of Estonia.

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<table>
<thead>
<tr>
<th>Author</th>
<th>Estimated character</th>
<th>Study population</th>
<th>Period</th>
<th>Number of cases/ genetically confirmed diagnoses</th>
<th>Data</th>
</tr>
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<tbody>
<tr>
<td>AS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clayton-Smith and Pembrey [1992]</td>
<td>Incidence</td>
<td>Mainly referrals to genetic consultation, all ages</td>
<td></td>
<td>Not known</td>
<td>1:20,000</td>
</tr>
<tr>
<td>Clayton-Smith [1993]</td>
<td>Population prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen et al. [1995]</td>
<td>Prevalence rate</td>
<td>Neuropediatric clinic</td>
<td>1983–1991</td>
<td>5/5</td>
<td>1:12,000</td>
</tr>
<tr>
<td>Buckley et al. [1998]</td>
<td>Incidence</td>
<td>Institutionalized, severe developmental disability</td>
<td></td>
<td>11/3</td>
<td>1:10,000</td>
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<tr>
<td>Thomson et al. [2006a]</td>
<td>Birth prevalence</td>
<td>Disability Services Commission</td>
<td>1953–2003</td>
<td>34/14</td>
<td>1:20,000</td>
</tr>
<tr>
<td>AS and PWS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Jacobsen et al. [1998]</td>
<td>Population prevalence</td>
<td>Institutionalized, moderate to profound MRa</td>
<td></td>
<td>285/4</td>
<td>1:20,000</td>
</tr>
<tr>
<td>Vercesi et al. [1999]</td>
<td>% among MRa</td>
<td>Boys with MRa</td>
<td></td>
<td>256/0</td>
<td>0%</td>
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<tr>
<td>PWS</td>
<td></td>
<td></td>
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<tr>
<td>Burd et al. [1990]</td>
<td>Population prevalence</td>
<td>9–30 years old</td>
<td></td>
<td>17/-</td>
<td>1:16,062</td>
</tr>
<tr>
<td>Akefeldt et al. [1991]</td>
<td>Population prevalence</td>
<td>0–25 years old</td>
<td></td>
<td>11/5</td>
<td>1:15,060</td>
</tr>
<tr>
<td>Whittington et al. [2001]</td>
<td>Population prevalence</td>
<td>0–15 years old</td>
<td>One UK Health Region, all ages</td>
<td>96/68</td>
<td>1:21,478</td>
</tr>
<tr>
<td>Smith et al. [2003]</td>
<td>Birth incidence</td>
<td>Australian Pediatric Surveillance Unit Flanders, referrals to four genetic centers, all ages</td>
<td>1998–2000</td>
<td>30/30</td>
<td>1:29,000</td>
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<tr>
<td>Vogels et al. [2004]</td>
<td>Population prevalence</td>
<td></td>
<td></td>
<td>78/78</td>
<td>1:25,000</td>
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<tr>
<td></td>
<td>Birth prevalence</td>
<td></td>
<td>1953–2003</td>
<td>46/30</td>
<td>1:29,500</td>
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</table>

*MR, mental retardation.*
On January 1, 2005, the population of Estonia was 13,47,510 (6,20,600 males; 7,26,910 females) [Statistical Office of Estonia]. From 2000 to 2004, we conducted a focused search for individuals with AS and PWS among children and adolescents aged 1 day to 18 years. During the year before the study was started, information about the study and detailed descriptions of AS and PWS were provided in national pediatric meetings and in the continuous medical education courses at the Department of Pediatrics of the University of Tartu, Faculty of Medicine (the only School of Medicine in Estonia). Information letters with descriptions of the syndromes were sent to each of the 879 family physicians in Estonia with a request to send persons with a similar phenotype for evaluation. According to a medical practice guideline for Estonian family physicians, all children under 18 years of age with developmental problems should be referred for evaluation to one out of two tertiary children’s hospitals, in Tallinn for northern Estonia and in Tartu for southern Estonia. At the beginning of the study, introductory meetings were held in both children’s hospitals. The study was approved by the Ethics Committee on Human Research at the University of Tartu. Informed consent was obtained from the parents or legal guardians of the children, and none refused to participate in the study.

The study included only individuals with a genetically proven diagnosis of AS or PWS. Index cases were selected from the referred patients using the consensus diagnostic criteria for AS [Williams et al., 1995] and PWS [Holm et al., 1993]. However, considering that many manifestations of AS and PWS are non-specific and/or evolve over time, we used less stringent selection criteria in infants aged less than 1 year. All infants with psychomotor developmental delay, congenital hypotonia or dystonia, and seizure disorder of unknown cause were included. Furthermore, persons who had been either diagnosed or suspected to have AS or PWS in the past without completing the diagnostic procedure were invited for genetic re-evaluation, diagnostics, and counseling. In order to find undiagnosed individuals, during 2002, two of us (E.O.-S., K.O.) visited all long-term-care institutions and special educational facilities for disabled children in Estonia (28 sites with 1298 residents). In all selected persons, blood (2–5 ml) was taken for the DNA methylation test. Persons with a positive test result were further investigated using cytogenetic analysis and fluorescent in situ hybridization (FISH). FISH-negative persons were studied for UPD using polymorphic DNA markers. Individuals with a strong clinical evidence of AS, but a negative methylation test were investigated for mutations in the UBE3A gene. Annual numbers of live births were obtained from the Statistical Office of Estonia, with a final update on December 22, 2005 [Statistical Office of Estonia]. Children who were born in 2004 were followed-up to the end of 2005. On the prevalence day (January 1, 2005), the number of persons 0–20 years old was 3,36,669 (1,72,496 males and 1,64,173 females).

**Statistical Analysis**

We estimated the livebirth prevalence with the Generalized Linear Model Analysis using GENMOD procedure of the SAS system, Release 8.2 [SAS Institute, Inc., 1999]. Distribution of the prevalence cases was assumed to be binomial, and the default logit link function was used. The only variable factor in the model was the observation year. The mean (expected) prevalence rate for a given year and a corresponding 95% confidence interval were predicted with the OUTPUT statement of the GENMOD procedure.

**Methylation-Specific PCR**

DNA was extracted from whole blood with a genomic DNA purification kit (Genta Systems, Minneapolis, MN) followed by sodium bisulfite treatment of the DNA [Kubota et al., 1997]. The DNA was purified using the Wizard® DNA clean-up system (Promega, Madison, WI). Methylation-specific PCR of the SNRPN exon 1 region was carried out with primers SNRPN-common 5'-CTC CAA AAC AAA AAA CT TAA AAC CCA AAT TCC-3', SNRP Mat 5'-TAT TGC GGT AAA TAA GTA CGT TTG CGC GTT C-3', and SNRPN-Pat 5'-GTG AGT TTG GTG TAG AGT GGA GTG GTT GGT G-3' [Zeschchnigk et al., 1997]. PCR products (313 bp for maternal product, 221 bp for paternal product) were analyzed using electrophoresis, 2.5% agarose gel, and TBE buffer.

**Cytogenetic Analysis and FISH**

Chromosomes were analyzed using peripheral blood and standard GTG banding (G bands by trypsin using Giemsa). A translocation of chromosomes 14 and 15 was studied using FISH and probes CP5032 (D14Z1/D22Z1, chromosome 14cen) (Oncor, Gaithersburg, MD), CEP 15 SG (D15Z1 classical satellite, chromosome 15p11.2), CEP 15 SO (D15Z alphoid DNA, chromosome 15cen), LSI SNRPN (SNRPN, chromosome 15q11.2-q12), and LSI PML (PML, chromosome 15q22) (Vysis, Inc., Downers Grove, IL), BAC RP11-463i22 (spanning from 25,725,185 to 25,892,792 Mb on chromosome 15q13.1, BAC ends A2515863 and AQ634845), and YAC 895h10 (D15S207, chromosome 15q26). All other methylation test positive patients were studied using a DNA probe for the Prader-Willi/ Angelman region (D15S65, SNRPN/imprinting center; chromosome 15q11-13) with a 15q telomere-specific control probe (154P1) (CytoCell Ltd., Oxfordshire, UK). Usually, 15 metaphases were analyzed per patient and test.
To trace the transmission of chromosome 15 from each parent to the child, the following set of microsatellites from outside of the PWS/AS critical region was used: D15S123, D15S153, D15S125, D15S131, D15S100, D15S211. PCR was performed using fluorescently labeled oligonucleotides and electrophoresis performed in ABI 310 Genetic Sequencer (Applied Biosystems, Foster City, CA).

**UBE3A Mutation Analysis**

Ten protein encoding exons of the *UBE3A* gene (exons 7–16) were screened for sequence alterations by using PCR and conformation sensitive gel electrophoresis (CSGE) and direct sequencing. Primers for each exon were as described by Rapakko et al. [2004]. CSGE was performed according to Körkkö et al. [1998]. All the band shifts detected by CSGE were further characterized by sequencing with LI-COR IR4200 DNA Analysis System (LI-COR, Inc., Lincoln, NE).

**RESULTS**

The study included a total of 188 persons (95 with suspected AS, 93 with suspected PWS) (Table II). Four persons (2 with AS, 2 with PWS) had a genetically confirmed diagnosis prior to this study, and 184 persons were selected and studied using the methylation-specific PCR test within the years 2000–2004. Test results were positive in 15 selected persons and therefore, the study comprised a total of 19 individuals with a DNA proven diagnosis. Seven persons had AS and six of them (85.7%; two females, four males) showed a deletion of chromosome 15q11-13. The remaining person, a female, demonstrated paternal UPD (paternal age at birth was 30 years). Twelve persons had PWS and of these, 4 (35%; 3 females, a male) had a 15q11-13 deletion and 6 (50%; 4 females, 2 males) had maternal UPD. Three mothers of six having a PWS child with UPD were older than 35 years (the rest were 24, 32, and 33 years old). Two persons with PWS had different chromosome rearrangements. A boy with positive methylation test showed a Robertsonian translocation of chromosomes 15q;15q, but he emigrated and materials for FISH and UPD studies were not available. A girl had an unbalanced translocation of chromosomes 14 and 15 resulting in a deletion of chromosome 15p13-q13. Using FISH, the deletion included the PWS critical region and BAC clone RP11-463i22, karyotype 45,XX,der(14)t(14;15)(p11; q13).ish der(14)t(14;15)(D14Z1/D22Z1+), D15Z1−, SNRPN−,bac463i22/AQ634845−,PML+, yac895h10+). Clone RP11-463i22 corresponds to the segment from 25,725 to 25,892 Mb on chromosome 15 [UCSC Genome Browser, May 2004 assembly]. The distal end of the typical 15q11-13 deletions in the PWS and AS is defined by BAC RP11-48j4 [http://www.sanger.ac.uk/PostGenomics/decipher], which spans from 24,346 to 24,490 Mb on chromosome 15 [UCSC Genome Browser]. Hence, this girl had a deletion at least 1.4 Mb larger than typical 15q11-13 deletions. None of the AS and PWS individuals in this study was conceived following assisted reproduction technologies.

*UBE3A* mutation screening was performed in six individuals with a normal methylation test result who were selected based on a strong clinical suspicion of AS [Moncla et al., 1999]. One person showed an aberrant fragment by CSGE in a large exon 9 of *UBE3A* gene and by sequencing, a missense mutation of codon 243 (at1315C>A, Asn243Lys) was detected. However, the father of the patient had the same sequence variation, supporting a phenotypically silent variant (polymorphism).

From 1984 to 2004, the annual number of births in Estonia decreased from 24,234 (peak in 1987–1988 with 25,086 and 25,060 births, respectively) to 13,992 newborns [Statistical Office of Estonia]. A total of 3,65,266 live births was recorded, indicating a minimum livebirth prevalence of 1:52,181 (95% CI 1:25,326–1:29,785) for AS and 1:30,439 (95% CI 1:17,425–1:58,908) for PWS. On the prevalence day, January 1, 2005, the total number of persons aged 20 years and less was 3,36,669. Among AS and PWS persons, a girl with PWS and a deletion [Oiglane et al., 2002] and a girl with AS and the deletion died before the prevalence day. Thus, among children and adolescents in Estonia, the prevalence of AS (six prevalent cases) was 1:56,112 (95% CI 1:25,780–1:52,899) and the prevalence of PWS (11 prevalent cases) was 1:30,606 (95% CI 1:17,105–1:61,311).

Statistical analysis showed an increase in the livebirth prevalence of AS during the years 1984–2004 from 0.88 cases per 1,00,000 livebirths or

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**TABLE II. Angelman Syndrome and Prader–Willi Syndrome:**

<table>
<thead>
<tr>
<th></th>
<th>AS</th>
<th>PWS</th>
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<tbody>
<tr>
<td>No. of index cases studied by methylation</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>No. of methylation specific PCR from 2000 to 2004</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>No. of patients diagnosed 1999 and earlier</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Genetically confirmed patients</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>15q11-13 deletion</td>
<td>6</td>
<td>5†</td>
</tr>
<tr>
<td>Chromosomal translocation</td>
<td>2α</td>
<td></td>
</tr>
<tr>
<td>UPD15</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>UBE3A mutation</td>
<td>1α</td>
<td></td>
</tr>
<tr>
<td>Birth prevalence</td>
<td>1:52,181</td>
<td>1:30,439</td>
</tr>
<tr>
<td>Population prevalence</td>
<td>1:56,112</td>
<td>1:30,606</td>
</tr>
</tbody>
</table>

*Including an unbalanced 14;15 translocation resulting in deletion of the PWACR.
†Including the unbalanced 14;15 translocation and a Robertsonian translocation 15q;15q.
‡Familial polymorphism, most likely not the causal mutation.
1:1,13,636 (95% CI 1:23,923–1:5,26,316) to 4.23 cases or 1:23,640 (95% CI 1:6,658–1:84,034). However, this trend was not statistically significant (\(P = 0.2\)) (Fig. 1). For PWS, we noticed a more substantial, statistically significant increase (\(P = 0.032\)) in the livebirth prevalence, from 1.13 cases per 100,000 livebirths or 1:88,495 (95% CI 1:24,390–1:3,20,580) to 7.97 cases or 1:12,574 (95% CI 1:540–1:29,154) (Fig. 2).

**DISCUSSION**

The epidemiology of rare genetic syndromes, such as AS and PWS, is not an easy target for physicians/geneticists, especially if the syndrome(s) is not clinically well defined and/or the genetic cause is not completely clarified. To the best of our knowledge, this is the first epidemiological study to estimate the birth prevalence and the population...
prevalence of the genetically proven AS and PWS in the same population at the same time. We retrospectively collected information about probable individuals with AS and PWS, and actively looked for new cases. The birth prevalence and population prevalence data presented by us for AS and PWS within 1984–2004 are somewhat lower than those previously reported (Table I). Moreover, both syndromes showed an increase in birth prevalence during these 20 years, and for PWS, this increase was statistically significant. Interestingly, the livebirth prevalence of AS was found to be 1.7 times less than that of PWS, challenging the opinion that both syndromes are equally represented.

We are not aware of any comparable epidemiological survey for AS. The first population-based data were provided by Clayton-Smith [1993] who estimated the minimum population prevalence in the UK as 1:62,000 considering clinically and genetically confirmed AS individuals mainly among referrals to genetic consultation. Other previous studies on AS ascertained patients based on their disabilities (mental retardation, epilepsy) [Kyllerman, 1995; Jacobsen et al., 1998; Vercesi et al., 1999], used a shorter study period [Kyllerman, 1995; Petersen et al., 1995], and/or included ≥50% persons without genetically confirmed diagnosis [Kyllerman, 1995; Buckley et al., 1998; Thomson et al., 2006a]. Our data for AS, a 1:52,181 prevalence in liveborns and a 1:56,112 population prevalence in persons under 20 years of age, are more conservative and based on a relatively large and well-defined set of data, and may be the most reliable. However, the expected birth prevalence at the end of this study period was 1:23,640 (2 times higher, $P = 0.2$). This could possibly be explained by either a true incidence increase of the syndrome, improved diagnostic possibilities, or a focused search for the syndrome.

Regarding the PWS, there have been two previous DNA methylation test-based studies providing similar data on the incidence at birth, 1:25,000 from Australia [Smith et al., 2003] and 1:26,676 from Flanders, Belgium [Vogels et al., 2004]. In this 21-year-study (1984–2004), our data indicate a mean livebirth prevalence of 1:30,439, and these differences are not statistically significant. However, we observed a higher prevalence (1:12,547, 3 times higher) at the end of the study period. This difference was statistically significant ($P = 0.032$). As a possible explanation, the early testing and improvement in neonatal care could have resulted in an increased diagnosis of PWS. The age of women giving a child birth has increased over study period from 25.9 in 1984 to 27.9 years in 2004; however, the proportion of those older than 30 years of age has remained the same. Therefore, a change in maternal age did not seem to be responsible for increased occurrence of PWS.

We included in our AS group only persons with a confirmed genetic diagnosis, considering the variety of mimicking conditions [Williams et al., 2001] and the debate over yet undetermined mechanisms causing AS in 10–15% of “clinically definite” cases [Rougeulle et al., 1998; Herzing et al., 2001; Lossie et al., 2001; Landers et al., 2005]. A phenotypic overlap has been reported between AS and MECP2 mutations, and MECP2 mutation screening has been proposed for AS patients without a demonstrable genetic lesion of chromosome 15q11-13 [Watson et al., 2001]. We collaborated in a study ascertaining the incidence of MECP2 mutations among the patients with an Angelman-like phenotype but no detectable lesion of chromosome 15. However, none of these persons, five boys and four girls, showed a relevant MECP2 mutation [Ylisaukko-Oja et al., 2005].

This study has considerably improved the awareness about AS and PWS in Estonia, and the thorough clinical investigations showed additional health problems in some 25% of these children (Table III). Since 2000, all children with PWS have been diagnosed in infancy, the last four patients in their first week of life [Oiglane-Shlik et al., 2006]. Early diagnosis of AS is more demanding due to the lack of seminal clinical signs and therefore, AS patients were diagnosed later (mean age at diagnosis 6.1 years) than PWS patients (mean age 4.3 years).

Our findings contradict the widespread opinion that AS and PWS are equally frequent. The birth prevalence and population prevalence of AS was lower than that of PWS by a factor of 1.7 and 1.8, respectively. We observed some periodic fluctuations in birthrates of both syndromes. There were several years with frequent or infrequent AS and PWS cases that could easily influence the prevalence data over short periods of time. We assume that we missed no AS and PWS patients during the last 5-year period (2000–2004). But there is a possibility that we lost

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<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Genetic diagnosis</th>
<th>Supplementary health problem</th>
</tr>
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<tbody>
<tr>
<td>AS</td>
<td>del(15)(q11q13)</td>
<td>Reye syndrome and sudden death at age 3.5 years</td>
</tr>
<tr>
<td>AS</td>
<td>del(15)(q11q13)</td>
<td>Unusual limb malformations; Oiglane-Shlik et al. [2005]</td>
</tr>
<tr>
<td>PWS</td>
<td>del(15)(q11q13)</td>
<td>Sudden death at age 3.5 years; Oiglane et al. [2002]</td>
</tr>
<tr>
<td>PWS</td>
<td>del(15)(q11q13)</td>
<td>X-linked ichthyosis (steroid sulfatase deficiency)</td>
</tr>
<tr>
<td>PWS</td>
<td>t(14;15) and del(15)(p13q13)</td>
<td>Severe PWS phenotype</td>
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</table>
patients before the study period due to death. Different medical complications may develop in individuals with AS or PWS [Clayton-Smith, 2001; Butler et al., 2002; Öiglane-Shlik et al., 2005], and during this study, a 3.5-year-old girl with AS died of Reye syndrome (Table III). However, early death appears to be more common in PWS [Öiglane et al., 2002; Schrander-Stumpel et al., 2004]. Furthermore, even with added 10–15% “clinically definite,” but not genetically confirmed cases of AS, the livebirth prevalence of AS remains 1.5 times lower than of PWS.

We identified no cases of \textit{UBE3A} gene mutations or imprinting mutations. These mutation types are rare. Imprinting mutations are primarily detected by the DNA methylation test and we probably missed none of these patients [Saitoh et al., 1997; Gillessen-Kaesbach et al., 1999]. On the other hand, the rate of UPD among the PWS individuals was surprisingly high, 50%, and three (50%) of the six mothers were older than 35 years. Another difference with previous findings is the relatively large number of girls (68%), whereas previously a predominance (68%) of males was reported among the UPD patients [Mitchell et al., 1996]. Furthermore, we identified two new cases of PWS caused by chromosomal translocations, a rare cause of PWS (<1%). These differences might be coincidental, as our group of patients was small, but taken together, they provide some additional argument that we most likely missed very few, if any, AS or PWS cases.

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REFERENCES


