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Eating behavior, prenatal and postnatal growth in Angelman syndrome

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ABSTRACT

The objectives of the present study were to investigate eating behavior and growth parameters in Angelman syndrome. We included 39 patients with Angelman syndrome. Twelve cases had a larger Class I deletion, eighteen had a smaller Class II deletion, whereas paternal uniparental disomy (pUPD) or a verified UBE3A mutation were present in five and four cases, respectively. Eating behavior was assessed by a questionnaire. Anthropometric measures were obtained from medical records and compared to Danish reference data. Children with pUPD had significantly larger birth weight and birth length than children carrying a deletion or a UBE3A mutation. We found no difference in birth weight or length in children with Class I or Class II deletions. When maternal birth weight and/or birth weight of siblings were taken into consideration, children with Class I deletion had a lower weight at birth than expected, and the weight continued to be reduced during the investigated initial five years of life. In contrast, children with pUPD showed hyperphagic behavior and their weight increased significantly after the age of two years. Accordingly, their body mass index was significantly increased as compared to children with a deletion. At birth, one child showed microcephaly. At five years of age, microcephaly was observed in half of the deletion cases, but in none of the cases with a UBE3A mutation or pUPD. The apparently normal cranial growth in the UBE3A and pUPD patients should however be regarded as the result of a generally increased growth. Eating behavior, pre- and postnatal growth in children with Angelman syndrome depends on genotype.

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1. Introduction

Angelman syndrome (AS) is a neurogenetic disorder caused by loss of expression of the maternally imprinted gene *UBE3A* which codes for the protein ligase E3A. *UBE3A* is bi-allelic expressed in all tissues except in the brain (Abu-Amero, Monk, Apostolidou, Stanier, & Moore, 1991).

Clinical characteristics features of AS include severe intellectual disability and developmental delay, lack of speech, a happy disposition, ataxia, and 80–90% are reported to have epileptic seizures (Buckley, Dinno, & Weber, 1998; Buntinx et al.,

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1995; Conant, Thibert, & Thiele, 2009; Lossie et al., 2001; Low & Chen, 2010; Oiglane-Shlik et al., 2006; Thibert et al., 2009; Tan et al., 2011).

Four known molecular mechanisms lead to deficiency of maternal *UBE3A* expression and AS: deletion of the AS critical region on the maternal chromosome 15q11.2-q13 (70–75% of cases), paternal uniparental disomy (pUPD) (5–10%), imprinting defects (2–5%), and mutations in or deletion of the maternal copy of *UBE3A* (10%) (Dagli, Buiting, & Williams, 2012). Among individuals with a 15q11.2-q13 deletion, approximately one-third carry a 5.9 Mb (Class I) deletion, whereas the remainder have a smaller 5.0-Mb (Class II) deletion; these deletions differ only in the location of the centromeric breakpoints of the deletion (Mertz et al., 2013; Tan et al., 2011).

Prader–Willi syndrome (PWS), a clinically distinct neurodevelopmental disorder that also maps to 15q11.2-q13, but different from AS, is due to the absence of normally active paternally expressed genes within 15q11.2-q13 (Buiting et al., 1998; Oiglane-Shlik et al., 2006). The clinical features of PWS include neonatal hypotonia, poor feeding and failure to thrive in infancy, followed by weight gain in early childhood that leads to severe obesity in later childhood, if the child's diet is not restricted. Mental retardation, behavioral problems, and neuroendocrine abnormalities are other characteristic findings in PWS (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007; Oiglane-Shlik et al., 2006). One striking feature of PWS is hyperphagia during childhood, which is due to an increased pre-occupation with food and failure of the normal satiety response (Brambilla et al., 2011; McAllister, Whittington, Holland, 2011). Eating behavior is therefore widely studied in PWS (Brambilla et al., 2011; Dykens et al., 2007). In contrast, very few data are available on eating behavior and growth in AS (Moncla et al., 1999; Smith, Marks, Haan, Dixon, & Trent, 1997; Tan et al., 2011).

The aim of the present study was to examine eating behavior and its relation to genotype and growth data. In addition, we wanted to investigate the relationship between genotype and anthropometric parameters at birth, and to examine weight and cranial increment relative to genotype.

2. Methods

2.1. Patients and samples

Children born in Denmark between 1991 and 2009 with genetically verified AS were identified through the Danish National Patient Registry (NPR) and the Danish Cytogenetic Central Registry (DCCR). This identification was supplemented by a personal contact with all pediatric and clinical genetic departments and with the Patient Organization of Angelman Syndrome in Denmark. NPR contains administrative and clinical data from all hospitalizations and out-patient clinics in Denmark. As reporting of data to the NPR is mandatory for all Danish hospitals and is further encouraged by the government funding system, data in the registry are known to be of very high validity (Andersen, Madsen, Jørgensen, Mellemkjaer, & Olsen, 1999). The recorded discharge diagnoses are in accordance with the 10th revision of the International Classification of Diseases (ICD-10) from the World Health Organization (WHO). The DCCR contains data from every prenatal genetic test and every postnatal karyotype performed in Denmark since 1960. It also contains national postnatal genetic data on selected diseases such as 22q11.2 deletion, Prader–Willi and Angelman syndromes. Data reporting is self-imposed by all clinical genetic departments that perform these genetic tests, and the registry is administered by representatives from these departments.

In total, we identified 51 patients with genetically verified AS born in Denmark in 1991–2009 (Mertz et al., 2013). The deadline for identification was January 1, 2012.

Anthropometric data were obtained from the hospital medical records, records generated by the home visitor, and records from the general practitioner, representing a continuously maintained history of treatments and measurements, thus eliminating recall bias. The National Ethic Committee (M-20090028) and the Danish Data Protection Agency (2009-41-3133) approved the study. The legal guardian of each participant provided verbal and written informed consent.

2.2. Genetic analysis

Patients previously diagnosed with a 15q11.2-q13 deletion were further investigated by 1000 kb comparative genomic hybridization (CGH). DNA was extracted from peripheral blood with an automated Chemagic Magnetic Separation Module (PerkinElmer, Waltham, MA, USA). DNA was purified prior to array CGH analysis with the DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA, USA). Deletion breakpoints were determined by microarray-based CGH with the SurePrint G3 Human CGH microarray 1 M (Agilent Technologies, Santa Clara, CA, USA). Patient and reference genomic DNA samples (1500 ng) were labeled with Cy5 (reference) or Cy3 (patient) with the Genomic DNA ULS labeling kit (Agilent Technologies) and purified as per the manufacturer's protocol. Labeled sample and reference DNA were pooled, and 50 μl of human COT-1 DNA (1 mg/ml), 10× blocking agent, and 2× hybridization buffer were added. Hybridization was performed for 40 h at 65 °C. Scanning and image acquisitions were carried out with an Agilent microarray scanner, and microarray image files were quantified with Agilent's Feature Extraction software version 10.7. Data analysis was performed with Genomic Workbench version 6.5 (Agilent Technologies).

Copy number was determined with the adm-2 algorithm. Profile deviations that consisted of six or more neighboring oligonucleotides were considered genomic aberrations, which yielded a resolution of approximately 12 kb. Deletion breakpoints were based on the position of the first and last oligonucleotide probes within the region of the deletion that

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