Abstract

Prader-Willi syndrome (PWS) is characterised by obesity, short stature, small hands and feet, neonatal hypotonia with difficulty in feeding at birth, hypogonadism and eye problems. At about two years of age the feeding difficulties with poor suck are gradually replaced by hyperphagia and obsession with food, leading to the obesity. In addition to developmental delay which is manifested by short stature, small hands and feet, growth hormone deficiency and hypogenitalism/hypogonadism, there are also behavioural characteristics including learning disabilities, temper tantrums, aggression, repetitive speech, obsessive compulsive behaviour, sleep disorder and skin picking (Cassidy and Driscoll, 2009). This disparate collection of symptoms led Holm et al (1993) to define the major and minor characteristics which allowed a clinical diagnosis of this the most common genetic form of obesity. Consensus diagnostic criteria were defined and weighted scores in which the major criteria were awarded one point and the minor criteria half a point calculated. A score of 8 or more is clinically diagnostic for PWS. The majority of people with PWS have a paternally derived deletion of approximately 5-7Mb in 15q11-q13, others have maternal disomy of chromosome 15 (UPD15mat) and a minority have a defect of the imprinting centre located in exon 1 of the SNRPN gene which leads to a maternal imprint on the paternally derived chromosome. Any of these abnormalities will result in loss of the paternal contribution to the Prader- Willi syndrome critical region (PWSCR), demonstrated by loss of a paternally derived unmethylated band at the imprinting centre and a lack of expression of the SNRPN gene. Although these do not differentiate between the different genetic types of PWS they are diagnostic for the syndrome (Cassidy and Driscoll, 2009; Ramsden et al, 2010; Zeschnigk et al, 1997). Within 15q11-q13 the complex imprinted SNURF/SNRPN gene hosts several untranslated snoRNA genes located within intronic sequences. The finding of a microdeletion involving SNORD116 in a boy with PWS led to the identification of this snoRNA as the candidate gene for the syndrome (Sahoo et al, 2008). In the course of a large study of PWS in the UK (Whittington et al, 2001; Soni et al, 2007) three people were identified who fulfilled the criteria for a clinical diagnosis of the syndrome but not the genetic laboratory diagnostic criteria. The Affymetrix Cytogenetics Whole-Genome 2.7M array while providing high resolution whole genome coverage reliably detects changes in copy number. Deletions and/or duplications present in all three participants if involved in annotated genes could potentially contribute to the Prader-Willi-like phenotype. Candidate genes can subsequently be evaluated to estimate their transcription levels and compared with those shown by people with PWS and with unaffected individuals.