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Prader-Willi syndrome and atypical submicroscopic 15q11-q13 deletions with or without imprinting defects

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Abstract

We report a 20 year follow up on a Caucasian female, now 26 years of age, with Prader-Willi syndrome (PWS) harboring an atypical 15q11-q13 submicroscopic deletion of 100–200 kb in size first detected in 1996 involving the imprinting center, SNRPN gene and surrounding region. PWS is a rare complex disorder caused by the loss of paternally expressed genes in the 15q11-q13 region. With high resolution chromosomal microarray and methylation – specific MLPA analysis, we updated the genetic findings on our patient and found a 209,819bp deletion including the *SNURF-SNRPN* gene complex which includes the imprinting center and the *SNORD116* region. We compared with four other similarly reported individuals in the literature with atypical submicroscopic deletions within this region but without imprinting center involvement to better characterize the specific genetic lesions causing PWS clinical findings. Clinically, our patient met the diagnostic criteria of PWS including infantile hypotonia, a poor suck with feeding difficulties, global developmental delays and later food foraging, childhood obesity, small hands and skin picking. Small atypical deletions of comparable sizes were seen in the 15q11-q13 region in all five cases and similar behavioral/physical characteristics were found despite an imprinting defect in our patient. These results further support an overlapping critical deletion region involving the non-coding snoRNA *SNORD116* in common in the five individuals playing a key role in contributing to the PWS phenotype.

Keywords

15q11-q13 region; Atypical microdeletion; *SNORD116*; *SNURF-SNRPN*; Imprinting center defect; Prader-Willi syndrome

1. Introduction

Major characteristics of Prader-Willi syndrome (PWS) include infantile hypotonia, a poor suck with feeding problems and failure to thrive, hypogonadism/hypogenitalism and reduced

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Conflict of interest

The authors declare no conflict of interest.

growth hormone production causing short stature with small hands and feet, delayed development and minor facial abnormalities. Later in early childhood, food seeking and hyperphagia occurs leading to obesity which can be life-threatening, if not controlled along with compulsive behavior, self-injury and aggression with mild learning disabilities (Butler, 1990, 2011; Butler et al., 2006; Cassidy et al., 2012; Angulo et al., 2015; Butler et al., 2015). PWS has a frequency of about 1 in 10,000 to 20,000 livebirths (Butler, 1990) and affects an estimated 350,000–400,000 people worldwide (Butler and Thompson, 2000). PWS occurs by the loss of paternally expressed genes in the proximal long arm of chromosome 15 involving the 15q11-q13 region with approximately one dozen genes or transcripts playing a role in the pathogenesis of this disorder. These genes include *MRKN3, MAGEL2, NDN, NIPA1, SNURF-SNRPN* and noncoding RNAs located downstream in clusters as paternally expressed C/D box-containing snoRNAs representing an important subset with diverse function (e.g., Bittel and Butler, 2005; Cassidy et al., 2012; Butler et al., 2015).

PWS is a complex genetic disorder recognized as the first example of errors in parent-specific gene activation caused by genomic imprinting in humans. The sister syndrome to PWS, Angelman syndrome, results from a maternal deletion of the same 15q11-q13 region and with a different clinical presentation. About 70% of patients with PWS have an interstitial deletion of the 15q11-q13 region, about 30% have maternal disomy of chromosome 15 and the remaining have biparental inheritance of chromosome 15 with normal appearing 15s due to imprinting center defects or other rearrangements of the 15q11-q13 region (e.g., Butler et al., 2006; Cassidy et al., 2012; Angulo et al., 2015). The deletion class is subdivided into the typical Type I or Type II deletion based on their proximal 15q11-q13 breakpoints at BP1 or BP2 with the larger Type I deletion involving BP1 and the distally located BP3 with Type II deletions are due to breaks at BP2 and BP3 (e.g., Bittel and Butler, 2005; Cassidy et al., 2012; Angulo et al., 2015). Atypical deletions in PWS are either smaller or larger and rarer, occurring in about 5% of cases (Kim et al., 2012).

During a molecular and cytogenetic study of a large cohort of subjects with PWS in 1996, Butler and others reported a 5 year old female with a PWS phenotype and a small 100–200 kb submicroscopic deletion including the DNA methylation pattern seen in this imprinting disorder (Butler et al., 1996). This patient was the first report of its kind, and since then other additional individuals with features of PWS have been described with rare atypical sub-microscopic deletions of the SNURF-SNRPN gene complex and/or surrounding region including non-coding snoRNAs (*SNORD64*, *SNORD107, SNORD108, SNORD109, SNORD116* and *SNORD115*) (Sahoo et al., 2008; de Smith et al., 2009; Duker et al., 2010; Bieth et al., 2015) but not of the imprinting center. The deletions of the four additional patients described in the literature ranged from 118 to 236 kilobases in size.

We report an update of the clinical, molecular and cytogenetic findings of our patient originally reported in 1996 and detail a 20 year follow up study. Utilizing information compiled over the past two decades and comparing findings with other reports with rare atypical small deletions in the 15q11-q13 region without imprinting defects, we lend evidence to better characterize and understand the importance of this overlapping region in the development of PWS and features seen in those with and without the imprinting center defect.

2. Clinical report

Our patient with PWS was first reported in 1996 by Butler and others due to an atypical submicroscopic deletion of the chromosome 15q11-q13 region, novel at that time and with an altered DNA methylation pattern seen in PWS (Butler et al., 1996). Advances in genomic technology have led to refinement of the size and location of the deletion as well as genes/transcripts within the region. She weighed 3,334 g (30th centile) and was 54.6 cm (90th centile) in length at birth. A clinical genetic evaluation at 3 days of age showed severe hypotonia, a poor suck reflex, a weak cry and micrognathia. A muscle biopsy was not diagnostic and EEG, EMG, auditory BAER and head MRI studies were normal. Ophthalmology and hearing evaluations were normal. Rapid weight gain was first observed at 2½ years of age but without observed hyperphagia. By 6 years of age, her appetite increased and her height was 104.2 cm (10th centile) and weight was 23.3 kg (>95th centile). Follow up studies showed staring spells at two years of age, and recurred at 13 years of age. These spells lasted for a few seconds, occurred about 10 times per month, and were more frequent when tired or related to laughter. She was prescribed Lamictal at 13 years of age which has decreased the number of events.

She graduated from high school with a regular diploma and attended a day program for special need adults. She lived at home with close supervision for dietary control. In 2008 at 20 years of age, she had a height of 152.4 cm (4th centile), a weight of 125 kg (97th centile) and a BMI of 52. She had morbid obesity and diabetes mellitus managed with daily insulin injections. At the age of 22 years, she was administered the Kaufman Brief Intelligence Test (KBIT 2nd edition) which revealed IQ scores of 73 for verbal which placed her at the 4th centile (below average level) and 90 for nonverbal or at the 25th centile (average level). The Autism Diagnostic Observation Schedule (ADOS) was administered at 22 years of age as a structured tool to assess communication, social interaction and creativity designed for individuals suspected of having autism or other pervasive development disorders. The test results were not consistent for the diagnosis of autism. Visual and motor deficits were noted with the Visual-Motor Integration (VMI) test and resulted in a standard score of 74 placing her at the 4th centile. Child-Behavior Checklist (CBLC) scores to assess specific emotional and behavioral problems such as anxiety, depression, attention problems, social problems, thought problems, and aggression at 22 years of age showed no significant clinical problems.

She had a 30 kg weight gain from 20 to 21 years of age which was thought to be due to decreased physical activity. At 23 years of age, her height and weight were unchanged with a BMI of 52 (see Fig. 1). There was no history of alcohol consumption or smoking. She was allergic to Codeine and Diphenhydramine HCL and continued insulin use for diabetes treatment. A colonoscopy was performed due to rectal bleeding and two polyps were found with the largest measuring 6 mm in size, but no dysplasia or malignant cells were found. She had a history of microcytic iron deficiency anemia and was prescribed iron.

Through stricter dietary control and weight management at 25 years of age, her weight dropped to 96 kg (97th centile) and her BMI was 40. She continued to have occasional seizure activity, diabetes, hyperlipidemia, hypertension, vitamin D deficiency, dyslipidemia and thyroid disease. She was prescribed metformin for diabetes, Lamictal for partial

seizures, Lovastatin for high cholesterol levels, ferrous sulfate for low blood iron levels, Levothyroxine for hypothyroidism and hydrochlorothiazide for high blood pressure. She had gall bladder removal and tonsillectomy performed at 18 years of age. At her last follow up evaluation, at 26 years of age, her height was 152.4 cm (10th centile) and weight was 106 kg (>90th centile) with a BMI of 46. She has continued with the listed medication as previously described and in regular consultation with a dietitian for weight and dietary management. She lives at home with her parents. She is considered to have higher function than the typical adult patient with PWS and successfully attends a day program for adults with special needs from Monday through Friday from 9am to 2pm. She enjoys her time during the day and is well received by staff and others working at the program.

2.1. Cytogenetic and molecular findings

At 5 years of age, she was reported with a submicroscopic deletion in the center area of the 15q11-q13 region at approximately 100–200 kb in size identified by using fluorescence in situ hybridization (FISH), Southern hybridization and microsatellite DNA studies with probes located within this region (Butler et al., 1996). FISH probes for *SNRPN, D15S10, D15S11* and *GABRB3* revealed a submicroscopic deletion of SNRPN only. Quantitative hybridization using radio-labeled PCR products and standard PCR amplification of 18 short tandem repeats from the 15q11-q13 region also supported a submicroscopic deletion in this region. The deletion observed was paternal in origin (Butler et al., 1996).

A high-resolution microarray analysis was performed to update the genetic status using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) and chromosome 15 methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) kit containing 32 sequence specific probes along the length of the 15q11.2-q13 region (MRC Holland, Amsterdam, The Netherlands) (Bittel et al., 2007; Henkhaus et al., 2012). The microarray identified a loss within the chromosome 15q11-q13 region with 106 probes from the cytoband 15q11.2 located at genomic coordinates 25,165,212–25,375,031bp (hg19) with a total loss of 209,819 base pairs including the imprinting center and non-coding RNAs [*SNRPN* (protein coding), *SNURF* (protein coding), *SNORD107* (snoRNA), *PAR-SN* (ncRNA), *PAR5* (ncRNA), *SNORD64* (snoRNA), and *SNORD116* (snoRNA)]. The imprinting center overlaps with the complex *SNURF-SNRPN* gene complex and *SNORD116* which is distal to *SNURF-SNRPN*. Our subject also displayed the abnormal DNA methylation pattern consistent with the diagnosis of PWS using the MS-MLPA kit with several methylation-specific probes further supporting a disturbance of the imprinting center.

3. Discussion

Patients with an atypical deletion involving only the central and critical region of the 15q11-q13 sequence are very rare. The typical genetic lesion in patients with PWS is a de novo deletion of the 15q11-q13 region (i.e., larger Type I and smaller Type II deletions) involving the paternal chromosome, uniparental maternal disomy 15 or an imprinting defect (e.g., Butler, 2011; Cassidy et al., 2012; Angulo et al., 2015; Butler, 2016). Our report details a 20 year follow up of the first patient clinically described with an atypical submicroscopic

deletion of the central 15q11-q13 region including the imprinting center leading to PWS. She had the associated clinical and behavioral features seen in PWS including feeding difficulties, infantile hypotonia, childhood onset of obesity, global developmental delay and behavioral problems. The clinical, behavioral and molecular findings were compared to other patients with similar genetic abnormalities in the central area of the 15q11-q13 region involving *SNURF-SNRPN* and stretches of non-coding RNA but without a deletion of the imprinting center (see Table 1).

A similar case was later reported by Sahoo et al., (2008) in a male child with a de novo 174,584bp microdeletion within the same 15q11-q13 region at genomic coordinates 25,284,501–25,459, 086bp (hg19) including *SNORD116*, *SNORD109A* and part of the *SNORD115* RNA cluster but not including the imprinting center. The patient met the clinical criteria for PWS but with a height at the 95th centile, which is atypical for PWS. A deficiency of *SNORD116* appeared sufficient to cause the PWS phenotype including morbid obesity with cognitive and behavioral problems (see Table 1).

Another individual, a 19 year old South Asian Indian male with a 186,940 bp microdeletion at genomic coordinates 25,206,126–25, 393,065bp (hg19) involving the chromosome 15q11eq13 region encompassed non-coding RNAs but with normal DNA methylation (de Smith et al., 2009). At 13 years of age his height was 155 cm (43rd centile) and weight was 101 kg (99th centile) with a BMI of 42. He exhibited a typical PWS phenotype including delayed puberty, skin picking, gynecomastia and stubbornness with temper tantrums.

An African-American male at 11 years of age was reported with a 236,295bp microdeletion in the 15q11.2 region meeting most of the major diagnostic criteria for PWS (Duker et al., 2010). Microarray analysis revealed a deletion of the C/D box snoRNAs, *SNORD107*, *SNORD64, SNORD108, SNORD109, SNORD116* clusters (1–29) and *SNORD115* clusters (1–24) but not the imprinting center. Break-points were assigned at genomic coordinates 25,223,754–25,456, 690bp (hg19). No pregnancy problems were noted. Yet, hypotonia, a weak cry and poor suck requiring nasogastric feeding and undescended small testicles were identified during infancy. Infantile seizures resolved by 2 years of age with a BMI of 33. At 11 years of age, generalized obesity was present along with mild hypotonia, moderate learning problems with stubbornness, speech articulation defects, thick saliva, food foraging with hyperphagia, a small penis and normal sized hands (see Table 1).

A 23 year old female was also reported with an 118,159bp deletion in the 15q11-q13 region of paternally expressed genes exhibiting the clinical criteria for PWS at genomic coordinates 25,257,217–25,375,376bp (hg19) (Bieth et al., 2015). Quantitative multiplex PCR of short fluorescent fragments from the 15q11-q12 region revealed 50% reduction consistent with a heterozygous deletion for *SNORD109A* and *SNORD116* further supported by DNA sequencing but did not include the imprinting center. These genetic results showed the smallest deletion discovered to date demonstrating the critical region for PWS encompassing deletions in the previous four cited patients involving *SNORD109A* and *SNORD116* (see Table 1).

She was born with an appropriate weight and length but experienced severe hypotonia and a poor suck reflex requiring tube feeding. She had mild developmental delay (walked at 18 months), became obese at 3 years, had strabismus and typical PWS related behavioral problems along with growth hormone (GH) deficiency diagnosed at 9 years of age. GH treatment was not indicated as her height was within normal range at that time. She was treated for hypothyroidism at 10–13 years of age due to central hypothyroidism and had incomplete puberty with no menarche. She displayed frequent skin picking, mild cognitive impairment and was main-streamed in normal education programs (no IQ testing performed). Her adult height was at the 20th centile.

The deletion of *SNORD109A* and *SNORD116* is a common trend in patients thus far examined with evidence in mice that the *Snord116* cluster functions in the hypothalamus and plays a role in the maturation of feeding circuits (Zhang et al., 2012; Qi et al., 2016). Knockout *Snord116* mice displayed a hyperphagic phenotype and reduced postnatal growth potential, bone size and mass (Bieth et al., 2015; Ding et al., 2008; Skryabin et al., 2007; Zhang et al., 2012).

The compiled results gained from the additional findings of patients in the literature with overlapping microdeletions point to a minimal critical region of approximately 95,000bp in size involving both *SNORD109A* and *SNORD116* (at genomic coordinates 25,280,000–25,375,000bp). Three of the five patients had larger microdeletions including a partial deletion of *SNURF-SNRPN*. Two of the five had partial deletions of the SNORD115 clusters (see Fig. 2). Previous studies of *SNORD116* C/D box proposed that the minimal critical region for PWS contains the *SNORD116* snoRNA cluster and *SNORD109A* snoRNA as the only putative functional genes (Gallagher et al., 2002). A complete loss of the *SNORD115* snoRNAs was not associated with any obvious clinical feature and did not play a major role in PWS granted that no other deletions in the 15q11-q13 region were present (Runte et al., 2005).

In review of the clinical overlap in individuals with involvement of the minimal critical cytogenetic region, fewer problems with growth failure (stature and hands/feet size) were seen than found in those with the typical genetic lesions seen in PWS. Fewer cognitive problems may also be present but more research is required to better understand the functional role of *SNORD116* which was consistently deleted in all five reported patients and how it plays into the pathogenesis of this rare obesity-related genetic disorder. Potential therapies should be directed at the *SNORD116* locus as performed by Powell et al., (2013) using candidate topoisomerase inhibitors such as topotecon in cell lines established from Angelman syndrome to activate genetic information. Alternative studies would suggest activation of the PWS critical region and associated genes on imprinted regions as possible therapeutic strategies (Rozhdestvensky et al., 2016).

In this report, we detailed a 20 year longitudinal study of a Caucasian female with the first report of a rare atypical submicroscopic deletion encompassing the *SNURF-SNRPN* gene complex and adjacent non-coding RNA, specifically *SNORD116*. We examined her development and natural history over time and compared her findings to other individuals in the literature with similar atypically sized deletions to identify the minimal overlapping

deletion but without involvement of the imprinting center. An attempt was made to correlate the clinical symptoms in each of the five patients with the chromosome 15 breakpoints. For example, the reports by Sahoo et al., (2008) and Duker et al., (2010) showed the most distal chromosome 15 breakpoints when compared with the other three subjects but no obvious clinical differences were seen. The clinical reports by Butler et al., (1996) and de Smith et al., (2009) involved the *SNURF-SNRPN* gene complex but again showed no obvious clinical differences compared to the three subjects with their proximal breakpoints distal to this gene complex (see Fig. 2). The subject reported by Bieth et al., (2015) at 23 years of age with the smallest atypical deletion interestingly had no history of food foraging and had the lowest BMI at 31 with a range of 39–50 for the other subjects.

In summary, these cases support atypical deletions in the central 15q11-q13 region contributing to the PWS phenotype and PWS - like features and behaviors particularly when the *SNURF-SNRPN* gene complex and adjoining non-coding RNAs are deleted. Our patient was the sole case in which the deletion encompassed the imprinting center with abnormal methylation resulting in lack of expression of genes in the PWS region upstream of the *SNURF-SNRPN* gene complex (e.g., *MRKN3, MAGEL2, NDN* and *NPAP1*) and the paternally expressed non-coding RNAs downstream. The imprinting center in the other four patients was not deleted and by inference leaves these genes intact and functional. However, the phenotypic characteristics associated with PWS were similar in all five patients indicating that non-coding RNA plays a large role in the presentation of the PWS phenotype. Specifically, *SNORD116* becomes a key target development for therapeutic interventions.

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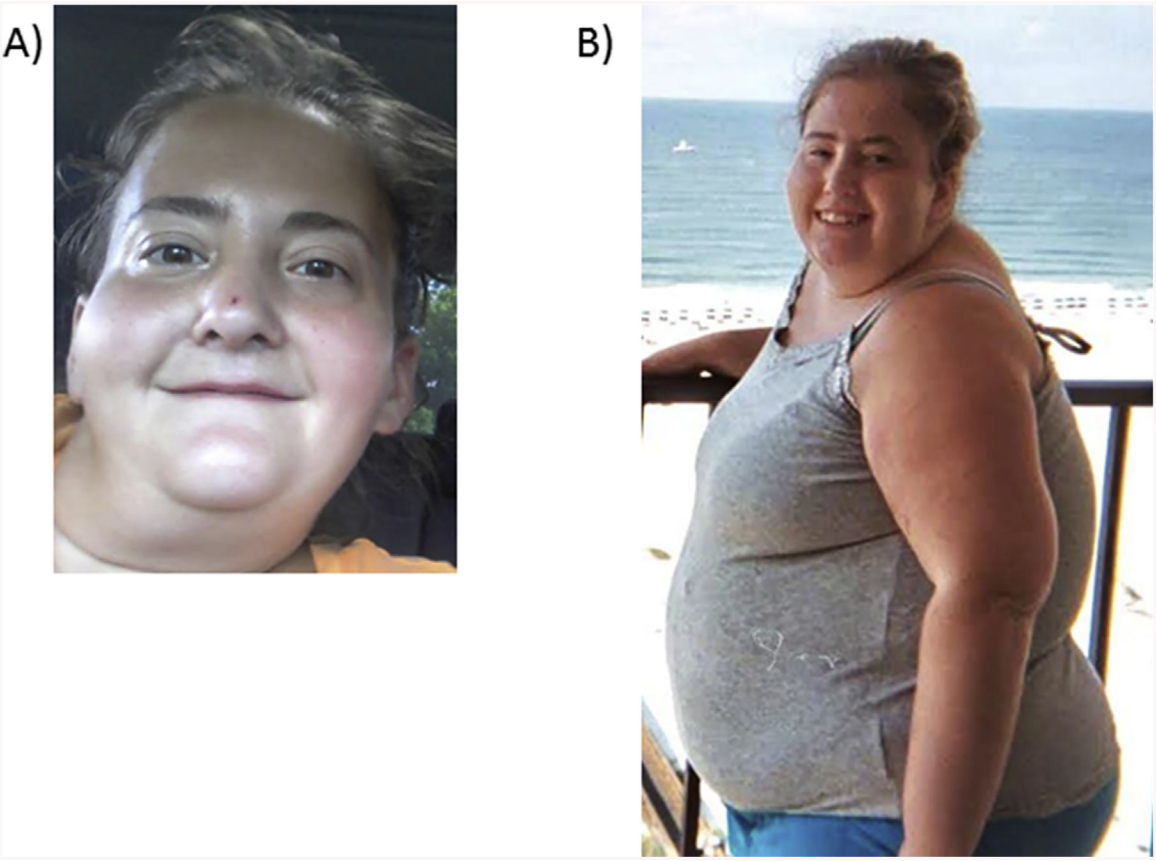

Fig. 1.

A) Frontal facial view of our patient at 25 years of age showing narrow bifrontal diameter, areas of skin picking, nasal appearance and almond-shaped eyes indicative of PWS. **B)** Side profile view of our patient at 23 years of age showing the marked central obesity typical for individuals with PWS.

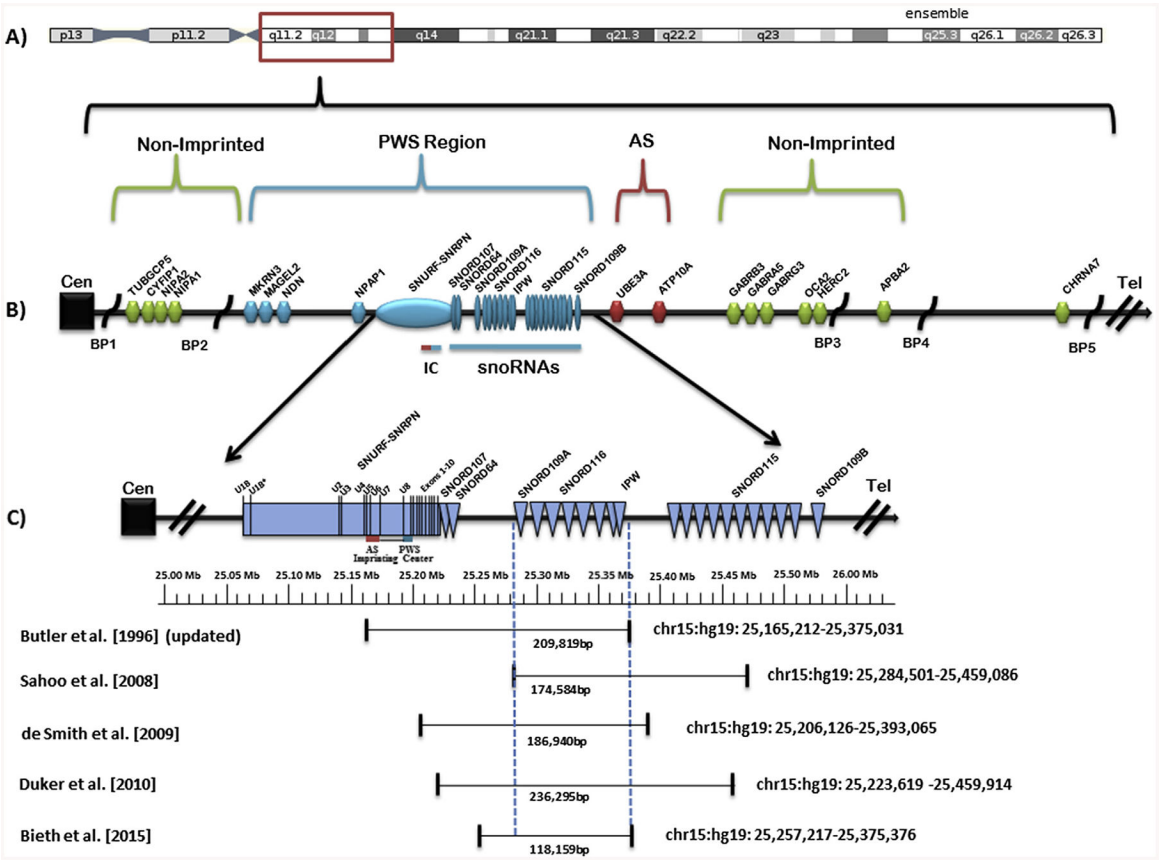

Fig. 2. -

A) Ideogram of chromosome 15 with the q11-q13 region specified. **B)** Schematic representation of the 15q11-q13 region displaying genes from *TUBGCP5* to *CHRNA7*. Genes in the non-imprinted region are shown in green, genes involved within the PWS region are shown in blue and genes involved in Angelman syndrome are shown in red. **C)** View of the PWS region shown to scale with physical distance represented in Mb. The rectangle displays the *SNURF-SNRPN* gene complex and upside down triangles depict non-coding SNORDs and IPW. The reported deletions are shown at the bottom drawn to scale and depicting genomic deletion coordinates for build hg19. Minimal critical region spans from about 25,280,000bp-25,375,000bp as shown by the dotted lines encompassing *SNORD109A* and *SNORD116*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Comparisons of patients with the PWS phenotype and similar atypical 15q11-q13 deletions.

Clinical Category	Butler et al. (1996) (updated)	Sahoo et al. (2008)	de Smith et al., (2009)	Duker et al., (2010)	Bieth et al. (2015)
Demographics					
Age (yr)	26	5	19	11	23
Ethnicity	Caucasian	Caucasian	South Asian Indian	African-American	Caucasian
Gender	Female	Male	Male	Male	Female
Current Height (cm) [%]	152.4 [10th]	[95th]	167.5 [25th]	[25th]	N/A
Current Weight (kg) [%]	106 [90th]	N/A	109[>97th]	94 [>97th]	N/A
Body Mass Index	46	N/A	39	50	31
Birth Length (cm) [%]	54.6 [90th]	N/A	N/A	53 [90th]	48 [25th]
Birth Weight (g) [%]	3334 [30th]	N/A	2800 [10th]	3020 [10^{th}-25th]	2780 [10^{th}-25th]
Clinical Features					
Neonatal Feeding Difficulty	Yes	Yes	Yes	Yes	Yes
Hypotonia	Yes	Yes	Yes	Yes	Yes
Small Hands/Feet	Yes	Yes	Yes	Feet	N/A
Hypogonadism	N/A	Yes	Yes	Yes	Yes
Scoliosis	Mild	No	No	N/A	No
Intellectual Disability	Borderline (IQ = 79)	Mild	Mild	Mild	Mild
Seizure Activity	Yes	N/A	N/A	Yes	N/A
Behavioral Features					
Skin-Picking	Yes	N/A	Yes	No	Yes
Food-Foraging	Yes	N/A	N/A	Yes	No
Hyperphagia	No at 5 years of age Yes at 10 years of age	Yes	Yes	Yes	Yes
Other Behavior	OCD	Argumentative	Temper Tantrums Stubbornness	Argumentative OCD	Argumentative Aggressive
Molecular Genetics					
Deletion Size (bp)	209,819	174,584	186,940	236,295	118,159
Genomic Coordinates (hg19 build)	25,165,212–25,375,031	25,284,501–25,459,086	25,206,12–25,393,065	25,223,754–25,456,690	25,257,217–25,375,376
Deleted Genes/Non-coding RNA	SNURF-SNRPN,	SNORD115,	SNURF-SNRPN,	SNORD107, SNORD64,	SNORD109A,

Clinical Category	Butler et al. (1996) (updated)	Sahoo et al. (2008)	de Smith et al., (2009)	Duker et al., (2010)	Bieth et al. (2015)
	SNORD107, SNORD64 SNORD109A PAR-SN, SNORD116	SNORD109A, SNORD116	SNORD109A, SNORD116	SNORD108, SNORD109A, SNORD116, SNORD115	SNORD116
DNA Methylation	PWS Pattern (Imprinting Defect)	Normal Pattern	Normal Pattern	Normal Pattern	Normal Pattern
Parental Origin Of Deletion	Paternal	Paternal	DNA not available on mother	Paternal	Paternal