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Copy Number Variations in a Population with Prune Belly Syndrome

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Abstract

Prune Belly Syndrome (PBS) is a congenital multisystem myopathy with mild to lethal severity. While of uncertain etiology, 95% male predominance and familial occurrence suggest a genetic basis. As copy number variations (CNVs) can cause unexplained genetic disorders, we tested for novel CNVs in a large PBS population. We genotyped 21 unrelated PBS patients by high-resolution array comparative genomic hybridization (aCGH) and phenotyped using a novel PBS severity scoring system. Available parents were screened for detected CNV via quantitative PCR (qPCR). We additionally screened for recurrence of identified novel candidate CNVs on 106 PBS probands by qPCR. We identified 10 CNVs in 8 of 21 PBS patients tested (38%). Testing confirmed inheritance from an unaffected biological parent in 6 patients; parental samples were unavailable in 2 probands. One candidate CNV includes duplication of the X-chromosome *AGTR2* gene, known to function in urinary tract development. Subsequent screening of the larger PBS cohort did not identify any recurrent CNVs. Presence of CNV did not correlate with PBS severity scoring. CNVs were uncommon in this large PBS population, but analysis of identified variants may inform disease pathogenesis and reveal targets for therapeutic intervention for this rare, severe disorder.

Keywords

Prune belly syndrome; copy number variations; genetics; myopathy; urology

INTRODUCTION

Prune belly syndrome (OMIM# 100100), also known as Eagle-Barrett or Triad Syndrome, is a rare congenital disorder that is classically defined by three phenotypic features including 1) varying degrees of an enlarged urinary bladder, dilated ureters, and hydronephrosis with poorly contractile and disorganized detrusor and ureteral smooth muscle 2) hypoplastic or absent midline abdominal skeletal musculature and 3) bilaterally undescended testes in males. The phenotypic spectrum ranges from mildly affected individuals to lethality and the spectrum has been characterized in our group by a PBS clinical severity scoring system

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Disclosure/Conflict of Interest

The authors declare no conflict of interest.

(Wong et al., In press). Extra-genitourinary features may also be present, including gastrointestinal, cardiopulmonary and orthopedic anomalies (Grimsby, Harrison, Granberg, Bernstein, & Baker, 2015). The incidence of PBS is estimated to be between 1:35,000 to 1:50,000 with a significant bias for male prevalence (Tonni, Vito, Ventura, & Bonasoni, 2013).

While the majority of PBS cases occur sporadically, numerous cases of familial recurrence and 95% male predominance are suggestive of an underlying genetic component. Mode of inheritance is hypothesized to be influenced by a sex-linked genetic factor that is caused by an X-chromosome hemizygous variation or an autosomal dominant sex-limited trait expressed only in males (Adeyokunnu & Familusi, 1982; Afifi, Rebeiz, Mire, Andonian, & Kaloustian, 1972; Balaji et al., 2000; Feige, Fiedler, Rempen, & Osterhage, 1984; Gaboardi et al., 1982; Garlinger & Ott, 1974; Harley, Chen, & Rattner, 1972; Lockhart, Reeve, Bredael, & Krueger, 1979; Riccardi & Grum, 1977). The literature contains several suggestions for candidate genes causal for PBS; however, single nucleotide or structural variations affecting these genes (*CHRM3*, *HNF1 β* , *ACTA2* and *ACTG2*) only account for single cases and six affected brothers from one consanguineous family, suggesting that other causal genes remain to be identified (Brodsky, Turan, Khanna, Patton, & Kirmani, 2014; Granberg et al., 2012; Haeri et al., 2010; Murray et al., 2008; Richer et al., 2012; Wangler et al., 2014; Weber et al., 2011). Previous studies also reported the occurrence of PBS with chromosomal abnormalities including trisomy 13, 18, 21 and large deletions of chromosome 6, further supporting a genetic etiology (Amacker, Grass, Hickey, & Hisley, 1986; Frydman, Magenis, Mohandas, & Kaback, 1983; Fryns, Vandenberghe, & Van den Berghe, 1991; McKeown & Donnai, 1986). Finally, a recent study evaluated the presence of CNVs in a birth registry cohort of 34 PBS-affected individuals and identified 17 candidate autosomal variations of which one CNV was observed in two independent patients, suggesting genetic heterogeneity for this disorder (Boghossian et al., 2017). However, a major limitation of that study was absent inheritance testing due to lack of parental samples, making it difficult to truly assess significance of the detected CNVs (Kearney et al., 2011).

For our current study, we screened for the contribution of CNVs to disease pathology in 21 PBS probands by array-comparative genomic hybridization (aCGH), a type of cytogenomic microarray analysis (CMA). We identified 10 unique, previously unreported genomic aberrations in 8 of 21 patients, tested whether they were inherited from an unaffected biological parent, and further assessed for recurrent CNVs in a larger population of affected individuals. We used a comprehensive scoring system for degree of severity to determine if the presence of a CNV correlated with more severe PBS phenotypes (Wong et al., In press). We further summarize and contribute to the growing body of evidence that PBS is a heterogeneous genotypic and phenotypic disorder that in rare cases may be explained by structural or single nucleotide variations in genes affecting development and maintenance of muscle and the urinary tract.

MATERIALS AND METHODS

Subjects, phenotyping, and DNA sample collection:

From 2001–2015, PBS patients and family members were prospectively enrolled into our Pediatric Genitourinary DNA Repository. When available, the patients' medical records were retrospectively reviewed and in person and/or telephone interviews were performed to obtain medical, surgical, and family history. Each PBS patient was assigned a PBS RUBACE severity score, ranging from 0 to 31, per a protocol described by our group (Wong et al., In press). In brief, this comprehensive scoring system grades the anatomical and functional phenotypes of the (R) renal, (U) ureteral, (B) bladder, (A) abdominal wall and (C) cryptorchid testes as well as (E) extra-genitourinary manifestations [including gastrointestinal, respiratory, cardiac and musculoskeletal findings]. The mean RUBACE score was compared by two-tailed Student's t-test (GraphPad Prism) between our PBS patients identified to have a normal CMA report versus those with an abnormal CMA result. Blood samples were collected from all PBS participants and parents when available. Lymphocyte genomic DNA was extracted from ethylenediamine tetra-acetic acid (EDTA)-treated peripheral venous blood using the Qiagen Autopure LS automated Nucleic Acid Purification Instrument at the University of Texas Southwestern Medical Center Clinical Genetics Laboratory and then prepared for CMA and qPCR.

CNV identification:

Cytogenomic Microarray Analysis (CMA) using the Oligo V8.1/V8.3 (Baylor College of Medicine Medical Genetics Laboratories) or AGILENT™v1.0 4-plex (UT Southwestern) were used to identify CNVs in a subset of PBS patients. Digestion, labeling and hybridization were completed based on manufacturer's protocols and variant calls were made by each clinical laboratory per facility established criteria (Kearney et al., 2011). When possible, *de novo* versus parental inheritance was assessed through fluorescence *in situ* hybridization (FISH) following clinical laboratory standard protocol, by qPCR or by CMA. The ClinGen (<https://www.clinicalgenome.org/>) and DECIPHER (<https://decipher.sanger.ac.uk/>) databases were searched for individuals that carried the same novel CNVs as well as to identify additional novel CNVs in cases with a PBS phenotype (Firth et al., 2009).

Testing for recurrent CNVs:

In our research laboratory, TaqMan Copy Number Assays (ABI) using qPCR were performed to quantify copy number of 10 genes that are within the CNV regions identified by CMA, including ABI probes for *TAAR6* (Hs01574669_cn), *EXOC4* (Hs04934540_cn), *XRCC6P5* (Hs04097838_cn), *AGTR2* (Hs00069365_cn), *IMMP2L* (Hs03623618_cn), *TMEM131* (Hs03406682_cn), *DST* (Hs068118310_cn), *SYNE1* (Hs01157475_cn) or a SYBR based assay for *BRCA1* (F: 5' AAGGCAACTTATTGCAGGTGA 3'; R: 5' TTTTAAAAAGAGAGAAACATCAATCC 3'), and *MYLK* (F: 5' CCCGTGACATGTGTGATTTTC 3'; R: 5' CGTTATTGGGAGGTCTGAGG 3'). For TaqMan assays, a 20uL reaction containing 8ng genomic DNA, FAM dye-labeled target gene probe, VIC-TAMRA dye-labeled reference gene (Human RNaseP, ThermoFisher #4403326) and TaqMan Genotyping Master Mix (ThermoFisher #4371355) was amplified on the CFX-Connect Real Time System (BioRad)

using the following PCR protocol: 95° for 10 min followed by 40 cycles of 95° for 15 seconds and 60° for 1 minute. All DNA samples were run in triplicate to account for technical error. All 8 PBS patients with the novel 10 CNVs were validated by qPCR. Controls included the PBS patient with the identified CNV (positive), a PBS patient with a normal CMA report (negative) and water (blank). The delta-delta CT method was used to obtain copy number values.

RESULTS

Clinical information:

In the CNV microarray screening stage of this study, 21 unrelated PBS patients (1 female and 20 males) underwent CMA at median age 13 years (IQR 6.5–17.5). Of patients tested, 33.3% (n = 7) are black non-Hispanic, 23.8% (n = 5) are Hispanic, 38.1% (n = 8) are white non-Hispanic and one patient is interracial black-white non-Hispanic. One patient has a positive family history of PBS (Figure 1) and one patient is now deceased. The clinical characteristics of 8 of 21 patients (38%) identified to have CNVs are described in Table 1. The mean RUBACE PBS severity score of PBS subjects with and without novel CNVs was 14.7 and 14.2, respectively (p=0.7113).

Copy number screening:

10 unique genomic aberrations were identified across 8 patients- two patients had two variations each (Tables 2 and 3). Six deletions and four duplications were detected, ranging in size from 9kb - 485kb. No CNVs were overlapping. Inheritance testing by qPCR identified that six of 8 patients inherited the genomic aberration from an unaffected biological parent. Parental DNA was unavailable for PBS Sporadic 1 and 5; thus inheritance testing was not performed. Three of six deletions were paternally inherited while one was maternal. Three of four duplications were maternally inherited. Two patients were identified to have imbalances on the X-chromosome: 1) a maternally inherited 0.113 Mb deletion of Xp22.1 observed in PBS Sporadic 3 which impacts an intron of the *XRC66P5* pseudogene and 2) a 0.324 Mb duplication of chromosome band Xq23 observed in PBS Sporadic 5 affecting three genes *AGTR2*, *SLC6A14* and *CXorf61*. A favored hypothesis suggests that PBS may be caused by an X-linked genetic factor, making these CNVs of particular interest.

One patient (PBS Familial 1) had a positive family history of PBS. The mother of the two PBS affected brothers had a brother that died at 6.5 months of gestation and was said to have a PBS-like anomaly. CMA analysis of one affected brother revealed a 0.362 Mb duplication of Chr6p12.1. qPCR validation of this CNV and inheritance testing in the family found this maternally inherited duplication to not only be present in the affected PBS brother but also in the unaffected brother, while sister and father are both wild type (WT) for the duplication (Figure 1).

Finally, we identified two additional PBS patients from the DECIPHER database with CNVs. One PBS patient had a 10.13 Mb *de novo* constitutive loss of chromosome 1q23.3-q24.3 which includes 128 genes. The second PBS patient had a 1.56 Mb loss of chromosome 16p13.11 encompassing 31 genes including *MYH11*, a smooth muscle myosin.

No detailed phenotypic data and parental samples were available for testing on these two PBS cases (Firth et al., 2009).

Screening of identified CNVs in large PBS population

Because CMAs are cost-prohibitive for screening purposes, in order to test for recurrent CNVs across a larger population of PBS patients, we evaluated an additional population of 106 PBS probands for the identified candidate PBS CNVs using a qPCR assay. The qPCR assay did not identify any additional PBS probands with copy number changes in any of the 10 genes screened.

DISCUSSION

In this report, we applied high-resolution copy-number analysis to 21 unrelated PBS affected patients and detected novel chromosomal variations in 38% (n = 8) of cases. We identified 10 unique candidate regions ranging in size from 9 kb to 485 kb including a duplication of Xq23 of unknown genetic origin (Table 3). The mean RUBACE PBS severity score of PBS subjects with and without novel CNVs was found to be no different, suggesting that the presence of a novel CNV does not correlate with severity of disorder. Because no CNV was overlapping or recurrent across our larger cohort of 106 probands, consistent with the literature, our data suggest that PBS is not frequently caused by a recurrent copy number variation. Compiling our findings with the candidate genomic loci identified by others reveals that there are 31 candidate PBS CNVs published (Figure 2) (Boghossian et al., 2017; Haeri et al., 2010; Murray et al., 2008). Thus, PBS may be caused by aberrations in a heterogeneous group of genes which encompass regulators of mesodermal development (e.g. TGF β /BMP and WNT signaling) and muscle organization including cytoskeletal components (Boghossian et al., 2017; Brodsky et al., 2014; Richer et al., 2012; Wangler et al., 2014). While an X-linked recessive mode of inheritance is still the most attractive genetic model, it is possible that causal genes for PBS may be found on autosomes with sex-limited (male) expression. As evidence for genetic causes of PBS is growing, these data suggest that PBS is not a monogenic condition and rather may be due to genetic variants of many genes, in line with the phenotypic variability observed across patients (Grimsby et al., 2015).

Our study identified candidate CNVs including genes involved in urinary tract development and muscle maintenance. Of interest, a maternally inherited 0.485 Mb duplication of 16q11.2 includes the *MYLK3* gene which encodes for myosin light chain kinase 3. A related member of this gene family, *MYLK*, was recently shown to be causal for the smooth muscle enteric myopathy, megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMIHS; OMIM#155310), making this duplication an interesting candidate for PBS (Halim et al., 2017). Further, the 1.56 Mb loss of chromosome 16p13.11 identified from searching the DECIPHER database includes the *MYH11* gene. Autosomal recessive variants in *MYH11* are also causal for MMIHS, suggesting a possible related etiology between these two phenotypically-overlapping disorders (Gauthier et al., 2015; Levin, Soghier, Blitman, Vega-Rich, & Nafday, 2004; Oliveira, Boechat, & Ferreira, 1983).

While the impact of the 0.123 Mb loss of 6q25.2 in PBS Sporadic 8 is unclear due to paternal inheritance, this loss includes the *SYNE1* gene. *SYNE1* encodes for a spectrin repeat-containing nuclear envelope protein that is known to cause autosomal dominant Emery-Dreifuss muscular dystrophy 4, a muscle weakening or wasting disease that impacts skeletal and cardiac tissues. While in contrast PBS can be thought of as a congenital myopathy as opposed to dystrophy, many parallels can be drawn between the muscle atrophy phenotypes between these two diseases. Further, *SYNE1* is expressed in both skeletal and smooth muscle cells, thus possibly explaining the rectus abdominis skeletal muscle and detrusor smooth muscle phenotypes observed in PBS.

We also identified a 0.324 Mb duplication of chromosome band Xq23 including the *AGTR2* gene. *AGTR2* encodes for the angiotensin receptor II which is not only expressed in the bladder detrusor muscle but also plays an important role in the regulation of renal and smooth muscle development and the production of collagen (Cheng, Decker, & Lee, 1999; Hohenfellner et al., 1999). Not only does this candidate fit the proposed model of X-linked recessive mode of inheritance, a duplication of the *AGTR2* gene may explain the increased collagen and poorly contractile muscle observed in PBS patients. Unfortunately, inheritance testing was not available for this PBS case.

Concerning the case of PBS Familial 1 with the maternally inherited 0.362 Mb gain of 6p12.1 shared by both the affected and PBS-unaffected brother (Figure 1), the significance of this non-segregating genetic aberration is unclear, ranging from it being non-causal to a significant CNV with variable expressivity, parent of origin imprinting effects, somatic mosaicism, or incomplete phenotypic penetrance modulated by other genetic, epigenetic and environmental factors. However, the genes within the duplication do not have a functional role or expression pattern that would easily explain the PBS phenotype.

A literature review has identified several potentially causal chromosomal variants. Two independent reports identify *de novo* microdeletions of Chr17q12 encompassing the *HNF1β* (hepatocyte nuclear factor-1-β) gene, a homeobox transcription factor that regulates mesodermal and endodermal development. While haploinsufficiency of *HNF1β* could plausibly result in maldevelopment of the urinary tract, our group did not identify additional patients with functionally deleterious *HNF1β* sequence variants and further, the two PBS patients with 17q12 microdeletion had additional phenotypic features beyond those of the patient with classic PBS (Granberg et al., 2012; Haeri et al., 2010; Murray et al., 2008). A recent report screened a total of 34 patients with PBS and identified 17 candidate autosomal CNVs. A microduplication encompassing intron 1–2 of *STIM1* was the only recurrent finding, reported in two patients, however inheritance testing could not be performed to assess whether these aberrations are *de novo* or inherited (Figure 2) (Boghossian et al., 2017). Finally, an analysis of seven families presenting with intestinal pseudo-obstruction or bladder distension were identified to have overlapping microduplications on ChrXq28, encompassing the *FLNA* gene. Two male siblings from one family presenting with severe bladder dysfunction, including a thick walled bladder, were described to have a maternal uncle with a history of PBS (Clayton-Smith et al., 2009). Genetic studies of PBS patients to date have revealed several interesting candidate deletions and duplications that encompass

numerous chromosomal regions (Figure 2). Thus, further testing will be needed to validate these candidates as PBS causal dosage sensitive genes.

Our study benefits from its large population size (n=127 PBS patients), phenotypic validation, parental inheritance testing in most PBS patients with novel CNVs, and a tiered analysis approach. However, it does have its limitations. Overall, our study could have a sampling bias in that with only one exception, our cohort of patients are a living cohort. It is possible that more CNVs would have been detected in a cohort of antenatal cases which would include the 20–30% that might die in the first two years of life (Routh, Huang, Retik, & Nelson, 2010). Additionally, CNV testing is unable to detect copy neutral structural rearrangements, such as Robertsonian translocations, balanced rearrangements or inversions, thus not detecting important structural variants. Further, a limitation of all previously reported studies, including this one, is lack of functional evidence showing causality of gene(s) within the chromosomal alteration to explain PBS pathology. Concerning our qPCR screening for recurrent CNVs of our detected candidate PBS CNVs, this study was limited by screening with only one probe set for one gene of interest within each genomic aberration, thus not comprehensively covering the entire CNV region and potentially missing a recurrent CNV.

Despite the fact that familial evidence and association of PBS with various genetic aberrations strongly support a genetic basis, the mechanism for PBS pathogenesis is not clear. Long-range effects of the identified chromosomal abnormalities, including impact on local and distal gene expression, cannot be ignored. Clearly, functional experiments are required to accurately assess the contribution of the identified structural and single nucleotide variations to PBS pathology. Our study contributes to the growing body of knowledge of genetic aberrations identified in PBS patients and provides leads for intense investigation to better characterize the mechanism for this rare and devastating disorder.

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Figure 1.

Pedigree of PBS Familial 1. Three generations of this family are presented. PBS affected individuals are filled in black. Arrow represents PBS affected proband that underwent CMA. Individuals II-1, II-2, III-1, III-2, and III-4 were tested for the CNV by *DST* gene qPCR. Two affected brothers (III-3 and III-4) and one unaffected brother (III-2) are positive for the maternally-inherited (II-2) chr6p12.12 0.362 Mb duplication (dup) while II-1 and III-1 are wild type (WT). Individual II-3 (male) died at 6.5 months gestation and was believed to have PBS; no DNA was available for testing.

Figure 2.

Human chromosomal map summarizing candidate PBS variants identified in this study and other studies highlighting genetic variability observed in PBS. Data from our study are represented with green (deletion) and red (duplication) arrowheads pointing to region of abnormality. Results from other studies are represented in yellow (deletion) or purple (duplication) arrowheads (Boghossian et al., 2017; Clayton-Smith et al., 2009; Haeri et al., 2010; Murray et al., 2008). Data from the DECIPHER database (<https://decipher.sanger.ac.uk/>) which identified two CNVs (including a 10.13 Mb *de novo* loss of chromosome 1q23.3-q24.3 and a 1.56 Mb loss of chromosome 16p13.11) are presented by blue arrowheads. Recurrent observed CNVs include two PBS cases of chromosome 11p15.4

duplication including *STIM1* of unknown inheritance and 2 PBS cases (one unknown and one *de novo*) with chromosome 17q12 deletion including *HNF1 β* .

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Table 1.

y score of PBS patients with abnormal CMA.

(R)enal	(U)reters	(B)ladder	(A)bdominal Wall	(C)ryptorchid Testes	(E)xtragenitourinary Manifestations	RUBACE		
(Center:Right) VUR reflux grade (range I-V)	Ureters	Bladder	Bladder Emptying	Abdominoplasty	Testes Location	Development delay	Other	PBS Severity Score (range 0- 31)
Kidney and collecting system abnormalities								
Am J Med Genet A. Author manuscript; available in PMC 2019 November 01.								
Subcentimeter right renal cysts, atrophic center kidney, stone	Unknown	Augmentation, APV	Intermittent catheterization	Yes	Abdominal	Yes	Deaf, poor vision	12
Moderate hydronephrosis	Bilateral ureteral reimplants, bilateral ureterostomies	Thickened bladder wall (US)	Ureterostomy	Yes	Abdominal	Yes	DMD, language delay	20
Unknown	Bilateral tapered reimplants	APV, PUV s/p ablation, patent urachus,	Intermittent catheterization	Yes	Bilateral retroperitoneal below lower pole of kidneys	No	Pectus excavatum	14
Bilateral hydronephrosis	Bilateral reimplants	Reduction cystoplasty	Voids per urethra	Yes	Bilateral orchioepexies, unknown location	Yes	G-button, PDA, constipation, pulmonary hypoplasia, hearing loss	22
Bilateral hydronephrosis	Reconstructive ureter and bladder surgery	Thickened bladder wall (US)	Indwelling catheter (at night)	Yes	Bilateral orchioepexies - unknown location	No	Club feet	11
Bilateral hydronephrosis	Bilateral tapered reimplants	Thickened bladder wall (US)	Voids spontaneously	Yes	Center abdominal 4cm above internal ring; right abdominal 3cm above internal ring	No	Unknown	9
Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Unknown	Unknown	APV	Intermittent catheterization	Unknown	Bilateral undescended - unknown location, unknown if orchioepexies	Unknown	Affected brother	Unknown

al reflux), APV (Appendicovesicostomy), US (Ultrasound), PUV (Posterior Urethral Valves), DMD (Duchenne's muscular dystrophy), G-button
S/P (Status Post), ESRD (End Stage Renal Failure), NA (not ascertainable)

Table 2.

Copy number deletions observed in PBS patients.

Case ID	Size (Mb)	Locus	Coordinates	Inheritance	Genes	Associated clinical phenotype
PBS Sporadic 1	0.066	6q23.2	132,851,779–132,917,431	Parental DNA unavailable	<i>TAAR9</i> <i>TAAR8</i> <i>TAAR6</i> <i>TAAR5</i>	
PBS Sporadic 7	0.123	6q25.2	152,621,387–152,744,883	Paternal	<i>SYNE1</i> <i>SYNE1-AS</i>	EMD4 (AD), SCA8 (AR) *
PBS Sporadic 2	0.271	7q31.1	110,815,047–111,085,739	Paternal	<i>IMMP2L</i>	
PBS Sporadic 1	0.151	7q33	133,425,804–133,574,035	Parental DNA unavailable	<i>EXOC4</i>	
PBS Sporadic 6	0.009	17q21.31	41,240,896–41,249,833	Paternal	<i>BRCA1</i>	Breast-ovarian cancer (AD)
PBS Sporadic 3	0.113	Xp22.1	98,731,352–98,844,764	Maternal	<i>XRCC6P5</i>	

* EMD4 (Emery-Dreifus muscular dystrophy 4), SCA (Spinocerebellar ataxia), AD (Autosomal dominant), AR (Autosomal recessive)

Table 3.

Copy number duplications observed in PBS patients.

Case ID	Size (Mb)	Locus	Coordinates	Inheritance	Genes	Associated clinical phenotype
PBS Sporadic 4	0.360	2q11.2	97,815,897–98,175,877	Maternal	<i>TMEM131</i> <i>VWA3B</i>	SCA22 (AR) *
PBS Familial 1	0.362	6p12.1	56,589,352–56,951,469	Maternal	<i>DST</i> <i>LOC101930010</i> <i>BEND6</i> <i>KIAA1586</i>	HSAN VI (AR), EBSB2 (AR) *
PBS Sporadic 6	0.485	16q11.2	46,500,741–46,985,642	Maternal	<i>ANKRD26P1</i> <i>SHCBP1</i> <i>VPS35</i> <i>ORC6</i> <i>MYLK3</i> <i>C16orf87</i> <i>GPT2</i>	Parkinson disease (AD) Meier-Gorlin syndrome 3 (AR) Mental retardation 49 (AR)
PBS Sporadic 5	0.324	Xq23	98,731,352–98,844,764	Parental DNA unavailable	<i>AGTR2</i> <i>SLC6A14</i> <i>CXorf61</i>	

* SCA (Spinocerebellar ataxia), HSAN VI (Neuropathy, hereditary sensory and autonomic, type VI), AD (Autosomal dominant), AR (Autosomal recessive)