CLINICAL REPORT

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Inherited dup(17)(p11.2p11.2): Expanding the Phenotype of the Potocki–Lupski Syndrome

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Potocki–Lupski syndrome (PTLS, OMIM: 610883) is a microduplication syndrome characterized by infantile hypotonia, failure to thrive, cardiovascular malformations, developmental delay, intellectual disability, and behavior abnormalities, the latter of which can include autism spectrum disorder. The majority of individuals with PTLS harbor a de novo microduplication of chromosome 17p11.2 reciprocal to the common recurrent 3.6 Mb microdeletion in the Smith–Magenis syndrome critical region. Here, we report on the transmission of the PTLS duplication across two generations in two separate families. Individuals in these families presented initially with developmental delay, behavior problems, and intellectual disability. We provide a detailed review of the clinical and developmental phenotype of inherited PTLS in both families. This represents the second report (second and third families) of PTLS in a parent–child pair and exemplifies the under-diagnosis of this and likely other genetic conditions in adults with intellectual disability and/or psychiatric disorders. © 2013 Wiley Periodicals, Inc.

Key words: Potocki–Lupski syndrome; PTLS; RAI1; microduplication syndrome; dosage sensitivity

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INTRODUCTION

Potocki–Lupski syndrome (PTLS) (OMIM: 610883) is a chromosomal microduplication syndrome that results from an interstitial duplication within chromosome 17p11.2 [dup(17) (p11.2p11.2)] [Potocki et al., 2000, 2007]. The clinical presentation of individuals with PTLS is variable and includes intellectual disability, developmental delay, behavioral problems, autistic features, hypotonia, poor feeding, failure to thrive, and cardiovascular abnormalities [Potocki et al., 2007; Treadwell-Deering et al., 2010; Soler-Alfonso et al., 2011; Sanchez-Valle et al., 2011; Jefferies et al., 2012]. As the clinical features may be subtle, a chromosomal disorder may not be suspected and the diagnosis of PTLS may be delayed.

The majority (~67%) of persons with PTLS harbor a common recurrent 3.6 Mb microduplication which is the recombination reciprocal of the Smith–Magenis syndrome (SMS)(OMIM: 182290) microdeletion—del(17)(p11.2p11.2) [Bi et al., 2003; Liu et al., 2011]. As this genomic region is rich in low-copy repeats (LCRs) both larger and smaller recurrent duplications, as well as non-recurrent duplication events—all containing the dosage-sensitive *RAI1* gene—have been observed in PTLS [Zhang et al., 2010; Lee et al., 2012]. Clinical features are similar amongst individuals with small, common, and large duplications within 17p11.2. Chromosomal microarray analysis will detect 100% of PTLS duplications whereas G- banded chromosome analysis and/or FISH analysis are far less sensitive [Stankiewicz and Beaudet, 2007].

To date, there is only one other report of a parent with PTLS [Yusupov et al., 2011]. Here we report two additional families, both

Conflict of interest: none.

Abbreviations: CNV, copy number variation; Mb, megabases; PTLS, Potocki–Lupski syndrome; SMS, Smith–Magenis syndrome; NAHR, nonallelic homologous recombination; kb, kilobase; aCGH, array comparative genomic hybridization.

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with the common recurrent duplication, wherein the PTLS duplication was maternally transmitted.

CLINICAL REPORT

Family #1

The proband was 5 years old when he presented for evaluation of intellectual disability and seizures. He was conceived naturally by a 34-year-old mother. Both parents were Caucasian. The father's age and medical history are unknown. The proband was born via spontaneous vaginal delivery at approximately 40 weeks of gestation. Birth parameters were appropriate for gestational age—birth weight 3,000 g (10th–25th centile) and birth length 55 cm (95th centile). He was hospitalized in the neonatal intensive care unit for 1 week due to hypotonia and mild feeding difficulties that did not require tube feeding. Hypospadias repair was performed at 7 weeks. He had global developmental delay (walked at 18 months) and received early childhood intervention including speech and physical therapy. He developed tonic–clonic seizures at age 3 years, which were treated with levetiracetam and oxcarbazepine. At examination at age 5 years, he was in pre-kindergarten and enrolled in general and special education classes. He was able to follow two-step commands, but required constant repetition and redirection. At age $6^{1}/_{2}$ years, he had approximately 15–20 words and was unable to use two-word combinations. Behaviorally, he had a short attention span, low frustration tolerance, and difficulty with transitions and changes in his routine.

On physical examination at $6^{1}/_{2}$ years of age, his height was 119 cm (50–75th centile) and weight was 21.3 kg (25–50th centile). The patient had no strikingly dysmorphic features yet had a triangular face, prominent nasal tip, and short philtrum (Fig. 1a). Examination of the extremities revealed generalized joint hypermobility. Neurological examination was significant for mild generalized hypotonia. He exhibited poor balance and poor coordination when walking, but was not frankly ataxic.

MRI of the brain and spine performed at 4 years of age showed no anatomic brain abnormalities, and a thin syringohydromyelia from C4 to T12. Prior diagnostic studies had included, newborn screening, high-resolution chromosome analysis, plasma amino acid analysis, and acylcarnitine profile, all of which were normal.

The proband's mother was 40-years-old at the time of examination (Fig. 1a and b). She was conceived naturally by a 20-year-old mother and 23-year-old father. She was born at 40 weeks gestation. Her birth weight was 2,296 g (<5th centile). There were no concerns in the neonatal period and she was discharged with the mother. She was readmitted to the hospital at 3 months of age for 1 week due to feeding difficulties, failure to thrive, and hypotonia. No feeding tubes were used. She had a history of developmental delay; sitting unassisted at 9 months and walking at 16 months. Her neurodevelopmental and psychological history was significant for intellectual disability, seizures, bipolar disorder, anxiety, and attention deficit disorders. She is otherwise described as having a history of substance abuse, lack of inhibition, and poor judgment.

She had a history of three pregnancies, two of which were miscarried and one term pregnancy. Both she and her son live with her parents (grandparents of the proband) as she is unable to care for him independently. Her physical examination was remarkable for bulbous nasal tip, short and smooth philtrum, and thin upper lip. Other past medical history included dental overcrowding that required dental surgery.

Family #2

The proband was a 24-year-old woman who was referred to Genetics during her first pregnancy because the fetus was found to have talipes equinovarus on a 20-week ultrasound and both

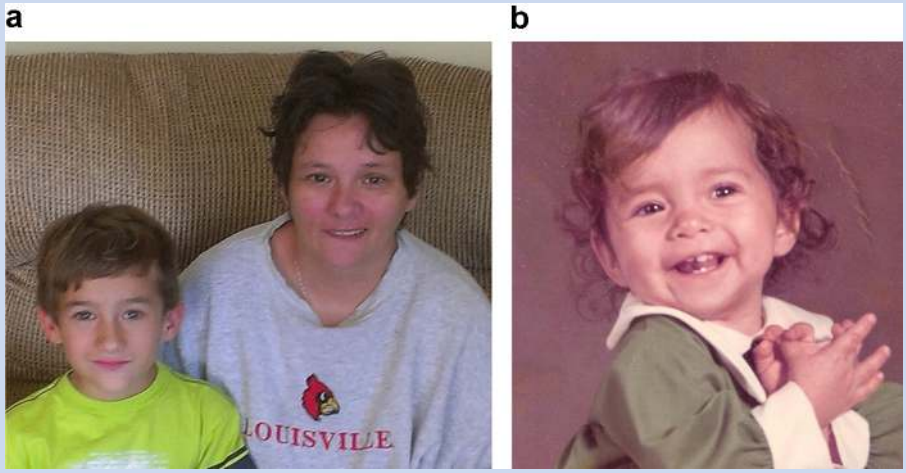

FIG. 1. a: Family #1: The proband and his mother at age 5 and 40 years, respectively. b: Family #1: The proband's mother at age 9 months of age.

parents had a history of learning difficulties. The proband was born at term to consanguineous (first cousin) parents. Her birth weight was 2.7 kg. She was admitted to the neonatal unit soon after birth because of respiratory distress and was treated with antibiotics for possible sepsis. She had a history of conductive hearing loss in early childhood and had pressure equalization tubes placed at 2 years of age. Family history was significant for a first cousin with learning difficulties who is able to live independently.

Developmentally, she smiled at 5 weeks, rolled front to back at 7 months and back to front at 9 months, sat unsupported at 7 months, and walked at 15 months. She had substantial speech delay and required speech and language therapy. She spoke her first words after 2 years of age and had two words by the age of 3 years. She had learning difficulties and attended mainstream school with one-to-one help. She attained low grades in secondary school and is now able to maintain a job as a housekeeper at a hotel. Formal intelligence testing was not performed. She has a uterine septum, however puberty was normal with menarche at 11 years. She has mild asthma, and no other significant medical history. An echocardiogram and electrocardiogram were normal. On physical examination, her head circumference was 54.7 cm (25th centile), height was 150 cm (<3rd centile). She had a bulbous nasal tip, mild micrognathia, and brachydactyly (Fig. 2a).

Her pregnancy was conceived naturally. First trimester screening was negative for Down syndrome. A 20-week ultrasound showed bilateral talipes equinovarus. A baby girl was born at 40 weeks gestation by elective caesarean because of breech presentation. Birth weight was 2,970 g (10–25th centile). She had difficulty nursing in the neonatal period. At $6^{1}/_{2}$ months, she was able to sit unsupported and had normal tone and strength. She was able to bear weight on her legs, and was babbling with intonation. She had just started solid foods and was managing well with purees.

On examination at 6 months of age, she had a broad nasal bridge and micrognathia (Fig. 2b). She required surgery on her left ankle secondary to her tailpes equinovarus. An echocardiogram was normal.

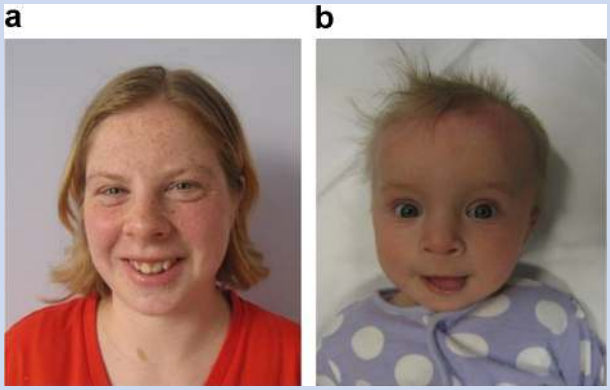

FIG. 2. a: Family #2: The proband (mother) at age 24 years. b: Family #2: The proband's daughter at age 6 months.

MOLECULAR FINDINGS

Clinical array CGH (aCGH) studies were performed on each proband and the daughter of proband 2, and revealed a microduplication within 17p11.2. Informed consent under a Baylor College of Medicine Institutional Review Board approved protocol was obtained for molecular characterization of the microduplication in those clinically tested as well as in the mother of proband 1 (who had not undergone clinical aCGH). We then isolated DNA from blood from each of the subjects and performed aCGH using a region specific high-density Agilent customized design to characterize the size, extent, and genomic content of the duplication. In both families, a 3.6 Mb common recurrent PTLS duplication was identified in both the mothers and the children (Fig. 3). There was no evidence of somatic mosaicism based on the $\log_2$ ratio of hybridization signal from array CGH. Array results were normal for the maternal grandparents in both families.

DISCUSSION

Detection of numerous clinically relevant submicroscopic copy number gains or losses from the clinical implementation of genome-wide assays including array comparative genomic hybridization (aCGH) has led to improved characterization of genomic regions flanked by LCRs and their corresponding microdeletion/duplication syndromes [Liu et al., 2011; Dittwald et al., 2013]. Clinical phenotypes manifest when dosage of gene(s) map within these regions [Lu et al., 2007].

While nearly all reported cases of PTLS have occurred sporadically without bias in the parental origin, we describe two additional families of inherited PTLS with maternal transmission of the common recurrent duplication. The children in these cases presented with feeding difficulties, hypotonia, and developmental delay, whereas the parents presented with intellectual disability (ranging from mild to moderate) and varying degrees of neuropsychiatric phenotypes, such as bipolar disorder, anxiety disorder, attention deficit disorder, learning disability, and seizures. Though in retrospect, the mother in Family 1 had a history of feeding difficulties, failure to thrive, and hypotonia. In the previous clinical report from Yusupov et al. [2011] the child was ascertained first secondary to a more severe clinical phenotype that included hypoplastic left heart, failure to thrive, and dysmorphic facial features. The mother reported in Yusupov et al. [2011] also had a history of feeding issues during childhood, language delay, and learning difficulties [Yusupov et al., 2011] but was not ascertained until her child was diagnosed with PTLS.

It is interesting to note that the child in Family 2 with PTLS had severe talipes equinovarus requiring surgical intervention and diagnosed by prenatal ultrasound. Although this is a not an uncommon birth defect (occurring in 1/1,000 births) it is also a common presentation of Charcot-Marie Tooth (CMT) neuropathy [MIM#118220] [Dietz, 2002]. CMT is most often caused by a duplication of *PMP22*; a myelin gene that maps just distal to the PTLS duplication region in chromosome 17p12. Recent work from mouse models documents a "spreading effect" of perturbed gene regulation beyond the interval contained within the duplication apparently due to disturbed/distorted chromatin and gene

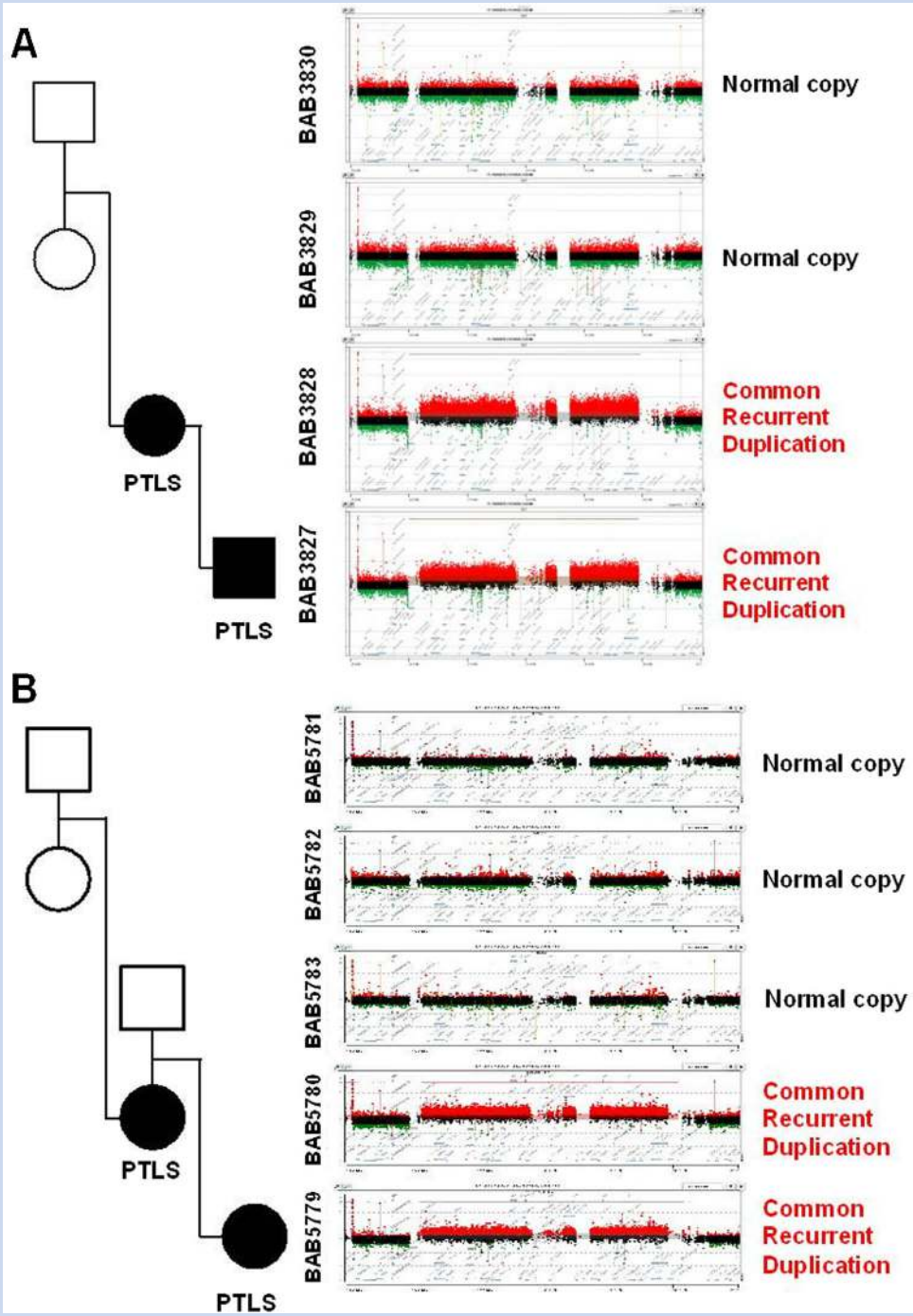

FIG. 3. Common recurrent PTLS duplication is transmitted from mother to child in two families (A - Family #1; B - Family #2). In both families, aCGH identified a 3.6 Mb common recurrent PTLS duplication in the mother and the child (BAB3828, BAB3827; BAB5780, BAB5779). There is no duplication in the other family members tested [color figures can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833].

dysregulation [Ricard et al., 2010]. One might speculate that the common 3.6 Mb PTLS duplication, although not containing the *PMP22* gene, might distort its regulation enough to contribute to the susceptibility to the talipes equinovarus deformity. Further studies in many individuals with PTLS will be required to confirm or refute such a hypothesis, but for many CNVs the contributions to abnormal phenotypes resulting from gene dosage versus position effects remains to be determined [Lupski and Stankiewicz, 2005].

Consistent with the contention that microduplications usually confer a relatively less severe phenotype when compared

to microdeletions, individuals with PTLS are generally thought to have a milder phenotype than individuals with SMS [Potocki et al., 2000]. When the transmission of the SMS deletion and PTLS duplication were investigated in the mouse model, it was shown that embryonic survival is significantly impaired in the deletion (SMS) mouse, but appears to be unaffected in the duplication (PTLS) mouse [Ricard et al., 2010]. Given the more severe birth defects, developmental, and intellectual impairments caused by the SMS deletion in humans, one would not expect a high incidence of germ line transmission in this population. To date, no constitutional SMS transmission has been reported. There is one case of mosaic transmission where the mother, who had low-level mosaic SMS deletion, and therefore a milder phenotype, transmitted the deletion to her child, who had the common SMS phenotype [Zori et al., 1993]. Based on these reports and the previous report in the literature, it appears that adults with PTLS have milder developmental and intellectual impairments when compared to SMS, therefore, the risk of transmission, as well as various reproductive options, should be discussed with all adults with PTLS as they approach reproductive age.

This report of two families with inherited chromosome 17p11.2 duplication illustrate the clinical and phenotypic variability of individuals with PTLS. The identification of adults with PTLS underscores the importance of genetic evaluation and testing in any adult with cognitive impairments or neuropsychiatric disorders. The diagnosis of adults with PTLS, or other genetic conditions, will enable better delineation of the natural history of these conditions while providing appropriate genetic counseling, reproductive options, and anticipatory guidance to the families. Further longitudinal studies of children and adults with PTLS are needed to identify the range of variability that can be observed within this syndrome, any age-dependent issues that may arise over time, and to establish the long-term prognosis for individuals with this condition.

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