Cognitive and Behavioral Characterization of the Potocki-Lupski Syndrome (Duplication 17p11.2)

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ABSTRACT: ***Objective:*** **To describe the cognitive and behavioral phenotypic features of the Potocki-Lupski syndrome (duplication 17p11.2), a recently recognized syndrome with multiple congenital anomalies and developmental delays.** ***Method:*** **Fifteen subjects were enrolled in an extensive multidisciplinary clinical protocol. Cognitive and behavior evaluations included a parent-report medical and psychological history form, intellectual assessment and assessments of adaptive behavior, executive functioning, and maladaptive behavior and emotions. Eight of the families completed an Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule-Generic.** ***Results:*** **The majority of patients (13 of 15) presented with intellectual disability. Moreover, the majority of patients also had moderate to severe behavioral difficulties, including atypicality, withdrawal, anxiety, and inattention. Many patients characterized also presented with autistic symptom pictures, some of whom (10 of 15) met diagnostic criteria for an autistic spectrum disorder, namely autistic disorder or pervasive developmental disorder not otherwise specified.** ***Conclusion:*** **This work expands on the behavioral phenotype of duplication 17p11.2 (Potocki-Lupski syndrome). Further phenotypic analysis will aid in clinical diagnosis, counseling, and management of this newly characterized microduplication syndrome. The association between this syndrome and autistic spectrum disorder may contribute to further understanding the etiology of the pervasive developmental disorders**

(*J Dev Behav Pediatr 31:*137–143, 2010) **Index terms:** Potocki-Lupski syndrome, autism spectrum disorder, intellectual disability.

The Potocki-Lupski syndrome (PTLS: MIM 610883) is a newly recognized microduplication syndrome and results from an interstitial duplication of Chromosome 17 band p11.2. This chromosomal aberration is the homologous recombination reciprocal of the 17p11.2 deletion, which is associated with the Smith-Magenis syndrome (MIM 182290).[1,2] Although PTLS and Smith-Magenis syndrome share the same genomic region, the clinical and behavioral features of each syndrome are distinct.[3,4] The features of PTLS have recently been characterized and include infantile hypotonia, failure to thrive, congenital cardiovascular anomalies, sleep-disordered breathing, developmental delay, intellectual disability, and autism.[4] The incidence of this microduplication is predicted to be ~1 of 25,000 based on the genomic mechanism[2] and the ascertainment of patients with Smith-Magenis syndrome by routine G-banded chromosome analysis[5]; however, this is likely to be an underestimate, given the low sensitivity of routine cytogenetic analysis in detecting these aberrations. The availability of targeted array-based comparative genomic hybridization (aCGH) in clinical diagnostic laboratories has revolutionized the early detection and diagnosis of these and other genomic disorders because the sensitivity for detection of microdeletions and microduplications of specifically targeted regions approaches 100%.[6]

Although PTLS was only recently characterized as a syndromic diagnosis, there are several clinical reports in the medical literature describing general features of persons with duplication in this portion of chromosome 17p, including nonspecific developmental delay, intellectual disability, and minor dysmorphic features (triangular face, down-slanting palpebral fissures, and mild micrognathia).[2,7–15] (Fig. 1 and figures, Supplemental Digital Content 1, http://links.lww.com/JDBP/A2). The most common medical clinical features in these patients included hypotonia, poor feeding, failure-to-thrive in infancy, obstructive and central sleep apnea, and electroencephalography abnormalities. Hypermetropia, mild scoliosis, and cardiovascular abnormalities were also found in a smaller portion of patients.[4] Only 2 patients in early reports[2,14] were recognized to have features of autism. The report by Potocki et al (2007) was the first

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Figure 1. 13-year, 11-month-old girl with PTLS. No strikingly dysmorphic features are present, yet she has facial features that are shared amongst other individuals with Potocki-Lupski syndrome (PTLS), including a triangular appearance to the face, a gentle down-slant of the palpebral fissures, hypoplasia of the alae nasi with the nasal tip protruding below the nares, and retrognathia.

to ascribe autism as a variable clinical feature of this microduplication syndrome. Subsequent case reports have inconsistently reported this finding.[16,17] Herein, the behavioral and cognitive profiles of 15 patients with PTLS, duplication 17p11.2, are reported.

METHODS

Patient Ascertainment

From June 1997 to June 2007, 15 subjects were enrolled in a multidisciplinary clinical study through the General Clinical Research Center at Texas Children's Hospital in Houston, under a 5-day protocol approved by the Baylor College of Medicine Institutional Review Board. Generally, families were referred to the study by the subjects' clinical geneticists, based on results of the subjects' genetic testing, previous publications by the authors about Potocki-Lupski syndrome and information about the study posted on the Baylor College of Medicine website. Some families were self-referred. Determination of participation was based on genetic testing results, age of the patient (older than 2 years), and availability and willingness of the family to travel to the study site and participate in the evaluation. During the study period, ~70 families contacted the project-seeking information. Protocol funding limited participation to 5 subjects per year. Subjects were accepted on a first-come, first-served basis. Symptom presentation and severity were not factors in selection for study participation by the research team. Clinical evaluations performed included physical examination, developmental and cognitive assessment, psychiatric history and examination, ophthalmologic and otolaryngologic examinations, audiological assessment, overnight sleep study and multiple sleep latency test, echocardiogram, renal ultrasound, scoliosis survey, radiographs of forearms and hands, lipid profile, and thyroid function studies. The initial protocol was identical to that used in the Smith-Magenis syndrom studies,[3,18] so that clinical features of patients with duplication at 17p could be directly compared with those patients with deletion at 17p. Informed consent was obtained from a parent or legal guardian of each patient. Cytogenetic and molecular analysis in this protocol has been previously described.[4,18]

Cognitive and Behavioral Assessment

Early in the project, psychological assessment was specifically developed around the cognitive and behavioral concerns that were presented by each family, including intellectual assessment and adaptive behavior. After the first 10 patients were assessed, and a better understanding of the phenotype evolved, a core evaluation battery was developed. Subsequently, each family completed a comprehensive parent report medical and psychological history form. For children younger than 5 years, 0 months of age, the following core battery was used: the Mullen Scales of Early Learning—American Guidance Service Edition,[19] the Vineland Adaptive Behavior Scales—Second Edition,[20] the Behavior Assessment System for Children—First or Second Edition,[21] and the Behavior Rating Inventory of Executive Functions—Preschool Version.[22] For children 5 years, 1 month and older, the following core battery was used: the Stanford-Binet Intelligence Scales, Fifth Edition, Abbreviated Battery,[23] the Leiter International Performance Scales,[24] the Vineland Adaptive Behavior Scales—Second Edition, the Behavior Assessment System for Children—First or Second Edition, and the Behavior Rating Inventory of Executive Functions.[25]

Psychiatric Assessment

The first 7 subjects underwent 2-hour psychiatric clinical evaluations, consisting of a 1-hour parent interview and a 1-hour interactive diagnostic interview with the patient. All of the patients except 1 were seen by the same child psychiatrist who incidentally had extensive experience diagnosing autism. Information that would support or refute a diagnosis of a disorder in the autistic spectrum was not systematically obtained, especially in the beginning of the study, because it had not been

hypothesized that this disorder was likely to be found in this population. Preliminary findings from the first 7 patients led to an alteration in the psychiatric assessment process, with eventual implementation of a more comprehensive, yet targeted parent-report medical and psychological history form, an Autism Diagnostic Interview-Revised[26] and an Autism Diagnostic Observation Schedule-Generic[27] by a clinician trained to research reliability. Eight families completed the history form and an Autism Diagnostic Interview-Revised and 8 patients participated in an Autism Diagnostic Observation Schedule-Generic, 5 with Module 1, 2 with Module 2, and 1 with Module 3.

RESULTS

Fifteen duplication 17p11.2 patients completed the evaluation. There were 9 boys and 6 girls. All patients were Caucasian. The age range was from 2 years, 1 month to 14 years, 5 months, with a mean age of 6 years, 1 month. Eleven patients had the common ~3.7 Mb interstitial duplication. The results of the molecular analysis were previously reported[4,8] (James R. Lupski, personal communication, 2009) and are summarized as follows: 2 patients had duplications larger than the common duplication (5 Mb, 8.2 Mb); 1 patient had a small duplication (1.3 Mb); and 1 patient had a mosaic marker chromosome containing the 17p11.2 region.

Cognitive and Behavioral Assessment Results

Within the current sample, 6 children were assessed with the Mullen Scales, 7 with the Stanford-Binet, Fourth Edition or Fifth Edition, and 1 with the Wechsler Intelligence Scales for Children—Third Edition. All 15 children were administered the Vineland Adaptive Behavior Scales (VABS) or VABS—II. In addition, 8 children were administered the Behavior Assessment System for Children—Second Edition; 5 children were administered the Behavior Rating Inventory of Executive Functions or Behavior Rating Inventory of Executive Functions—Preschool Version.

All children in the sample who were administered the Mullen Scales of Early Learning earned an Early Learning Composite score in the impaired range (mean = 52; range from 49 to 69). On the VABS/VABS-II, 5 of the 6 children earned an Adaptive Behavior Composite score in the impaired range (mean = 58.4; range from 48 to 74). As a result, 5 of the 6 children younger than the age of 5 years were found to be functioning in the mild to moderate intellectual disability (ID) range (Table 1).

With the older children, who were either administered the Stanford-Binet or the Wechsler Scales, 7 of the 8 children were performing in the impaired range (<70 T) on the Total or Combined IQ score (mean = 52.63; range from 36 to 80). Seven of the 8 children also had a Composite score in the impaired range (mean = 54; range from 28 to 78) on the VABS/VABS-II. Thus, 7 of the 8 older children were diagnosed with ID, all in the moderate range. The final child was functioning in the borderline range of intellectual ability but had a significant amount of scatter within his scores, spanning the moderately impaired to average range (Table 1).

Behavioral difficulties for the children in this study were assessed primarily through the use of the Behavior Assessment System for Children[28] and Behavior Assessment System for Children—Second Edition. On this instrument, the majority of the children had moderate to severe behavioral difficulties. Specifically, 100% of the 8 children were in the at risk to clinically significant range for atypicality; 88% were in the at-risk or clinical range for Withdrawal and Attention Problems; and 77% were in the at-risk or clinical range for somatization. Finally, >50% of the children's parents reported symptoms in the at-risk or clinically significant range for the Hyperactivity and Anxiety scales.

On the Behavior Rating Inventory of Executive Functions or Behavior Rating Inventory of Executive Functions—Preschool Version, all 5 children showed significant problems with executive functioning with a Global Executive Composite in the clinical range. More specifically, 4 of the 5 children were in the clinical range regarding their ability to shift from one activity to another, to initiate, and to use working memory. In the area of emotional control, 3 of the 5 children were reported to have clinically significant problems.

Psychiatric Interview Results

Parent histories and clinical interview reports were scrutinized to identify signs and symptoms that comprise a DSM-IV-TR[29] diagnosis in the autistic spectrum. A qualitative description of reported and observed behaviors follows.

Social Interactions

Five of the 7 subjects had limited eye contact that was not used appropriately to modulate social interaction; 1 subject clearly exhibited appropriate eye contact and also demonstrated initiation of joint attention, response to joint attention, appropriate play with toys for his developmental level, showing of items to others, and appropriate social overtures. Another subject demonstrated some social strengths, including response to joint attention, social smile, and showing items to others; however, the subject did not initiate joint attention and made some inappropriate social overtures. Three children did not respond to their names called by the examiner or by their parents. One youngster had a history of and clearly demonstrated the use of another's body to communicate. Two children had decreased or absent gesture usage, although this ability was specifically noted to be present in 1 youngster. A full range of facial expressions was particularly noted in 1 child.

Communication

All 7 subjects were reported to have and demonstrated significant language delay. This was also substantiated by their cognitive evaluations. Four subjects were echolalic, by report or observation. Three youngsters with communicative speech had intona-

Table 1. Intellectual Development and Adaptive Functioning in Children With PTLS

Age[a] and Gender	2–1 Female	2–8 Female	2–9 Female	3–3 Female	4–2 Male	4–10 Male
Mullen Early Learning Composite Standard Score (percentile)	50 (1st)	49 (<1st)	69 (2nd)	49 (<1st)	49 (<1st)	49 (<1st)
Gross Motor Age Equivalency	0–8	1–9	1–11	1–10	1–10	1–5
Visual Reception Age Equivalency	1–1	1–2	2–0	1–6	2–7	0–10
Fine Motor Age Equivalency	1–6	1–3	1–6	1–6	2–7	1–0
Receptive Language Age Equivalency	0–7	1–1	2–5	1–1	2–4	1–1
Expressive Language Age Equivalency	0–9	1–2	2–5	1–2	1–6	0–6
Vineland Adaptive Behavior Composite Standard Score (percentile)	54 (<1st)	67 (1st)	74 (4th)	53 (<1st)	49 (<1st)	48 (<1st)

	5–5 Male	5–9 Male	9–4 Female	9–6 Male	9–9 Male	9–10 Male	12–11 Female
Stanford-Binet Composite Standard Score (percentile)[b,c]	53 (<1st)	80 (9th)	69 (1st)	36 (<1st)	36 (<1st)	65 (<1st)	36 (<1st)
Verbal Reasoning Composite Score	62	89	69	38	37	78	36
Abstract/Visual Reasoning Composite Score	70	76	76	36	50	68	32
Quantitative Reasoning Composite Score	60	88	86	40	42	80	48
Short-Term Memory Composite Score	52	57	64	36	—	57	36
Vineland Adaptive Behavior Composite Standard Score (percentile)	—	78 (7th)	65 (1st)	32 (<1st)	20 (<1st)	—	30 (<1st)

[a]Age listed as years and months. [b]One child (14 yrs, 5 mo, male) was administered the Wechsler Intelligence Scales for Children—Third Edition; Verbal IQ for that child was 46, Performance IQ was 46, and Full Scale IQ was 40; Vineland Adaptive Behavior Composite Standard Score was 39. [c]One child (8 yrs, 1 mo, male) was administered the Leiter International Performance Scale-Revised; Non-Verbal Intelligence Quotient (NVIQ) was 42; Vineland Adaptive Composite Standard Score was 28. —indicates missing data.

tion and prosody abnormalities, pedantic language, running commentaries, and reference to themselves in the third person.

Restricted and Repetitive Behaviors

Five children were reported to have or demonstrated repetitive behaviors and/or odd preoccupations. Three were specifically noted to have extreme difficulty with transitions. Four were found to have sensory preoccupations and an overlapping group of 4 had abnormal responses to sensory stimuli. Four demonstrated motor mannerisms or posturing.

Other Behaviors

Three of the youngsters demonstrated significant hyperactivity. One was aggressive with self-injurious behavior by history. One youngster was reported to have unusual fears.

Systematic Evaluation of Autism Symptoms

Eight subsequent families completed an Autism Diagnostic Interview-Revised (ADI-R); these 8 children were also evaluated by the Autism Diagnostic Observation Schedule-Generic (ADOS-G), Modules 1, 2, or 3, based on expressive language skills and overall developmental level. The children evaluated by ADI and ADOS ranged in age from 2 years, 1 month to 9 years, 9 months. There were 5 boys and 3 girls. The youngest child's mental age was younger than 24 months, decreasing the strength and reliability of diagnostic conclusions; however, the findings are reported as accurate descriptions of her behavior. Five subjects were preverbal or used only single words, 2 used phrase speech, and 1 had fluent speech. Based on the combined scores of the ADI-R and ADOS-G, as well as clinical assessment, 5 children met criteria for autism or pervasive developmental disorder not otherwise specified. Three were not felt to meet criteria for any autistic spectrum disorder but did have features often seen in these disorders. (See Table, Supplemental Digital Content 2, for specific ADI-R and ADOS-G scores, http://links.lww.com/JDBP/A3).

Diagnostic Conclusions

Of the 7 children seen earlier, without the benefit of a more systematic evaluation for an ASD disorder, 2 children did not appear to meet criteria for any ASD;

Table 2. Diagnostic Conclusions for Children With PTLS

Age at Evaluation	Gender	Type of Duplication[c]	Intellectual Disability	Autistic Spectrum Disorder
2 yrs, 1 mo	Female	Large (5.0 Mb)	Yes	Yes[a]
2 yrs, 8 mo	Female	Common	Yes	Yes[a]
2 yrs, 9 mo	Female	Common	No	Yes[b]
3 yrs, 3 mo	Female	Common	Yes	No[b]
4 yrs, 2 mo	Male	Common	Yes	No[b]
4 yrs, 10 mo	Male	Large (8.2 Mb)	Yes	Yes[b]
5 yrs, 5 mo	Male	Common[d]	No	No[a]
5 yrs, 9 mo	Male	Common[d]	No	Yes[a]
8 yrs, 1 mo	Male	Small (1.3 Mb)	Yes	Yes[a]
9 yrs, 4 mo	Female	Mosaic marker[e]	Yes	Yes[a]
9 yrs, 6 mo	Male	Common	Yes	Yes[a]
9 year, 9 mo	Male	Common	Yes	No[a]
9 yrs, 10 mo	Male	Common	Yes	Yes[b]
12 yrs, 11 mo	Female	Common	Yes	Yes[b]
14 yrs, 5 mo	Male	Common	Yes	Yes[b]

[a]Diagnosed with the use of the ADI-R and the ADOS. [b]Diagnosed by review of records. [c]All patients reported in Potocki et al[4] except when noted. [d]Reported by J. R. Lupski, MD, personal communication. [e]Reported in Yatsenko et al.[8]

4 met criteria for autism or PDD-NOS and further evaluation would have been necessary to clarify the diagnosis of the final subject, who was not available for reassessment secondary to geographical constraints. Clinically, 5 of the 8 children evaluated by ADI-R and ADOS-G were felt to meet criteria for an autistic spectrum disorder. Two others had positive ADI-R results (parent report measures), although they did not meet criteria for ASD diagnoses based on their ADOS-G results. Only 1 child did not meet diagnostic criteria based on the results of both his ADI-R and ADOS-G.

Of the 15 children who had a systematic cognitive and behavioral assessment, 13 of the 15 children (86%) were found to have ID, mostly in the moderate range. Of the 2 children who were not found to have ID, 1 child failed to meet criteria because her Vineland Adaptive Behavior Scale score was not in the impaired range. The second child was found to be performing in the borderline to low average range of intellectual and adaptive functioning. Notably, this child also did not meet criteria for an autistic spectrum disorder (Table 2).

Behaviorally, most of the children had significant issues. All were reported to have a high number of atypical behaviors and executive functioning deficits, even those who did not meet criteria for an autistic spectrum disorder or ID. In addition, the majority also demonstrated problems with withdrawal, again, even those children who did not meet criteria for an ASD. Problems with attention, reported in all but 1 child, may have been related to the cognitive functioning profile of moderate ID that has been found with this population. Furthermore, the parents reported a high number of somatic complaints for their children. It is difficult to interpret this, given the number of medical problems that have been associated with Potocki-Lupski syndrome.[4] Finally, more than one half of the children were reported to have high levels of hyperactivity and anxiety.

DISCUSSION

This report describes the cognitive and behavioral profiles of 15 children with Potocki-Lupski syndrome (PTLS) (duplication 17p11.2). In contrast to earlier reports of a relatively mild behavioral phenotype of this chromosomal abnormality,[2] our findings indicate that PTLS is associated with autistic spectrum disorders, moderate intellectual disability, and significant behavioral disturbances. Autistic traits have been recognized in some patients with PTLS.[14,30] Our data, supported by others,[16,17] indicate that autistic spectrum disorder (ASD) is not an absolute feature of PTLS; however, our report strongly suggests that 17p11.2 is yet another genomic region implicated in the genetically heterogeneous disorder of autism.[31] The behavioral phenotype of children with PTLS in this small sample appears to include difficulties with atypicality, withdrawal, hyperactivity, inattention, anxiety, and somatic complaints. This small sample size does not allow for determination of the mechanism or explanation of the observed phenotypic variability. However, we speculate that, as with other genetic conditions, both environmental and genetic factors contribute to this finding. Specific factors that might relate to this genomic disorder include differences in the size of the duplication, the specific genes located in varying duplication intervals, and the effect of modifying genes outside of the locus of the duplication. However, it would not be unexpected to observe phenotypic variability even in patients with identical duplications be-

cause this phenomenon was demonstrated in a large cohort of subjects with Smith-Magenis syndrome with the common deletion.[18] The determination of the actual prevalence of ASD in PTLS will depend on neuropsychiatric evaluation of additional patients. The influence of ascertainment bias secondary to self-selection by families affected by PTLS cannot be accurately estimated: the severity of some children's symptoms may have precluded travel, whereas symptom severity may have prompted other families to participate in the project. Further delineation of cognitive impairments, behavioral disturbances, and psychological symptoms, as well as risk for ASDs, will be needed to enable health care providers and educators to monitor patients more effectively, deliver more appropriate interventions, and provide more reliable information regarding prognosis.

Advances in technology in the clinical genetic laboratory have allowed the identification of numerous regions across the genome that are associated with ASD.[32–34] Array-based comparative genomic hybridization, in particular, is an essential diagnostic tool because abnormalities in genomic copy number escape detection by routine chromosome analysis. To that point, PTLS is a previously unrecognized genomic disorder caused by an increased copy number of 17p11.2 including the dosage sensitive *RAI1* gene. Deletion or mutation of the retinoic acid-induced 1 (*RAI1*) gene within 17p11.2 results in Smith-Magenis syndrome,[35] whereas duplication of *RAI1* is implicated in PTLS. Although the exact function of *RAI1* has not been determined, murine models have shown that normal dosage of *RAI1* required for normal behavior.[36] Modifier genes both within the common (3.7 Mb) interval and at other loci likely play a role in the physical and neurological characteristics of these disorders. Our findings lend further support for use of microarray analysis in children and adults with developmental disorders, cognitive impairment, and ASD regardless of the presence or absence of distinctive or dysmorphic craniofacial features.

The association of ASD with PTLS may also add to the body of work that will explain the underlying architecture and pathophysiology of autism. Multiple rare mutations have been implicated in the etiology of autism, although causality remains to be strictly proven. Major gene effects, de novo mutations and inherited variants, may together represent 10%–20% of cases with ASD. Exploring the nature of variable expressivity and incomplete penetrance may reveal the manner in which common alleles interact with rare mutations. ASDs of varying etiologies may, or may not, share common molecular mechanisms or pathways. Therefore, the elucidation of any gene to clinical manifestation mechanism may illuminate processes common to many ASDs. The overlap between intellectual disability, or other neuropsychiatric symptoms such as inattention or anxiety, and autism at the level of brain structure and function may be better understood by studying those single gene conditions in which the combination of these disorders or symptoms occurs variably. Thus, the study of even quite rare genetic anomalies associated with ASDs may prove enormously fruitful.

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