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Case Report

Searching for Potocki–Lupski syndrome phenotype: A patient with language impairment and no autism

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Abstract

Potocki–Lupski syndrome (PTLS; OMIM 610883) is a genomic syndrome that arises as a result of a duplication of 17p11.2. Although numerous cases of individuals with PTLS have been presented in the literature, its behavioral characterization is still ambiguous. We present a male child with a *de novo* dup(17)(p11.2p11.2) and he does not possess any autistic features, but is characterized by severe speech and language impairment. In the context of the analyses of this patient and other cases of PTLS, we argue that the central feature of the syndrome appears to be related to diminished speech and language capacity, rather than the specific social deficits central to autism.
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1. Introduction

Potocki–Lupski syndrome—arising as a result of a duplication of 17p11.2—has been associated with a wide range of congenital anomalies such as ophthalmic, cardiovascular, orthopedic, oral-pharyngeal, and renal

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abnormalities, microcephaly, distinct facial features, including pronounced nose, ears, and forehead and geometrical (triangular or square) faces, and a number of cognitive and behavioral indicators of developmental delay. Intellectual functioning in described cases ranges from borderline to severe intellectual disability. Similarly, the range of behaviors is broad, with some reports citing autism-spectrum disorder (ASD) behaviors, obsessive–compulsive behaviors, hyperactivity and aggression, or the presence of some or all such behaviors. Arguably, the most common features of patients with PTLS are feeding difficulties and failure to thrive in infancy, and speech and language impairments [1,2]. Here we report on a male child with *de novo* maternally inherited dup(17)(p11.2 p11.2) identified by the Human *1M*-Duo *Bead array* (*Illumina*). This patient has severe language difficulties without pronounced intellectual disability, autistic features or evidence of structural brain abnormalities.

2. Clinical report

The patient was referred to the Child Study Center of Yale Medical School at 10:10 years of age. During an otherwise uneventful pregnancy, amniocentesis performed at 16 weeks indicated a paracentric inversion on the long arm of chromosome 8, which is also present in the patient's father and paternal grandmother, both of whom are high-functioning individuals. The patient was a full-term baby boy, 2890 gm at birth, delivered via an uncomplicated vaginal delivery. His APGAR scores were 7 at 1 min, and 9 at 5 min. Immediately after birth, the patient reportedly had difficulty learning to nurse but readily drank from a dosing cup. Within 4–5 days he began nursing and was eventually weaned at 10 months. Although motor milestones (sitting independently at 9 months, standing at 12, walking at 13–15) were all met at the late end of normal limits, his fine motor skills remained challenged for a while. The patient's first words (i.e., "moo", "maa") appeared at 18 months, but he did not say his first real words until 3 years of age, and did not start generating simple 3–5 word phrases until 4. Reportedly, his early speech was "very difficult to understand". At the time of evaluation, a consistent misarticulation of the /r/ phoneme was observed. An oral-mechanism examination ruled out the presence of gross anomalies of oral structures and functioning, although several mild to moderate deviations were observed. The patient could follow spoken directions if they were repeated, which was especially necessary for multi-step directions. He began speech therapy at 2:8 years, which was reportedly "initially unproductive"; he was then taught sign language at 2:10 and started to sign as soon as he was exposed to it. Multiple developmental and psychological evaluations were performed. Table 1 summarizes past diagnoses and the results of psychometric assessments (a range of percentiles is shown for a variety of assessments). The patient attended a regular public school in the USA, but received special education accommodations. His cognitive performance was remarkably uneven, ranging from extremely low to average; specifically his performance was consistently low in the verbal domain and higher in the visual-spatial domain. The patient had learned how to read and write and his mathematic skills were in the average range. Both the receptive and expressive skills of the patient remained low or extremely low, regardless of the intensive therapies he received. There is no indication that aggression, lack of sociability (or any autism-related features), or obsessive–compulsive behavior had been registered. Functional MRI studies (Supplementary data) did not detect any pronounced structural or functional brain abnormalities, with the exception of, compared to his typical peers, the relatively low activation levels in the left transverse temporal gyrus (for speech perception

Table 1
The patient's phenotype across ages and multiple domains.

Assessments and diagnoses	Age					
	4:9	5:7	6:4	8:7	10:10	11:5
				%-ile[b]	%-ile	%-ile
Diagnoses[a]	E, D, DD	SLD	RD, DWE, LD, ELD			
Intellectual functioning				1–50	2–37	1–18
Adaptive functioning						6–53
Speech and language				1–6	1–6	1–6
Academic functioning				1–16		1–32

[a] E = encephalopathy, unspecified; D = dyspraxia or lack of coordination; DD = developmental delay (delayed developmental milestones); SLD = speech and language disability; RD = reading disorder; DWE = disorder of written expression, LD = learning disorder not otherwise specified (NOS); ELD = expressive language disorder.

[b] Range of percentiles on a wide variety of psychological and psychoeducational assessments. As for Standard Scores (SS) for the patient's two evaluations at Yale, they were 80 and 75 at the 9th and 5th percentile ranks on fluid and crystallized indexes, respectively, of the Kaufman Assessment Battery for Children, Second Edition. For reading, SS were 71, 67, and 68 at the 2nd, 1st, and 2nd%-ile on the Word Recognition, Pseudoword Decoding, and Reading Comprehension subtests of the Kaufman Test of Educational Achievement. For writing, SS were 75 and 63 at the 5th and 1st%-ile on the Spelling and Written Expression subtests of the Kaufman Test of Educational Achievement. For mathematic skills, SS were 93 and 82 at the 32nd and 12th%-ile on Computation and Concepts and Application subtests of the Kaufman Test of Educational Achievement.

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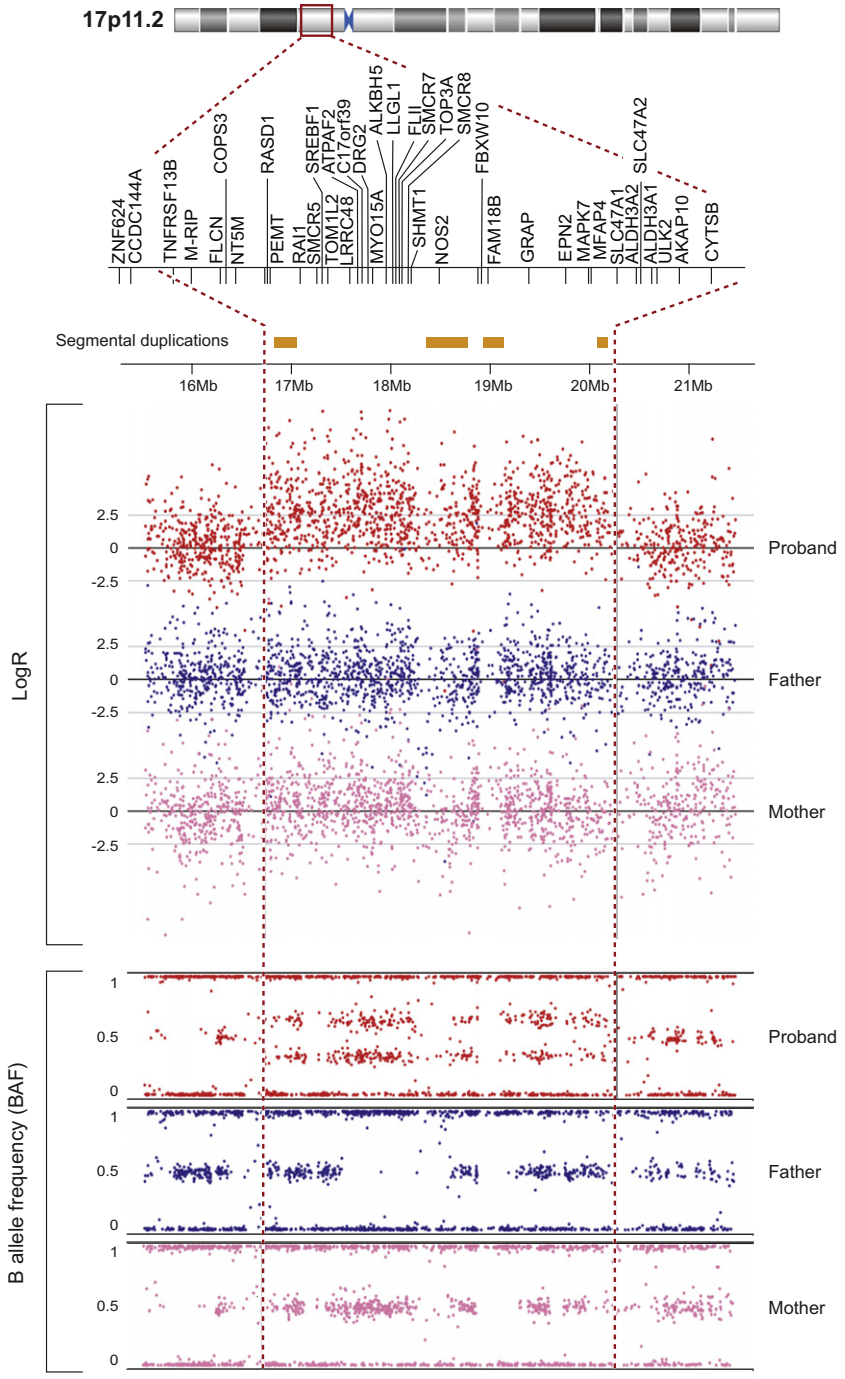

Fig. 1. Figure shows duplication at 17p11.2 at positions 16,497,803 and 20,292,768 bp of build NCBI36/hg18. The increase in the log *R* ratio values (log *R* ratio zero represents diploid copy number and increased log2 ratios represents duplicated regions) and the split in the B allele frequencies (BAF; allelic composition) plotted for each SNP.

tasks) and relatively high activation levels in the left fusiform gyrus (Supplementary data).

3. Discussion

We presented here a case of PTLS which, both behaviorally and in terms of the specifics of his brain functioning, does not fit the categorization of ASD and permits the formulation of the hypothesis that the central feature of PTLS is in language (not social) dysfunction. Although it has been reported that 80% of PTLS patients show some autistic features [2,3], there are reports of individuals with PTLS who demonstrate none of these features [1,4]. Whereas the centrality of autism-associated features for

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the phenotype of PTLS has been questioned, what has not been questioned is the presence of speech and language impairments in this genomic disorder. However, the types and degrees of these impairments have been neither qualified nor quantified precisely. With the exception of a recent publication that details the behavioral phenotypes of 15 individuals with PTLS [3], the majority of existing reports provide only very general, clinical accounts of the speech and language challenges encountered by individuals with this syndrome. Of critical importance is that although the extent of intellectual disability and social functioning appears to be quite variable across patients with the syndrome, speech and language impairment so far emerges as a consistent finding. Moreover, there are reports of cases in which general cognitive functioning, and especially nonverbal functioning, is higher than the levels of speech and language functioning, suggesting that these difficulties in PTLS are not simply a consequence of global intellectual delay. Also of interest are reports of prominent sucking/feeding difficulties in individuals with PTLS; there is evidence connecting such difficulties, regardless of their etiologies, with speech and language disorders [5,6].

In addition to the 17p11.2 duplication (Fig. 1), the patient was known to carry a paracentric inversion of 8q21.3–q24.1 (Supplementary data) and the same rearrangement had previously been confirmed in both the unaffected father and the paternal grandmother. Fine mapping using FISH showed that the inversion disrupts the gene, *EFCBP1*/*NECAB1* (EF hand calcium binding protein 1) [7] and syntrophin beta 1 (*SNTB1*), a dystrophin-associated protein [8]. *EFCBP1* has no expression in peripheral lymphocytes; this prevented a direct quantitative assessment of *EFCBP1* mRNA in the patient. We detected no change in the expression levels of *SNTB1* in the proband. Nonetheless we cannot rule out the contribution of these genes to the phenotype without measuring their expression in the brain cells.

Phenotypic variability appears to be quite common in genomic syndromes, and a variety of hypotheses, ranging from a two hit model [9], to occult compound heterozygous mutations within deleted regions [10], to epigenetic effects and environmental contributors, are all of intense interest with regard to understanding the complex genotype–phenotype relationships we observed. This manuscript contributes to the field's understanding of non-linear and complex relationships between the genome and behavior.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.braindev.2011.11.003.

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