CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Establishing *SON* in 21q22.11 as a Cause a New Syndromic Form of Intellectual Disability: Possible Contribution to Braddock–Carey Syndrome Phenotype

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Manuscript Received: 19 March 2016; Manuscript Accepted: 13 May 2016

A recent study of exome analyses in 109 patients with undiagnosed diseases included a 5-year-old girl with intellectual disability and multiple congenital anomalies, who had an apparently de novo frameshift mutation in *SON*. However, the combination of the truncating mutation in *SON* and the phenotype has not been reproduced until date, and it remains unclear if this combination represents a distinctive disease entity. Here we report an additional male with intellectual disability, congenital heart disease, distinctive facial features with curly hair and protruding ears, and long slender extremities, and hyperextensible joints. Exome analysis showed that he had the same de novo frameshift mutation in *SON* in a heterozygous state. Along with the first and original description of the apparently de novo truncating mutation in *SON* mentioned above, we have established that haploinsufficiency of *SON* causes a new recognizable syndrome of intellectual disability. *SON* is located within 21q22.11, a critical region for Braddock–Carey syndrome, which is characterized by congenital thrombocytopenia, intellectual disability, micrognathia, and a distinctive facies. Therefore, we suggest that the intellectual disability observed in Braddock–Carey syndrome could be accounted for by haploinsufficiency of *SON*. © 2016 Wiley Periodicals, Inc.

Key words: *SON*; intellectual disability; 21q22; Braddock–Carey syndrome; thrombocytopenia

How to Cite this Article:
Takenouchi T, Miura K, Uehara T, Mizuno S, Kosaki K. 2016. Establishing *SON* in 21q22.11 as a cause a new syndromic form of intellectual disability: Possible contribution to Braddock–Carey syndrome phenotype.
Am J Med Genet Part A 170A:2587–2590.

INTRODUCTION

Causative gene mutations in patients with intellectual disability/autistic spectrum disorders with or without accompanying malformations are currently being investigated in various exome analyses [de Ligt et al., 2012]. In a recent study of exome analyses in 109 trios with undiagnosed diseases, the supplemental information included a 5-year-old girl with intellectual disability, seizures, minor dysmorphisms, brain white matter abnormalities, intestinal atresia, and ventricular septal defect [Zhu et al., 2015]. This patient had two apparently de novo candidate genetic mutations: a missense mutation in *C5AR1* and a frameshift mutation in *SON*; which is a ubiquitously expressed and phylogenetically conserved gene that encodes a DNA-binding protein [Khan et al., 1994; Wynn et al., 2000]. Because typical newborns acquire at least one new de novo deleterious mutation per generation [Lynch, 2010], it remains unclear if the observation was a chance association or whether either/which of the two mutations was responsible for the phenotype. Documentation of the second, confirmatory patient with the combination of a phenotype similar to the first patient and a frameshift mutation in the same gene, *SON*, resolved the "n-of-1

Festschrift honoring John C. Carey
Grant sponsor: Ministry of Health, Labour, and Welfare; Grant sponsor: Keio University Research Grants; Grant sponsor: Japan Foundation for Pediatric Research; Grant number: 14-002; Grant sponsor: Grant-in-Aid for Scientific Research; Grant number: 16K09974.
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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 3 June 2016
DOI 10.1002/ajmg.a.37761

problem," and our data established an existence of a new human disease entity caused by a mutation in *SON*.

CLINICAL REPORT

The propositus was the first child of healthy unrelated parents. At delivery, the mother was 35 years old and the father was 30 years old. The pregnancy course was uneventful, except for mild maternal anemia. The propositus was born at 40 and 1/7 weeks of gestation by cesarean section, indicated for breech presentation and cephalopelvic disproportion. His birth weight was 2,560 g (−1.7 SD), length was 47 cm (−1.4 SD), and OFC was 35.0 cm (+1.2 SD). During the neonatal period, he had severe hypotonia and poor feeding, although he was able to take orally. He showed significant delay in psychomotor development. He rolled over at 20 months, crawled at 30 months, sat without support at 30 months, and walked with the support of a brace at 9 years of age. He showed severe intellectual disability. His developmental quotient was 23 at the age of 5 years, according to the Kinder Infant Development Scale, a developmental scale widely used in Japan.

At the age of 8 years, an echocardiography showed aortic valve regurgitation not associated with enlargement of the aortic root. Magnetic resonance imaging of the brain showed no abnormalities, and an electroencephalogram obtained at the age of 1 year was normal. Since his infancy, he continued to have polyuria of unknown cause, with screening ultrasonography showing no abnormalities of the renal or genitourinary systems.

At the age of 13 years, the patient still said no meaningful words, but he understood simple sentences and enjoyed emotional interactions with others. He was found to show poor growth at this age, with relative macrocephaly, height of 146 cm (−2 SD), weight of 27 kg (−2.5 SD), and OFC of 54 cm (+0.5 SD). He showed distinctive facial features with a prominent forehead, curly hair, sparse eyebrows, epicanthal folds, a flat nasal bridge, protruding ears, a short nose, and full cheeks (Fig. 1). His skeletal features included long, slender extremities with an arm span/height ratio of 105%, hyperextensibility of the interphalangeal joints of the hand and elbow joints, and maxillary hypoplasia. He had hyperextensible, velvety smooth skin.

MOLECULAR ANALYSES

The present research protocol was approved by the local institutional board review. Informed consent was obtained from the parents. DNA was extracted from a peripheral blood sample using the standard phenol extraction protocol. Exome analyses of the propositus, and his parents were performed on HiSeq 2500 platform (Illumina, CA) and SureSelectXT Human All Exon V6 (Agilent Technologies, Santa Clara, CA). The mean coverage of the exome sequencing was 102. The exome data from the propositus and his parents were filtered for candidate mutations using DeNovoCheck. In this algorithm, variants that were not identified in either parent with >2% variation reads were considered to be candidate de novo mutations [de Ligt et al., 2012]. After this filtering process with default parameters, a de novo frameshift mutation in exon 3 of *SON*, that is, c.5753_5756delTTAG (NM_138927.2) p.Val1918Glufs*87 (NP_620305.2) remained as the only variant in the coding region and represented a frameshift mutation in the patient. This mutation was the same as that previously reported in [Zhu et al., 2015]. Sanger sequencing confirmed the results. There were no other candidate genes in the autosomal recessive or X-linked inheritance models. Biologic parentage was affirmed by multiple mendelian consistencies in the exome data.

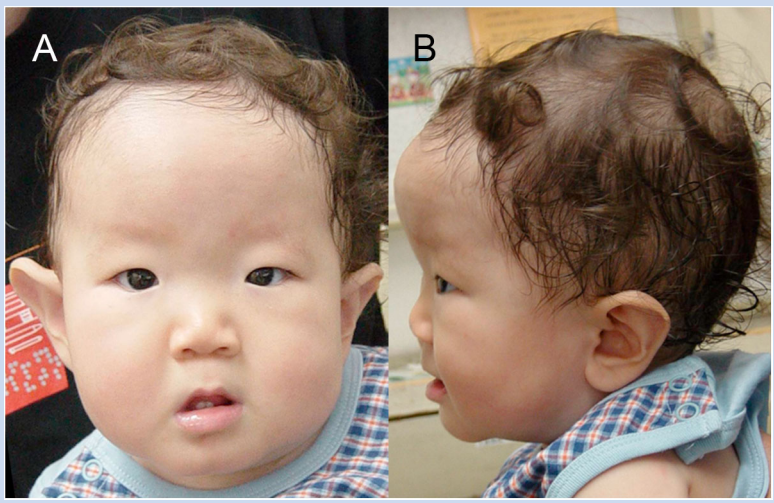

FIG. 1. Facial features in the propositus. Note the prominent forehead, curly hair, sparse eyebrows, epicanthic folds, flat nasal bridge, protruding ears, short nose, and full cheeks.

TABLE I. Clinical Characteristics of Patients With Braddock–Carey Syndrome and Patients With a *SON* Mutation

	Patient 1	Patient 2	Patient 3
Conditions	**Braddock–Carey syndrome (microdeletion syndrome)**		**Patients with *SON* mutation (single gene alteration)**
References	Braddock and Carey [1994]		Present report
Age/sex	30 months/female	3.5 years/female	13 years/male
Developmental delay/intellectual disability	+	+	+
Growth deficiency	+	+	+
Pierre Robin sequence	+	+	−
Thrombocytopenia	+	+	1[a]
Megakaryocytes in bone marrow	+	+	2[b]
Enamel hypoplasia	+	+	−
Large, posteriorly rotated ears	+	+	+
Curly hair	+	+	+
Renal malformation	−	+	−
Congenital heart disease	+	−	+
Camptodactyly/clinodactyly	+	+	−
Neuroimaging	Agenesis of corpus callosum	Agenesis of corpus callosum	No abnormalities

ND, not documented.
[a]1 because *RUNX1* Locus is spared.
[b]2 clinically not indicated.

DISCUSSION

Through trio exome analysis, we have identified a de novo heterozygous frameshift mutation in *SON* in a male patient with postnatal growth retardation with relative macrocephaly, distinctive facial features, infantile hypotonia, intellectual disability, long extremities with hyperextensible joints, cardiac abnormalities and a smooth velvety skin. His phenotype was similar to that in the previously reported patient with the same apparently de novo frameshift mutation in *SON* [Zhu et al., 2015]. The co-occurrence of a mutation in the same gene and similar clinical presentations in multiple unrelated individuals meets the currently proposed criteria for causality of sequence variants in humans [MacArthur et al., 2014]. The minimum number of patients with a de novo mutation that is required to establish a new disease entity has not yet been clearly defined. However, according to a simulation study performed in a systematic investigation of autism genes, two nonsense and/or splice site de novo mutations were highly unlikely to occur by chance when the candidate genes are expressed in the brain [Sanders et al., 2012]. Considering that *SON* is one of brain-expressed genes, it is strongly suggested that the de novo frameshift mutation in *SON* is responsible for neurological phenotype in the two patients. Therefore, we have established that haploinsufficiency of *SON* leads to a distinctive Mendelian disorder with intellectual disability. The shared features between the propositus and the previously reported patient reported by Zhu et al. [2015] included apparent intellectual disability, cardiac disease, and minor dysmorphic features of the face and limbs. Further investigation in a large cohort of patients is warranted to delineate the exact phenotypic spectrum of this new entity.

The microdeletion syndrome spanning the *SON* locus at 21q22 is known as Braddock–Carey syndrome. Braddock–Carey syndrome is characterized by congenital thrombocytopenia, intellectual disability, micrognathia, and a distinctive facies [Braddock and Carey, 1994]. There is a debate on the causative gene that is responsible for the developmental delay observed in the microdeletion syndrome in 21q22 (Table I). Using the classic approach of exclusion and inclusion mapping of microarray data, Fukai et al. [2014] proposed that *ITSN1* is responsible for the developmental delay. However, it remains unclear if other flanking genes also contribute to the developmental delay. The present observation of developmental delay in the setting of a truncating mutation in *SON* is not inconsistent with this hypothesis, but further demonstrates that haploinsufficiency of *SON* does play a significant role in the developmental delay observed in Braddock–Carey syndrome.

ACKNOWLEDGMENTS

We thank Mrs. Yumi Obayashi for her technical assistance in the preparation of this article. This work was supported by Research on rare and intractable diseases from the Ministry of Health, Labour, and Welfare, Japan, Initiative on rare and undiagnosed diseases from Japan Agency for Medical Research and Development, Keio University Research Grants for Life Science and Medicine, the Japan Foundation for Pediatric Research Grant No. 14-002, and Grant-in-Aid for Scientific Research (16K09974) from the Japan Society for the Promotion of Science.

INTERNET RESOURCES

DeNovoCheck: http://sourceforge.net/p/denovocheck/

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