INVITED COMMENT

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Jacobsen Syndrome, Braddock–Carey Syndrome, and Beyond: Reflections on Intellectual Disability Accompanied with Thrombocytopenia

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Intellectual disability accompanied by thrombocytopenia signifies a group of genetic disorders. This is best exemplified by 11q terminal deletion syndrome, so-called Jacobsen syndrome (OMIM #147791). The first set of patients reported by Jacobsen et al. [1973] exhibited intellectual disability, thrombocytopenia, and chromosomal translocation. This illustrates that careful clinical observation of patients supported by genetic evidence is the key to find new disease entities. The genotype–phenotype correlation in Jacobsen syndrome was later extensively delineated in a larger cohort of patients in this journal [Grossfeld et al., 2004].

Twenty years after the first description of Jacobsen syndrome, Stephen R. Braddock and John C. Carey from the University of Utah described two unrelated individuals with congenital thrombocytopenia, intellectual disability, Pierre Robin sequence, (i.e., cleft palate with micrognathia), microcephaly, and distinctive facial features [Braddock and Carey, 1994]. This led to the second recognizable syndromic form of thrombocytopenia, termed Braddock–Carey syndrome. Another 20 years elapsed after their first description of Braddock–Carey syndrome until the advent of microarray chromosomal testing, which led to the definition of this syndrome as a microdeletion syndrome at 21q22. Haploinsufficiency of *RUNX1* was considered as the cause of the thrombocytopenia [Braddock et al., 2011; Izumi et al., 2012].

After the identification of the genetic locus for thrombocytopenia in Braddock–Carey syndrome, the loci for the intellectual disability in this syndrome have also been gradually uncovered; the critical region for Braddock–Carey syndrome was shown to overlap with that of Down syndrome. Our group described a patient who presented with intellectual disability accompanied by thrombocytopenia together with a cleft uvula (i.e., a microform of cleft palate) and microcephaly, who had an apparently de novo 4 Mb deletion at 21q22, spanning the Down syndrome critical region. Intellectual disability accompanied by microcephaly in this patient could be attributable to haploinsufficiency of *DYRK1A* [Fujita et al., 2010a]. Similar observations have been documented in a larger cohort of patients [Fukai et al., 2014]. Recently, we encountered a patient with intellectual disability, cardiac disease, and dysmorphic facial features. This patient had an apparently de novo frameshift mutation in *SON*, which is located within the critical region for Braddock–Carey syndrome. Although pinpointing the cause of the intellectual disability is difficult, taking into consideration the prior report of a patient with a similar phenotype and the same frameshift mutation in *SON* [Zhu et al., 2015], we suggest that the developmental delay observed in Braddock–Carey syndrome may be attributable to haploinsufficiency of *SON* [Takenouchi et al., 2016a]. Because Braddock–Carey syndrome is a contiguous gene syndrome in 21q22, genes other than *SON* could contribute to its overall phenotype. The causative gene for cleft palate is yet to be identified.

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Besides Jacobsen syndrome and Braddock–Carey syndrome, we recently documented the existence of a yet another entity characterized by intellectual disability with thrombocytopenia [Takenouchi et al., 2015, 2016b]. This condition is caused by an apparently de novo mutation in *CDC42* at 1p36, a critical regulator of the cell cycle and actin cytoskeleton, and is now referred to as Takenouchi–Kosaki syndrome (OMIM #616737). A diagnostic caveat in this new entity is that measurement of hematological indices and blood smear examination are necessary to confirm the presence of macrothrombocytes.

As illustrated above, a single genomic alteration can lead to distinctive and typical combinations of malformations in addition to thrombocytopenia in Jacobsen syndrome, Braddock–Carey syndrome, and Takenouchi–Kosaki syndrome. The spectra of

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each of these malformation syndromes could be further masqueraded by the non-genetic disruptive effect of fetal hemorrhage occurring as a result of the thrombocytopenia. von Bubnoff et al. [2004] reported a transverse upper limb defect in a patient with Jacobsen syndrome. At that time, it was unclear if it was a chance association. Description of additional cases of Jacobson syndrome with a transverse limb defect by our group [Fujita et al., 2010b], and So et al. [2014] gave further credence to the hypothesis that the association had an etiological basis, presumably attributable to the thrombocytopenia.

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Professor Carey has always been a warm and encouraging teacher to Japanese authors submitting manuscripts for consideration of publication in this Journal. His enthusiasm in stimulating young scholars in medical genetics led to his making a trip to Japan in April 2008, which none of us can ever forget. In his memorable address entitled, "The role of case reports in the advancement of scientific knowledge," he urged us to always question ourselves, "Does this case report add new information or generate a hypothesis on the etiology of the disorder?" Dr. Carey's delineation of Braddock–Carey syndrome from Jacobsen syndrome evidently evolved into multiple concepts on intellectual disability and thrombocytopenia. The evolvement itself embodies his great teachings on the importance of case reports.

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