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Original article

Distinctive facies, macrocephaly, and developmental delay are signs of a *PTEN* mutation in childhood

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Abstract

Background: Germline mutations of the *PTEN* gene are responsible for several PTEN hamartoma tumor syndromes. They are also implicated as a cause of macrocephaly and mild to severe developmental delay, regardless of the presence or absence of hamartomas in childhood. Nevertheless, because of limited information, the clinical features present during childhood in patients with a *PTEN* mutation are yet to be elucidated.

Methods: *PTEN* mutations were investigated by multiplex targeted sequencing of genomic DNA from 33 children with increased head circumference (>+2 SD) and developmental delay. The clinical features of all the patients with a *PTEN* mutation were abstracted by dysmorphologists.

Results: We have identified six children with a *PTEN* mutation. Clinical dissection of these six patients, in addition to patient reports in the literature, revealed distinctive facial features that included frontal bossing, dolichocephaly, horizontal eyebrows, and a depressed nasal bridge. Macrocephaly (+3.2 to +6.0 SD) was noticeable compared to their height (−0.8 to +2.1 SD), and the difference in the SD value of head circumference and height was more than 3 SD in all patients.

Conclusion: The presence of distinctive facies, extreme macrocephaly with normal to mildly high stature, and developmental delay may be useful for identifying patients with a *PTEN* mutation in childhood. Early identification of patients with a *PTEN* mutation would help uncover the natural course of tumor development in this group of individuals who have a possible predisposition to cancer, and be important for the development of an optimal surveillance strategy.

Keywords: Facial dysmorphism; Hamartoma; Intellectual disability; Tumor predisposition

1. Introduction

The *phosphatase and tensin homolog* (*PTEN*) gene, located on chromosome 10q23, is a tumor suppressor gene that has a significant role in the molecular pathways

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mediating cellular proliferation, migration, and apoptosis. Germline *PTEN* mutations were conventionally known as a cause of PTEN hamartoma tumor syndromes (PHTS), including Cowden syndrome (CS, OMIM 158350) and Bannayan-Riley-Ruvalcaba syndrome (BRRS, OMIM 153480) [1,2]. BRRS is a pediatric syndrome characterized by the classic triad of macrocephaly, hamartomas and pigmented macules of the glans penis. CS is representative of a PHTS that occurs in adulthood, and has a phenotype with many clinical features that overlap those seen in BRRS. In fact, these two syndromes are considered to represent one condition that is subject to age-related penetrance.

Some individuals affected in childhood with PHTS also exhibit developmental delay [3]. In addition, *PTEN* mutations have been identified in children presenting with macrocephaly and mild to severe developmental delay without hamartomas [4]. Thus, in contrast to the well characterized PHTS phenotype defined by the triad of BRRS and CS diagnostic criteria, there remains a subset of patients carrying a *PTEN* mutation that have developmental delay, and for whom the other distinctive phenotypic features in early childhood are not well characterized.

We have identified six children with a *PTEN* mutation through genetic investigation of 33 Japanese patients with macrocephaly and developmental delay. Macrocephaly is the most consistently observed and well known feature of patients with a *PTEN* mutation, however, many diseases present with macrocephaly and developmental delay, and in isolation they are of limited diagnostic use. The aim of this study, therefore, is to identify additional, distinctive clinical features that may be used to specifically diagnose the presence of a *PTEN* mutation in early childhood. Given the possible genetic predisposition of these patients to cancer, this information would present a valuable opportunity for earlier monitoring and detection of tumors.

2. Materials and methods

2.1. Genetic analysis

PTEN mutations were detected by multiplex targeted sequencing of genomic DNA from children with increased head circumference (>+2 SD) and developmental delay. Genomic DNA was extracted from peripheral blood using the QIAamp DNA Blood Midi Kit according to the manufacturer's instructions (Qiagen, Hilden, Germany). Fifteen target genes involved in the mTOR pathway, including *PTEN,* were selected for the preparation of amplicon libraries using an Ion AmpliSeq Custom Panel (Thermo Fisher Scientific, Waltham, MA, USA) [5]. Library preparation, emulsion PCR, multiplex targeted sequencing using an Ion Torrent Personal Genome Machine (PGM) system, and sequence data analysis using a CLC Genomics Workbench 7.0 (CLC bio, Aarhus, Denmark) were performed as reported previously [5]. All mutations were confirmed by Sanger sequencing of PCR-amplified products (reference sequence: Genbank No. NM_000314.4). Experimental protocols were approved by the Ethical Committee for the Study of Human Gene Analysis at Nagoya City University Graduate School of Medical Sciences. Written informed consent was obtained from all patients or their parents.

3. Results

3.1. Genetic analysis

We have investigated multiplex targeted sequencing analysis in 33 pediatric patients with macrocephaly and developmental delay, and identified six children with a *PTEN* mutation. The results of total reads by target sequencing ranged between 247 K and 1.58 M reads. The mean depth of target region was 459–3112, and 381–3357 in particular of *PTEN*. The other genes identified pathogenic variants are *PIK3R2* (n = 3), *AKT3* (n = 2), and *PIK3CA* (n = 1).

3.2. Clinical report

The clinical manifestations of patients with a *PTEN* mutation are summarized in Table 1. The clinical features of all the patients were abstracted by dysmorphologists.

3.2.1. Patient 1

Patient 1 was a 4½-year-old girl, and the second child of healthy, unrelated parents. Pregnancy and delivery were uneventful and her body size including birth weight, length, and head circumference was normal at birth. Macrocephaly, short stature, and muscular hypotonia were identified at 1 and 4 month routine health checks, and the patient was referred to the local hospital at 5 months of age. Blood examination and urine organic acid analysis did not reveal any significant findings. At 10 months of age, the patient presented with hypoglycemia when she caught a common cold. IGF-1 was lower than the detection limit (4 ng/mL), and the peak GH level detected by an L-DOPA stimulation test was 2.04 mg/dL (90 min). On the basis of these results, she was diagnosed as having a growth hormone deficiency, and growth hormone replacement therapy was initiated. Motor development was delayed, with the patient acquiring head control at 6 months and walking at 28 months. At age 4½ years, she presented with macrocephaly (+4.9 SD) and normal height. The overall developmental quotient (DQ) was 76 by the Kinder Infant Development Scale (KIDS) [6]. The patient showed dysmorphic features, including frontal bossing,

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