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Array Analysis and Molecular Studies of INI1 in an Infant With Deletion 22q13 (Phelan–McDermid Syndrome) and Atypical Teratoid/Rhabdoid Tumor

Shyam Sathyamoorthi¹, Jaime Morales^{2,3}, Jose Bermudez⁴, Lori McBride⁴, Mark Luquette^{2,5}, Robin McGoey^{2,5,6}, Nora Oates⁷, Stephen Hales⁷, Jaclyn A. Biegel⁸, and Yves Lacassie^{2,6,*}

¹ Volunteer student at Children's Hospital, currently pre-med student at Tulane University, New Orleans, Louisiana

² Department of Pediatrics, Children's Hospital and LSU Health Sciences Center, New Orleans, Louisiana

³ Department of Oncology, Children's Hospital and LSU Health Sciences Center, New Orleans, Louisiana

⁴ Department of Neurosurgery, Children's Hospital and LSU Health Sciences Center, New Orleans, Louisiana

⁵ Department of Pathology, Children's Hospital and LSU Health Sciences Center, New Orleans, Louisiana

⁶ Department of Genetics, Children's Hospital and LSU Health Sciences Center, New Orleans, Louisiana

⁷ Hales Pediatrics and Children's Hospital, New Orleans, Louisiana

⁸ Division of Human Genetics, Department of Pediatrics, University of Pennsylvania and The Children's Hospital of Philadelphia, Pennsylvania

TO THE EDITOR

The 22q13.3 deletion syndrome, also known as Phelan–McDermid syndrome, is a relatively newly described microdeletion syndrome characterized by developmental delay, hypotonia, delayed or absent speech, autistic-like behavior, normal to accelerated growth, and minor dysmorphic features including dolichocephaly, full brow and large or prominent ears [Cusmano-Ozog et al., 2007; Phelan, 2008]. Current thinking suggests that the reported prevalence of the 22q13.3 deletion syndrome, with its nonspecific physical findings, may be underestimated. Now, with the more frequent clinical use of array comparative genomic hybridization (aCGH) in the “genotype-first” approach to syndrome identification [Shaffer et al., 2007], its incidence is expected to increase.

Atypical teratoid/rhabdoid tumors (AT/RTs) are extremely aggressive and rare cancers of the central nervous system, primarily affecting children less than 3 years of age [Rorke et al., 1996; Hilden et al., 2004]. In the past, many AT/RTs have been misclassified as medulloblastomas, or other malignant brain tumors, owing to their overlapping clinical,

histological, and radiographic features [Rorke et al., 1996; Burger et al., 1998]. Currently, with the application of immunohistochemistry using antibodies to INI1 (BAF-47) [Judkins et al., 2004] and molecular analysis, more specific differential diagnosis of brain tumors is feasible. Up to 90% of AT/RTs have been shown to involve deletions of chromosome 22 and inactivating mutations of the tumor suppressor gene, *hSNF5/INI1/SMARCB1* located in chromosome band 22q11.2 [Versteeg et al., 1998; Biegel et al., 1999, 2002].

We report on an infant with deletion 22q13.3 (Phelan–McDermid) syndrome diagnosed by aCGH who subsequently developed an AT/RT. Molecular testing of both the patient's blood and tumor tissue was performed. The apparent existence of other similar cases [Phelan, 2008, personal communication] suggests that this malignant tumor may add an extremely poor prognosis in Phelan–McDermid syndrome.

The patient is a 2-year-old Caucasian female referred to genetics at 13 months of age with a history of torticollis, plagiocephaly, hypotonia, hydronephrosis, and strabismus. The patient was the product of the second pregnancy between a 37-year-old mother and a 31-year-old father, both in good general health. Consanguinity was not reported and the family histories were both negative. The patient's siblings, an older brother, and a younger sister were also in good health and developmentally normal. The pregnancy was complicated by placenta previa and fetal hydronephrosis. Delivery was at 38½ weeks gestation via normal spontaneous vaginal delivery. BW was 3,880 g and BL was 48 cm. Torticollis was noted at birth. Hydronephrosis and vesicoureteral reflux were confirmed necessitating prophylactic antibiotic treatment for several months. In the first year of life, strabismus, hypotonia, developmental delay, plagiocephaly, and poor communication skills were also noted. Major findings on physical examination at 13 months of age (Fig. 1a) included very good growth with length and HC in the 97th and 90th centile, respectively. Large ears (97th centile), circumferential skin creases in arms, forearms, and legs, inverted nipples, mild lipomastia, a deep sacrococcygeal crease, overriding second toes, long middle toes, upturned toenails on toes second and fourth, and atrophic toenails on her fifth toes were also detected. Increased secondary creases in both soles, disruption of the vertical palmar flexion creases, and an increased number of whorls in the finger patterns and transverse mainline endings were the only dermatoglyphic findings. Array CGH analysis of a peripheral blood specimen revealed a subtelomeric deletion of the long arm of chromosome 22 at 22q13.2q13.33 (~7.2 Mb in size). The study of the parents demonstrated that this was a de novo abnormality.

At 23 months of age, the patient presented to the emergency room with a 2-month history of worsening headaches, irritability, and persistent vomiting (Fig. 1b). An MRI of the brain demonstrated a 2.5 cm enhancing mass in the fourth ventricle. Spinal MRI was unremarkable. The pre-operative diagnosis was presumptively a medulloblastoma and the patient underwent a complete surgical resection. The post-operative MRI showed no evidence of residual tumor. The histopathological diagnosis was AT/RT (World Health Organization, WHO, grade IV). An abdominal ultrasound ruled out the presence of any renal masses and cerebrospinal fluid obtained 2 weeks after surgery was positive for malignant rhabdoid cells consistent with leptomeningeal metastases. After a progressive decline, the patient died at 26 months of age.

Frozen tissue from the AT/RT was utilized for DNA extraction. Sequence analysis of the nine coding exons of the *INI1/SMARCB1* gene was performed. A frameshift mutation in exon 9, c.1145delC (codon 382) was identified, predicted to result in elimination of the normal stop codon (after codon 385) and the creation of a novel stop codon (after codon 485). This mutation is the most common sequence abnormality detected in central nervous system RTs. The mutation was not present in the DNA from the blood. Additionally, a Multiplex Ligation-Dependent Probe Amplification (MLPA; MRC, Amsterdam, The

Netherlands) assay for detecting individual exon copy number variations in the *INI1* gene was performed on frozen tumor DNA, revealing a heterozygous deletion of not only all nine *INI1* coding exons but also of all other proximal and distal 22q probes. The MLPA of the blood was normal with the exception of a heterozygous deletion of the 22q13.33 probe (PLXNB2). Findings then, based on the molecular analyses of both blood and tumor, were reported to be consistent with a de novo germline 22q13 deletion of the chromosome 22 that was subsequently lost in tumor tissue. Combined with a somatic mutation in exon 9 of the remaining copy of the *INI1* gene, the overall net effect was a homozygous inactivation of the *INI1* gene, leading to development of the AT/RT.

In summary, the coexistence of AT/RT in a child with a large germline deletion 22q13 as well as a somatic mutation in the *INI1* gene localized to 22q11.2 is highly unusual. The relationship between the 22q13 deletion, subsequent loss of the deleted chromosome in the tumor, and the acquired mutation in the *INI1* gene is unknown. It may be coincidental or argue for an underlying genetic instability in this patient. As all of the events were de novo or somatic in origin, there was no perceived increased risk of RT in the other family members.

We did not include in this report a similar case known to Phelan [2008, personal communication] as we were unable to get sample for molecular studies on this deceased patient. Although our patient would be the first reported case of Phelan–McDermid syndrome associated with this malignant brain tumor, we do not know if this will be a rare phenomenon. This highlights the importance of regular screening for earlier detection of CNS and/or renal rhabdoid tumors in patients with more extensive deletion of both 22q13 and 22q11.2.

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FIG. 1. Patient at age (a) 13 months and (b) 23 months showing subtle dysmorphism. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]