CLINICAL REPORT

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Delayed Diagnosis in a House of Correction: Smith–Magenis Syndrome Due to a De Novo Nonsense *RAI1* Variant

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We report a 25-year-old female confirmed to have Smith–Magenis syndrome (SMS) due to a de novo *RAI1* variant. Her past history is significant for developmental and intellectual delay, early and escalating maladaptive behaviors, and features consistent with significant sleep disturbance, the etiology of which was not confirmed for over two decades. The diagnosis of SMS was initially suspected in 1998 (at age 12 years), but that was 5 years before the initial report of *RAI1* variants as causative of the SMS phenotype; cytogenetic fluorescence in situ hybridization studies failed to confirm an interstitial deletion of 17p11.2. Re-evaluation for suspected SMS was pursued with *RAI1* sequencing analysis in response to urgent parental concerns of escalating behaviors and aggression with subsequent incarceration of the subject for assault of a health professional. Genetic analysis revealed a de novo *RAI1* (NM_030665.3) nonsense variant, c.5536C>T; p.Q1846X. This case illustrates the importance of confirming the SMS diagnosis, which is associated with cognitive and functional impairment, as well as significant psychiatric comorbidities and behavioral problems. The diagnosis was particularly relevant to the legal discussion and determination of her competence to stand trial. As other similar cases may exist, this report will help to increase awareness of the possibility of a very late diagnosis of SMS, with the need for re-evaluation of individuals suspected to have SMS who were initially evaluated prior to the identification of the *RAI1* gene.

Key words: aggressive behavior; incarceration; legal discussion; psychiatric comorbidity; *RAI1*; Smith–Magenis syndrome

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INTRODUCTION

Smith–Magenis syndrome (SMS, OMIM#182290) is a complex congenital disorder that is characterized by craniofacial abnormalities, otolaryngologic abnormalities, developmental delay, cognitive, and functional impairment, chronic sleep disturbance, behavioral abnormalities, and other distinctive physical variations [Edelman et al., 2007; Gropman et al., 2007; Elsea and Girirajan, 2008; Smith et al., 2012]. The prevalence of SMS is estimated to be 1:15,000 to 1/25,000 live births [Greenberg et al., 1991; Smith et al.,

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2012]. SMS is caused by a de novo interstitial deletion of chromosome 17p11.2 (~90% of cases) or by a de novo genetic variant within the *RAI1* gene (~10% of cases) [Smith et al., 1986; Slager et al., 2003; Elsea and Girirajan, 2008; Vilboux et al., 2011]. The phenotype of subjects with a disease causing variant differs slightly in that there is generally a lack of short stature and visceral anomalies (Table I) [Girirajan et al., 2006; Vilboux et al., 2011]. The diagnosis of SMS is based on the presence of typical clinical findings followed by molecular confirmation. The traditional method to detect the 17p11.2 deletion is chromosome G-banding at >550 band resolution and/or confirmation by FISH using a specific 17p11.2 probe overlapping the *RAI1* gene region [Vlangos et al., 2005]. Suspected cases without an identifiable 17p11.2 deletion warrant *RAI1* gene mutation analysis [Slager et al., 2003; Elsea and Girirajan, 2008; Vilboux et al., 2011].

We describe a subject who was suspected to have SMS as early as age 12, due to her history of developmental and intellectual delay as well as features consistent with significant sleep disturbance and early and escalating recidivistic behaviors. We confirmed the diagnosis of SMS by identifying a novel, de novo nonsense *RAI1* variant. The diagnosis had major relevance to the legal discussion and determination of her competence to stand trial. Earlier diagnosis might have led to implementation of intervention strategies and supportive services and programs to avert her involvement in the criminal justice system.

MATERIALS AND METHODS

Subject and Cells

The subject was enrolled in NIH clinical protocol 01-HG-0109 approved by the National Human Genome Research Institute (NHGRI) institutional review board to evaluate the clinical and molecular manifestations of SMS (www.clinicaltrials.gov, NCT00013559). Due to the subject's cognitive impairment, written

TABLE I. Clinical Comparison of SMS Features

Smith–Magenis syndrome clinical features	17p11.2 deletions cases[a]	*RAI1* variants cases[b,c]	*RAI1* de novo variant cases[a]	Current case
		~13 cases	Five cases: 3F/2M	F, 25 y
Craniofacial features	>75%	80%	5/5	Yes
Intellectual disability	100%	100%	Four mild ID; one moderate	Mild ID
Speech delay	>90%	70%	3/5	Yes
Motor delay	>90%	70%	5/5	Yes
Sleep disturbance	90–100%	100%	5/5	Yes
Middle ear/laryngeal anomalies	80–90%	55%	5/5 OM	OM 2/yr
Hearing loss	60–70%	10–25%	4/4	No
Hoarse, deep voice	>80%	100%	5/5	No
Ocular abnormalities	50–80%	40–60%	5/5	Myopia/glasses
Short stature (<5%tile)	50–75%	10–20%	1/5*	No (HT 53%)[f]
Obesity	13% (<9 y); 95% (>9 y)	67%	4/5 (>98%)	Yes (WT >97%)[f]
Mean BMI (kg/m^2)[d]	20.3 ± 5.8*	NR	31.3 ± 10.1*	46.1[f]
Scoliosis	40-70%	36%	2/5	Kyphoscoliosis
Brachydactyly	80-90%	83%	3/5	Yes (hands)
Cardiac defects	<25%	0%	0/5	Normal echo
Renal anomalies	30–45%	0%	0/5	Normal U/S
Urinary tract problems	20%	NA	3/4	Kidney infections
History enuresis	82% enuresis		3/5 enuresis	No
Genital anomalies	6/16 (38%)	NA	2/5	Polycystic ovaries
Laboratory				
Hypercholesterolemia	57%[e]	NA		Yes
Low immunoglobulins	44%	NA		No; normal
Behavioral features				
Attention seeking	80–100%	100%	4/4	Yes
Anxiety/rapid mood shifts/emotional lability	89%	NA	4/5	Yes; PTSD
Self-injurious behaviors	75–92%	100%	5/5	Yes
Self-hugging/hand wringing	50–80%	100%	5/5	Yes
Onychotillomania (nail damage)	25–85%	90%	5/5	Yes
Polyembolokoilamania	25–85%	80%	3/5	No

Data not available, NA; intellectual disability, ID; height, HT; weight, WT; otitis media, OM; post-traumatic stress disorder, PTSD.
[a]Vilboux et al. [2011].
[b]Girirajan et al. [2005].
[c]Edelman et al. [2007].
[d]Growth data (n = 49 del17p11.2; n = 5 *RAI1*) from Vilboux et al. [2011]; significance $P < 0.0005$ (*).
[e]Smith et al. [2002].
[f]Measurement at age 27 years.

informed consent was obtained from her parents who were her legal guardians. Peripheral blood was collected and employed for extraction of genomic DNA (gDNA) and for Epstein Barr Virus (EBV) immortalization of B-lymphocytes, using standard protocols.

DNA Analysis

Copy number analysis was performed by SNP genotyping, the subject's gDNA was run on a Human 1M-Duo DNA Analysis BeadChip and the data were analyzed using the GenomeStudio software (both Illumina, San Diego, CA). For sequencing, primers were designed to PCR-amplify all coding *RAI1* (NM_030665.3) exons (exons 3, 4, 5, 6) and flanking intronic regions (Primer sequences available on request). All PCR products were directly sequenced as described [Vilboux et al., 2011].

RAI1 mRNA Expression

Total RNA was isolated from subject or control EBV-immortalized lymphoblastoid cell lines using the RNeasy Mini-Kit (Qiagen, Valencia, CA). First strand cDNA was synthesized from DNase-treated RNA (Applied Biosystems, Austin, TX) using a high capacity RNA-to-cDNA kit (Applied Biosystems). qPCR was performed utilizing two *RAI1* Assays-On-Demand Taqman primer-probe assays (Applied Biosystems), Hs00430773_m1 (Assay 1; exons 2–3 boundary) and Hs01554690_m1 (Assay 2; exons 3–4 boundary), and β-actin gene (Hs99999903_m1) for control. PCR amplifications were performed using 100 ng of cDNA using TaqMan Gene Expression Master Mix reagent (Applied Biosystems) and were carried out on an ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems). Results were analyzed with the comparative CT method as described [Livak, 1997; Livak and Schmittgen, 2001].

RESULTS

Clinical Data

We report a 25-year-old Caucasian female with developmental and intellectual delays, significant sleep disturbance and early and escalating maladaptive behaviors, the etiology of which was suspected at age 12, but not confirmed for over two decades. The proband was born at full term after an uncomplicated pregnancy except for perceived decreased fetal movement and transient bradycardia during the neonatal period. She initially was a quiet and content infant who, with the exception of sleeping 8 hr through the night on her first day home, exhibited a disrupted sleep cycle with frequent nocturnal awakenings and increased daytime somnolence (napping) throughout early childhood. Speech and motor development were mildly delayed.

At age 11, brain MRI and EEG were normal and at 12, a diagnosis of SMS was suspected based on physical and behavioral characteristics. Her physical features (Fig. 1A) at age 12 years included height of 151.5 cm., weight of 67 kg. (BMI 29.2 kg/m^2; 98th centile), OFC 54.75 cm (75th %tile). She had brachycephaly, hypertrichosis including hair on the upper lip, tented upper lip, high arched palate, dental malocclusion, mild prognathism, brachydactyly (with short 4th–5th metacarpals) and 2–3 cutaneous toe syndactyly with broad long feet. There was also evidence of skin picking. She had 14 degrees of thoracic dextroscoliosis. Cognitive testing in kindergarten had documented her FSIQ to be 68–70 and she required a 1:1 aide in school due to behavior issues. At age 12, she was in a special education program, reading at a third-grade level with difficulties in math.

In addition to learning difficulties (graphomotor/visual motor delay), the subject exhibited maladaptive behaviors including wrist biting, skin picking, trichotillomania, and onychotillomania (nail yanking of fingers and toes). Her increased pain tolerance was evidenced by a history of a compound fracture of the wrist at age 3 years (trauma-sustained) that was not diagnosed for 2 days, a broken right arm at age 4 years, self-extraction of four teeth at age 4 years, and self-removal of orthodontic braces at age 11 years (applied for treatment of crossbite and dental misalignment). History was significant for recurrent sinusitis and mouth breathing, consistent with later evidence of turbinate hypertrophy documented during sinus reconstructive surgery at age 23 years. Irregular menses associated with generalized hirsutism of the face and back led to a diagnosis of polycystic ovaries at age 18 years. Sleep disturbance with nocturnal awakenings, early sleep offset, and daytime naps remained an issue into adulthood, including nighttime wandering and food foraging behavior.

Despite the suspicion of an SMS diagnosis, cytogenetic studies at age 12 failed to confirm a deletion of 17p11.2 by FISH [46,XX.ish 17p11.2(D17S258 × 2)], which had previously been associated with the SMS phenotype [Slager et al., 2003]. Other diagnostic possibilities were pursued with negative results, including screening for Fragile X (*FMR1* CGG allele size 22/29), and other chromosome variations, and encephalopathy. She was given several co-morbid psychiatric diagnoses including obsessive compulsive disorder, Tourette syndrome, posttraumatic stress disorder (PTSD), oppositional defiant disorder, and intellectual disability. Additional clinical features are shown in Table I.

From age 21 onward, with an intellectual functioning level of 8–9 years, her problems of behavior escalated. Over the next 3 years, she had episodes of severe agitation that led to several encounters with authorities, admissions to psychiatric hospitals, and was incarcerated twice for violent assaultive behavior. The series of events began at age 21 years during an in-office oral surgery procedure for impacted wisdom teeth that led to an acute stress response (fight-or-flight) and ultimate diagnosis of PTSD. Upon learning the oral surgeon was not her regular dentist, she was notably anxious prior to the in-office procedure; she became extremely agitated during the administration of anesthesia (IV valium (10 mg) and nitrous oxide/oxygen mask) and had a seizure-like episode (hyperventilating with tremors and rapid pulse) that resulted in a 911 call, 10-day hospitalization and a diagnosis of pseudoseizures. Two days after discharge, she was found wandering, confused and disoriented, and became extremely agitated threatening a clerk in a local store. This led to a 2-week crisis admission for suspected PTSD and medication overdose documented by hospital drug screen.

For the next 18–24 months her explosive behavior "normalized" and she did well, living under parental guardianship with a diagnosis of mild intellectual disability. At age 23 years, her parents

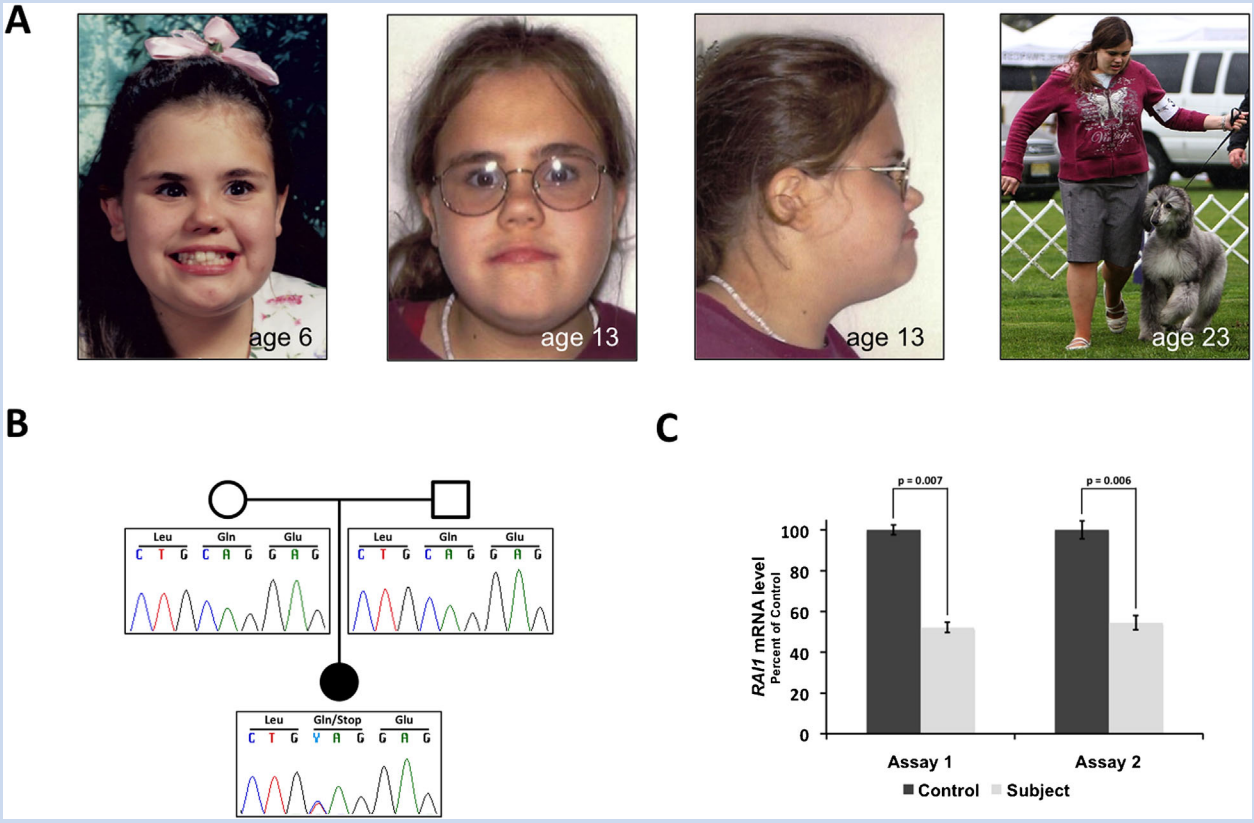

FIG. 1. Clinical and molecular data. (A) The proband at school age (6 years), adolescence (13 years) and prior to diagnosis (23 years). The proband has facial features that are consistent with SMS, including brachycephaly, deepset eyes, mild synophrys, and excess body hair on upper lip, dental malocclusion, and mid-face hypoplasia with relative prognathism. (B) Genetic analysis showed a de novo heterozygous *RAI1* nonsense variant (NM_030665.3:c.5536C>T; p.Gln1846*) in the proband, which was not detected in the parents. (C) The proband's lymphoblastoid cells showed a significant (~50%) reduction in *RAI1* mRNA expression by qPCR, compared to control cells, determined by two independent *RAI1* Taqman probes for RNA expression (Hs00430773_m1 = Assay 1 and Hs01554690_m1 = Assay 2). Values are a percentage of expression of *RAI1* in subject cells compared to control cells, normalized to Beta Actin (ACTB), error bars = ±1 SD, n = 4, *t*-test: $P < 0.01$.

again noted increased agitation and "anger" even with favored activities that coincided with renewed complaints of dental pain. On the day of a scheduled dental appointment, she experienced an acute stress response in which she fled the waiting room, crossed a 6-lane highway, entered a commercial building, and threatened several people, leading to her arrest. After her parents posted bond, she was released from county jail and admitted to a psychiatric facility with admitting diagnoses of depressive disorder not otherwise specified (NOS), PTSD, impulse control disorder NOS, mild intellectual disability, and personality disorder NOS. After suffering from an accidental head trauma while in the psychiatric hospital, she was also diagnosed with silent sinus syndrome, reflecting a chronic, asymptomatic maxillary sinus collapse [Setlur, 2010]. Two years after the initial dental surgery, she told caretakers that she felt the dentist "tried to kill her" by suffocating her during administration of nitrous oxide/oxygen, when he placed the mask on her face while holding her mouth closed.

At her most recent incarceration, she engaged in self-injurious behaviors that included constant skin picking. Ultimately it was discovered that she had inserted 24 inches of blanket yarn, hair and pencil lead in an self-inflicted arm wound after "chewing" out her own stitches. Her high pain tolerance and attention-seeking behavior, in combination with her clinical features and history, sparked a re-evaluation of the previously considered SMS diagnosis, with the approval of the prison medical officer.

Once confirmed to have a diagnosis of SMS at 25 years of age, her lawyers contacted county prosecutors in both jurisdictions, and, at two trials for the separate assault charges she was found not guilty by reason of insanity (NGRI) and put on "Krol status" (State v. Krol, 68 N.J. 236 [1975]). This verdict established that a person in New Jersey acquitted by reason of insanity may be held in continued confinement if he or she is a danger to self or others and is in need of medical treatment. The subject was sent back to the forensic center for continued confinement and ongoing psychiatric care. She remained under psychiatric care for

38 months (Axis 1: Impulsivity Disorder; Axis 3: SMS), responding well to a strict behavioral plan in combination with a psychotropic medication regimenthat included Clozaril, Effexor, and Lamictal. Behaviorally, she was more relaxed, less impulsive and demanding, with fewer meltdowns in response to unexpected changes in events/schedule. She also had notably improved communication skills. Medically she was hospitalized and treated for sinusitis, a urinary tract infection, and abdominal discomfort with projectile vomiting due to significant constipation. After 38 months, at age 29 years, plans for discharge from the psychiatric facility were initiated to transition her back to the home setting.

Molecular Analysis

To confirm the previous FISH findings of the lack of chromosome 17p11.2 deletion, allelic copy number analysis and whole genome SNP-array analysis of the proband's gDNA was performed, with normal results. There was no deletion in the 17p11.2 region (data not shown).

Sequence analysis of the *RAI1* (NM_030665.3) coding exons revealed that the proband harbored a novel heterozygous nonsense variant, designated as c.5536C>T in exon 3, resulting in a premature stop codon: p.Q1846X (Fig. 1B). This variant was de novo, since it was not found in the parents' DNA. This variant represents the most 3-prime SMS-related variant in *RAI1* reported to date. The proband's lymphoblastoid cells showed a significant (~50%) reduction in *RAI1* mRNA expression by qPCR compared to control cells (Fig. 1C). This reduction is similar to that found in other individuals with *RAI1* variants [Vilboux et al., 2011], and implies nonsense-mediated mRNA decay of the variant *RAI1* allele.

DISCUSSION

This report summarizes the ordeal of a subject with a rare genetic disorder as she passed through the legal and correctional systems. We hope that this report will help to inform the courts of the need to pursue diagnostic testing to improve services and patient outcomes based on an accurate diagnosis.

The subject's documented clinical phenotype in infancy and adolescence was consistent with SMS, but absence of the 17p11.2 interstitial genomic deletion prevented the diagnosis at 12 years of age. The subject was subsequently lost to follow up by medical geneticists; only the tireless efforts of the subject's parents ultimately led to her proper diagnosis and treatment at age 25. Genetic analysis identified a de novo nonsense *RAI1* variant, confirming that the phenotypic suspicion of SMS diagnosis, which was important to the adjudication of her case and to her subsequent care.

This subject's ordeal began with an acute stress response reaction to her initial sedated dental procedure and a subsequent assault. To our knowledge, this is not a common occurrence with SMS subjects, but may in retrospect reflect PTSD and craniofacial anatomy with turbinate hypertrophy, that contributed to inability to breathe through her nose and perception of being "suffocated" during administration of mask anesthesia. Her reaction is consistent with what Klein refers to as suffocation false alarm theory that can lead to a spontaneous panic response [Klein, 1993]. The latter includes sudden respiratory distress followed swiftly by hyperventilation, panic, and urge to flee, which is consistent with her "PTSD" response at age 23 years in anticipation of another scheduled dental procedure.

It is not known how many potential SMS subjects may be living in similar circumstances. Psychiatric co-morbidities with dual diagnoses remain common in SMS subjects, with many given functional psychiatric diagnoses of autism spectrum disorder (ASD), attention deficit/hyperactivity disorder, bipolar disorder, oppositional-defiant disorder, sensory integration disorder, obsessive-compulsive disorder, and/or pervasive developmental disorder [Laje et al., 2010]. In the context of forensic research, Harris suggested that the prevalence of 22q11 deletion syndrome (22q11DS) might be higher in correctional facilities than estimated community prevalence rates [Harris, 2005]. The ability to diagnose rare disease is limited in correctional facilities, especially after the failure of standard screening methods such as FISH or microarrays. New diagnostic algorithms and screening methods such as sequencing, Next Gen sequencing panels, and whole exome/whole genome analysis are evolving rapidly and should clarify more diagnoses in the future.

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