Identification of Nine New RAI1-Truncating Mutations in Smith-Magenis Syndrome Patients without 17p11.2 Deletions

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Mutation \cdot 17p11.2 \cdot RAI1 \cdot Smith-Magenis syndrome

Abstract
Smith-Magenis syndrome (SMS) is an intellectual disability syndrome with sleep disturbance, self-injurious behaviors and dysmorphic features. It is estimated to occur in 1/25,000 births, and in 90% of cases it is associated with interstitial deletions of chromosome 17p11.2. \textit{RAI1} (retinoic acid induced 1; OMIM 607642) mutations are the second most frequent molecular etiology, with this gene being located in the SMS locus at 17p11.2. Here, we report 9 new RAI1-truncating mutations in nonrelated individuals referred for molecular analysis due to a possible SMS diagnosis. None of these patients carried a 17p11.2 deletion. The 9 mutations include 2 nonsense mutations and 7 heterozygous frameshift mutations leading to protein truncation. All mutations map in exon 3 of \textit{RAI1} which codes for more than 98% of the protein. \textit{RAI1} regulates gene transcription, and its targets are themselves involved in transcriptional regulation, cell growth and cell cycle regulation, bone and skeletal development, lipid and glucide metabolisms, neurological development, behavioral functions, and circadian activity. We report the clinical features of the patients carrying these deleterious mutations in comparison with those of patients carrying 17p11.2 deletions.

Smith-Magenis syndrome (SMS; MIM 182290) involves multiple congenital anomalies and intellectual disability usually associated with an interstitial deletion of chromosome 17p11.2 [Smith et al., 1986; Greenberg et al., 1996; Dykens and Smith, 1998; Potocki et al., 2000; De Leersnyder et al., 2001; Edelman et al., 2007; Gropman et al., 2007; Elsea and Girirajan, 2008]. The common features include behavioral abnormalities with sleep disturbances, self-injurious and/or aggressive behavior, particular craniofacial and skeletal anomalies, and speech delay. The facial appearance is usually characterized by a broad square-shaped face, a tented (inverted V-shaped) upper lip with downturned corners of the mouth and upslanting palpebral fissures. Obesity is frequent.

The incidence of this syndrome has been estimated to be 1 in 25,000 births [Greenberg et al., 1991]. About 90%
of SMS patients present a heterozygous interstitial dele-
tion of chromosome 17p11.2: most (70% of SMS patients)
have a common ∼3.7-Mb deletion [Greenberg et al., 1991;
Juyal et al., 1996; Gropman et al., 2007] mediated by non-
allelic homologous recombination (NAHR) [Chen et al.,
1997; Park et al., 2002]; about 20% of SMS patients harbor
atypical deletions of ∼1.5–9 Mb mediated by an end-join-
ing mechanism [Trask et al., 1996; Bi et al., 2002; Stankie-
wicz et al., 2003; Vlangos et al., 2003; Shaw and Lupski,
2005]. More recently, point mutations in the RAI1 (reti
noic acid induced 1) gene have been identified in less than
10% of SMS patients [Slager et al., 2003; Bi et al., 2004,
2006; Girirajan et al., 2005, 2006; Vilboux et al., 2011; Vie-
ira et al., 2012]. This gene maps in the SMS critical region
[Bi et al., 2002; Vlangos et al., 2003]. About 36 mutations
have been described in RAI1 to date, and more than 50%
of them are truncating mutations; the deleterious role of
the missense mutations is not yet clearly established. The
RAI1 gene encodes a potential transcriptional regulator
and consists of 6 exons that span over 120 kb; the third
exon contains more than 98% of the coding sequence [Bi
et al., 2004, 2005]. The RAI1 protein contains polygluta-
mine and polyserine tracts, bipartite nuclear localization
signals and a plant homeo/zinc finger domain at the C-
terminus [Toulouse et al., 2003]. Murine Rai1 (originally
reported as GT1) is upregulated by retinoic acid treatment
in mouse embryonal carcinoma cells concomitantly with
neuronal differentiation [Imai et al., 1995].

We report 9 new RAI1-truncating mutations in SMS
patients without 17p11.2 deletions, describe associated
phenotypes and compare our results with published find-

### Methods

#### Patients and Samples

Patients presenting with clinical symptoms of SMS, but with-
out a 17p11.2 deletion, were referred from various clinical genetic
centers in France through the network of the reference centers for
developmental anomalies and malformation syndromes. All pa-
tient samples were collected after obtaining informed consent ac-
cording to the guidelines of the relevant institutional review
boards.

#### PCR and Sequencing

Patient DNA was amplified by PCR with overlapping primers
covering exons 2–6 of the RAI1 gene and using the conditions de-

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**Table 1. RAI1 PCR primers and conditions**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Forward primer (5′→3′)</th>
<th>Reverse primer (5′→3′)</th>
<th>Product size, bp</th>
<th>Annealing temp., °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>GGGGCTGCTAAGAAGCAAC</td>
<td>CGCCGAAAACACAAAGCTC</td>
<td>306</td>
<td>56</td>
</tr>
<tr>
<td>3.1</td>
<td>GGTGGTCGTGGAGGCGGCTTT</td>
<td>TGCTGCTCGTGAGCGGTAG</td>
<td>489</td>
<td>57</td>
</tr>
<tr>
<td>3.2</td>
<td>AGTAGCCAGGAGGAGCA</td>
<td>TCGGTGCTGTAGCAGCCTTA</td>
<td>498</td>
<td>57</td>
</tr>
<tr>
<td>3.3</td>
<td>CAGGGTACCCACTTCTTCTCA</td>
<td>AGTTTCCAGGTTGGGATC</td>
<td>496</td>
<td>57</td>
</tr>
<tr>
<td>3.4</td>
<td>CATCCTCGAGAACACCAGAG</td>
<td>GCTGCTGTGCTGACAGCCT</td>
<td>502</td>
<td>57</td>
</tr>
<tr>
<td>3.5</td>
<td>AGTCCGTGTGACACCTTCTG</td>
<td>TCAAAACGCTCAGAACAGC</td>
<td>504</td>
<td>57</td>
</tr>
<tr>
<td>3.6</td>
<td>CACTATCAGCAAAAGAGGAG</td>
<td>GCCGGAAGCAGGAGAGATA</td>
<td>499</td>
<td>57</td>
</tr>
<tr>
<td>3.7</td>
<td>AAGACCTATTGTCTCCCTGAA</td>
<td>TCTGCTAGAGCCTTCTGTTG</td>
<td>475</td>
<td>57</td>
</tr>
<tr>
<td>3.8</td>
<td>GACCATGACTCAGCAAC</td>
<td>CAGACACTTTGGCTCTCATGG</td>
<td>570</td>
<td>57</td>
</tr>
<tr>
<td>3.9</td>
<td>AGTGGCAATTGGGAGGAGAT</td>
<td>GCTCAGTGGTCTGAAAGCTC</td>
<td>530</td>
<td>57</td>
</tr>
<tr>
<td>3.10</td>
<td>GAGTCTCTCCTGTAATCTCT</td>
<td>TGGTCTGTGGCCTCTGTG</td>
<td>525</td>
<td>57</td>
</tr>
<tr>
<td>3.11</td>
<td>GAGGCTTCAAGGAGAAGC</td>
<td>AGGAGAAGGAGAGAGGAGAT</td>
<td>467</td>
<td>57</td>
</tr>
<tr>
<td>3.12</td>
<td>ACACGTGCCCTCCCACAAAAG</td>
<td>CTCAACGCACTGAGACACTG</td>
<td>550</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>CCAGCCTGAAGGAGCTGAG</td>
<td>GTGAGCTGAGGAGAGGAGT</td>
<td>207</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>TCCGCTGGTCTGAGAACAAAAC</td>
<td>GAAAGTTGAGGAGAACAAA</td>
<td>420</td>
<td>58</td>
</tr>
<tr>
<td>6.1</td>
<td>ACGTGTAGCCGGAGGTCTG</td>
<td>AGAGCCCAAGGAGGAGC</td>
<td>549</td>
<td>58</td>
</tr>
<tr>
<td>6.2</td>
<td>GACGTGTTTCAGAAGCACCCTTCC</td>
<td>GTCGCGGTACACCTTACC</td>
<td>489</td>
<td>58</td>
</tr>
<tr>
<td>6.3</td>
<td>GGACATGCTCAGCTGCTTCCC</td>
<td>CAGCTGAATCTGCTGAGAAT</td>
<td>545</td>
<td>62</td>
</tr>
<tr>
<td>6.4</td>
<td>GAACTATGCTCGTCTTCCC</td>
<td>CAGCTGAATCTGCTGAGAAT</td>
<td>545</td>
<td>62</td>
</tr>
</tbody>
</table>
scribed in table 1. PCR products were purified and then analyzed by direct sequencing using the BigDye terminator v3.1 Cycle Sequencing Kit and the ABI Prism 3130 Genetic Analyzer (all from Applied Biosystems, Carlsbad, Calif., USA). The gene mutation nomenclature used in this article follows the recommendations of den Dunnen and Antonarakis [2001]. When material from the parents was available, a family study was performed to prove that the mutation occurred de novo.

Results

Patients presenting with clinical symptoms of SMS (fig. 1; table 2), but without 17p11.2 deletion, were referred to us, and we screened them for mutations in the RAI1 gene. We report here 9 novel mutations, all in exon 3 of the gene (fig. 2), that support a diagnosis of SMS in these cases.

RNS78

RNS78 is the third child of healthy unrelated parents. Pregnancy was normal, but she had major reflux problems in the neonatal period. She developed overgrowth at ~5 months of age and is bulimic. In addition to facial dysmorphism and extremity anomalies, she suffers significant sleep disturbance including early awakening, early sleeping in the evening and multiple napping. She presents learning difficulties and an oppositional behavior with aggressiveness; she is, however, sociable.

Laboratory findings included a normal karyotype and normal FISH for del(17)(p11.2). RNS78 has a heterozygous cytosine to thymine transition at nucleotide 238 (c.238C>T) in the RAI1 gene, producing a nonsense substitution (p.Arg80*): the reading frame is interrupted by a premature stop codon.

RNS59

RNS59 presents with developmental delay, significant language retardation, behavioral problems, and major sleeping disturbance. He spoke his first word at the age of 3 years and his first sentence at 5. He displays impulsiveness and self- and heteroaggressiveness. A study of the rhythm of melatonin release gave a flat trace with an inversion of the circadian rhythm as early as at the age of 15 months. This patient is awake for long periods through the night and frequently naps during the day, with a shorter than usual total sleep time.

Pharmacogenetic analysis of cytochrome P450 2D6 revealed an ultrarapid metabolism.

RNS59 carries a duplication of a single adenine in exon 3 at nucleotide position 3,386 on one RAI1 allele (c.3386dupA). This duplication results in a frameshift starting at amino acid position 1130, leading to misincorporation of 35 amino acids and a downstream stop codon. Neither parent carried this p.Glu1130Glyfs*36 in DNA.

RNS101

RNS101 is the second son of healthy unrelated parents. Pregnancy was normal. Early problems included frequent bronchiolitis. Growth was steady over the 2 first years and then tended to obesity. He displays developmental delay, significant language delay, behavioral problems includ-
Table 2. Clinical characteristics of patients with RAI1 mutations

<table>
<thead>
<tr>
<th>RAI1 mutation</th>
<th>Age at time of report</th>
<th>Sex</th>
<th>Growth measures, percentiles</th>
<th>Overweight</th>
<th>Developmental delay</th>
<th>Facial dysmorphism</th>
<th>Short extremities</th>
<th>Sleep disturbance</th>
<th>Behavioral problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNS78</td>
<td>8 years</td>
<td>f</td>
<td>&gt;97&lt;sup&gt;th&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ aggressiveness, overeating</td>
</tr>
<tr>
<td>RNS59</td>
<td>19 years</td>
<td>m</td>
<td>92&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ impulsiveness, aggressiveness, self-injurious behavior</td>
</tr>
<tr>
<td>RNS101</td>
<td>14 years</td>
<td>m</td>
<td>73&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ rage attacks, hyperactivity, self-injurious behavior</td>
</tr>
<tr>
<td>RNS103</td>
<td>29 years</td>
<td>m</td>
<td>&gt;97&lt;sup&gt;th&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ self-injurious behavior</td>
</tr>
<tr>
<td>RNS86</td>
<td>7.5 years</td>
<td>m</td>
<td>95&lt;sup&gt;th&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ self-injurious behavior, aggressiveness</td>
</tr>
<tr>
<td>RNS105</td>
<td>5.5 years</td>
<td>m</td>
<td>90&lt;sup&gt;th&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ overeating</td>
</tr>
<tr>
<td>RNS131</td>
<td>6 years</td>
<td>m</td>
<td>75&lt;sup&gt;th&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ impulsiveness, aggressiveness, overeating</td>
</tr>
<tr>
<td>RNS165</td>
<td>9 years</td>
<td>m</td>
<td>90&lt;sup&gt;th&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ overeating</td>
</tr>
<tr>
<td>RNS208</td>
<td>9 years</td>
<td>f</td>
<td>&lt;3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ overeating</td>
</tr>
</tbody>
</table>

HC = Head circumference; + = present; – = absent.
ing fits of anger, and moderate sleeping disturbance with night awakenings. His hands are short, and his feet are broad. He presents joint hyperlaxity.

Laboratory findings included a normal karyotype, negative fragile X and subtelomeric microrearrangement results, normal FISH for 17p11.2 deletion, and normal pangenomic array CGH. RNS101 has a heterozygous insertion of 2 guanines after nucleotide position 2,869 (c.2869_2870insGG) in the \( RAI1 \) gene, resulting in a frameshift starting at amino acid residue 957, a misincorporation of 107 amino acids and a downstream stop codon (p.Asp957Glyfs*108).

**RNS103**

RNS103 is a 29-year-old man presenting syndromic obesity. There is no family history of mental handicap or congenital malformations, and the pregnancy was normal. Birth weight was 3,340 g, and there were no feeding difficulties during the neonatal period. He presented subsequently with developmental delay including walking and language delay, but he learned to read and write and now works in an ‘Etablissement et Service d’Aide par le Travail’ (French working environment adapted to those with difficulties). Behavioral problems include significant sleep disturbance and facial dysmorphisms as well as astigmatism and hypermetropia. His hands are short with a transverse palmar crease on the left hand, and he presents hyperlaxity. Over the past 2 years, his weight has increased substantially.

Metabolic balance, fragile X analysis, MRI, high resolution karyotype, and pangenomic array CGH did not reveal any anomaly.

RNS86 carries a deletion of a single cytosine in exon 3 at nucleotide 2,643 on one allele of \( RAI1 \) (c.2643delC). This deletion results in a frameshift starting at amino acid 882, leading to misincorporation of 67 amino acids and a downstream stop codon (p.Glu882Serfs*68).

**RNS105**

RNS105 presents with moderate developmental delay and significant language retardation. He could walk at 16 months. He displays a characteristic sleep disturbance including early sleeping in the evening, early waking and...
frequent napping; however, there is no aggressive behavior. He has shawl scrotum and shows hyperlaxity with bilateral sloped feet.

Additional laboratory findings include a normal karyotype, a normal pangenomic array CGH excluding an interstitial deletion of chromosome 17p11.2 and negative fragile X and FGD1 studies. RNS105 has a heterozygous cytosine to thymine transition at nucleotide 1,297 in the RAI1 gene, producing a nonsense substitution (p.Gln433*): the reading frame is interrupted by a premature stop codon.

**Discussion**

We report 9 patients with deleterious mutations in the RAI1 gene, all displaying similar features consistent with a diagnosis of SMS; in all 9 cases, a 17p11.2 deletion was excluded by FISH, MLPA or array CGH. Clinical symptoms observed in these patients correlate with previous reports of RAI1-mutated patients [Slager et al., 2003; Bi et al., 2004, 2006; Girirajan et al., 2005, 2006; Vilboux et al., 2011]. No immunologic, cardiovascular or renal features were noted.

The RAI1 gene, located on chromosome 17p11.2, comprises 6 exons generating a 7.6-kb mRNA [Toulouse et al., 2003]. This mRNA (GenBank NM_030665.3) contains a 470-bp 5′UTR (the first 2 exons and the 16 first nucleotides of exon 3) and a 1,452-bp 3′UTR (corresponding to the sixth exon). RAI1 encodes a nuclear protein containing a single zinc finger plant homeo domain, which is also present in the trithorax family of chromatin-remodeling transcriptional regulators, implicating RAI1 in the regulation of gene transcription [Bi et al., 2005, 2006]. RAI1 has 2 putative bipartite nuclear localization signals. Functional and cellular analyses of 5 mutated forms of the human RAI1 protein indicate that the N-terminal half of the protein has transcription factor activity (within the first 1,034 amino acids), and the C-terminal half is responsible for its transportation into the nucleus [Carmona-Mora et al., 2010].

All previously reported mutations map in exon 3 (5,581 bp) which codes for more than 98% of the protein. The mutations are scattered all along this third exon, and there is no evidence for a hot spot. We report 7 frameshift and 2 nonsense mutations, also all in the third exon (fig. 2). The nonsense and frameshift mutations are predicted to result in truncated proteins due to direct or downstream stop codons.

Indeed, most deleterious mutations identified in the RAI1 gene lead to the production of truncated proteins. These mutations are unique, dominant and, in cases for which familial analysis was possible, de novo.

Antonarakis et al. [2000] suggested that single-base deletions causing frameshifts occurred in runs of identical bases, and Truong et al. [2010] postulated a preferential frameshift mutation hotspot in the RAI1 gene in a heptameric C-tract (c.3097_3103). We did not detect any mutation at this site in RAI1; however, the c.2643delC alteration predicted to cause a p.Glu882Serfs*68 frameshift mutation occurred in a mononucleotide repeat of 4 cytosines. The c.2869_2870insGG frameshift mutation maps immediately downstream from a guanine and the

c.3386dupA from 2 adenines. These mutations may therefore have been the consequence of slipped mispairing [Streisinger et al., 1966; Tautz and Schlötterer, 1994]. It is noticeable, however, that guanine and cytosine runs have a higher mutation rate than adenine and thymine runs [Sagher et al., 1999; Boyer et al., 2002].

A polymorphic CAG repeat, starting from RAI1 nucleotide position 832, encodes a polyglutamine stretch in the N-terminus of the protein. Alleles of 10–16 glutamines have been described in the general population [Bi et al., 2006]. In our cohort of 80 patients with the clinical symptoms of SMS, but without 17p11.2 deletion, 44% have 14 glutamines, 52% 13 glutamines, 2% 15 glutamines, 1% 11 glutamines, and 1% 10 glutamines. Five of our nine patients with an identified RAI1 mutation have 14 glutamines and 4 have 13 glutamines. No significant association has been reported between the length of CAG repeats and the SMS phenotype when the number of CAG trinucleotides remains in the range from 10 to 16 repeats. However, large CAG repeats could influence expressivity and severity of the SMS phenotype in patients who present a RAI1 mutation on the second allele [Seranski et al., 2001; Bi et al., 2006].

Downstream targets of the transcription factor RAI1 are involved in transcriptional regulation (RXRB, ZNF236, ZIC1, RUNX1T1, AKR7A3, FBLN1), cellular growth and cell cycle regulation (SPTBN1, POLDIP3, PPP1R14D, GLI3, KMT2A, ADD3), bone and skeletal development (PSTPIP2, ANKH), lipid biosynthesis and cholesterol metabolism (LIPE, HMGCS1, INSI1), neurological development (ZIC1, PSEN2, RXRB, CLN8, SMA4, NF1, KMT2A), behavioral functions (SCN12A), circadian activity (NR1D2, PER2, PER3, CR1Y1, ARNTL), and insulin and glucose regulation (INSIG1, PIK3R1, ZNF236, LIPE) [Girirajan et al., 2009]. Interestingly, each of these biological functions is dysregulated in SMS patients: these patients present with, in particular, obesity, altered circadian rhythm, hypercholesterolemia, hypertriglyceridemia, intellectual disability, and abnormal behavior.

The role of RAI1 haploinsufficiency in the complex pathogenicity of obesity on the one hand and of sleep disturbances on the other hand has been demonstrated. First, expression analysis reveals that Bdnf (brain-derived neurotrophic factor), a gene associated with hyperphagia and obesity, is downregulated in the hypothalamus of RAI1+/− mice, and reporter studies show that RAI1 directly regulates the expression of BDNF [Burns et al., 2010]. Second, haploinsufficiency of RAI1 in SMS fibroblasts and in the mouse hypothalamus, respectively, results in the transcriptional dysregulation of the circadian clock and causes altered expression and regulation of multiple circadian genes, including PER2, PER3, CRY1, and ARNTL [Williams et al., 2012]. This study suggests that a heterozygous mutation of RAI1 alters the circadian rhythm and results in an abnormal sleep-wake cycle, which can contribute to an abnormal feeding pattern and dependent cognitive performance.

In summary, haploinsufficiency of RAI1 is the main responsible for the neurological, behavioral and craniofacial features of SMS, even if other genes or genetic background may play a role in modulating these features. Consistent with patients previously described with RAI1 mutations, the patients we report differ from patients carrying a 17p11.2 deletion: RAI1 mutations are associated with less substantial motor delay, greater inclination to overweight, no hearing loss, no seizures, and no associated systemic malformations. Therefore, one or more other genes in the 17p11.2 region are probably involved in these variable associated features more frequently observed in SMS patients with deletions [Gropman et al., 2007]. More research is required for a better understanding of the role of additional genes and to consider new treatment strategies.

Acknowledgements

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RAI1-Truncating Mutations in SMS

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