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121 | *RAI1*, the Smith–Magenis, and Potocki–Lupski Syndromes

WEIMIN BI AND JAMES R. LUPSKI

Smith–Magenis syndrome (SMS; MIM 182290) is a multiple congenital anomalies/mental retardation disorder with characteristic craniofacial and neurobehavioral features including sleep disturbance, self-injurious behaviors, and stereotypical behaviors. Most SMS patients have an approximately 3.7 Mb hemizygous interstitial deletion of chromosome 17p11.2, which is caused by nonallelic homologous recombination (NAHR) between two flanking low-copy repeats (LCRs) termed SMS-REPs. The reciprocal recombination results in duplication of the 17p11.2 region and the newly defined Potocki–Lupski syndrome (PTLS; MIM 610883), a neurological disease with features of autism. Mutations in the retinoic acid (RA) induced 1 gene (*RAI1*; MIM 607642) have been identified in phenotypic SMS patients without fluorescence in situ hybridization (FISH) detectable deletions. Haploinsufficiency of *RAI1* causes the majority of the SMS characteristics as determined by both human and mouse studies; whether or not PTLS results from *RAI1* gene dosage remains to be elucidated.

LOCUS AND DEVELOPMENTAL PATHWAY

Genomic disorders represent a category of human diseases that are caused by genomic rearrangement facilitated by genome structure features involving LCRs (**Lupski, 1998, 2003; Lupski and Stankiewicz, 2005, 2006**). Patients with SMS usually have a deletion in the short arm of chromosome 17 subband p11.2 (Fig. 121–1), a gene rich and highly unstable region near to the centromere (**Stankiewicz et al., 2006**). LCRs usually span approximately 10–400 Kb of genomic DNA and share ≥97% sequence identity. LCRs constitute >23% of the analyzed genomic sequence in proximal 17p—an experimental observation 4-fold higher than predictions based on virtual analysis of the genome (**Stankiewicz and Lupski, 2002; Stankiewicz et al., 2003**). The complex genome architecture in 17p was generated by a series of consecutive segmental duplications during primate genome evolution (**Stankiewicz et al., 2003, 2004; Ou et al., 2006**).

Genomic structure involving LCRs in 17p plays an important role in a variety of constitutional chromosome rearrangements generated in meiosis as well as somatic rearrangements during mitosis (Fig. 121–1). The common recurrent deletion of an approximately 3.7 Mb interval in SMS results from NAHR utilizing flanking LCRs, the proximal and distal copies of SMS-REPs, as recombination substrates (**Chen et al., 1997; Shaw et al., 2002; Bi et al., 2003**). NAHR between SMS-REPs also causes the reciprocal duplication of the same interval in patients with PTLS, a genomic disorder with neurological symptoms milder than SMS but can present clinically with autistic features (**Potocki et al., 2000a, 2007; Bi et al., 2003**). In 17p12, approximately 2 Mb distal to the SMS common deletion, two approximately 24 Kb LCRs, termed the "CMT1A-REP," serve as substrates for NAHR resulting in reciprocal duplication and deletion of an approximately 1.4 Mb genomic region in patients with Charcot–Marie–Tooth type 1A disease (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP), respectively (**Pentao et al., 1992; Chance et al., 1994; Reiter et al., 1996, 1997, 1998**). Seven other LCRs designed LCR17pA to G have been identified in 17p of which LCR17pA is also present in the mouse genome and is the progenitor of many repeats in 17p (**Stankiewicz et al., 2004; Zody et al., 2006**). The breakpoints of the evolutionary translocation t(4;19) in *Gorilla gorilla* (**Stankiewicz et al., 2001a, 2004**) and different chromosome aberrations including the uncommon recurrent deletions in SMS (**Shaw et al., 2004a**) were mapped within this approximately 383 Kb repeat. LCRs of approximately 50 Kb subunits in 17p11.2, some of which are inverted in orientation and may form cruciforms, are associated with the most common isochromosome, i(17q), one of the most common structural abnormalities in human neoplasms (**Barbouti et al., 2004**). Human disease genes in the SMS common deleted region include *FOLLICULIN* (*FLCN*) that is responsible for Birt–Hogg–Dubé (BHD) syndrome, a dominant condition characterized by a triad of fibrofolliculomas, trichodiscomas, and acrochordons (**Painter et al., 2005**), *MYO15A* that is responsible for profound autosomal recessive hearing loss (*DFNB3* in humans and *shaker-2* in mice) (**Liburd et al., 2001**), fatty aldehyde dehydrogenase (*ALDH3A*) that is mutated in Sjogren–Larsson syndrome (SLS), a recessive disorder characterized by a combination of mental retardation, congenital ichthyosis, and spasticity (**De Laurenzi et al., 1996**), and transmembrane activator and calcium-modulator and cyclophilin ligand interactor (*TACI*) that is associated with common variable immunodeficiency (**Castigli et al., 2005; Salzer et al., 2005**). Additionally, the lethal giant larvae homolog 1 (*LLGL1*) functions in regulation of cell proliferation and was suggested to be the gene involved in the 50% of medulloblastomas associated with a deletion of 17p (**Klezovitch et al., 2004**).

Identification of heterozygous point mutations in *RAI1*, a gene located within the Smith–Magenis critical region (SMCR), in 13 phenotypic SMS patients without FISH detectable deletions strongly suggests that *RAI1* is the major causative gene for SMS (Table 121–1) (**Slager et al., 2003; Bi et al., 2004, 2006; Girirajan et al., 2005, 2006**). *RAI1* lies in the middle of the SMCR and consists of six exons spanning over 120 Kb. The third exon contains >90% of the coding region and is the exon in which all point mutations have been identified to date. *RAI1* (transcript AY172136) encodes a 1906 amino acid protein (**Toulouse et al., 2003**). In the RAI1 amino terminus, a polymorphic CAG repeat, starting from nucleotide 832, encodes a polyglutamine stretch (Fig. 121–2). RAI1 has two bipartite nuclear localization signals (NLS) for transporting RAI1 into the nucleus and two serine-rich stretches whose function remains unknown. Existence of splice variants is indicated by several bands in Northern blot analysis and several overlapping transcripts identified (cDNA accession numbers: AJ271790, AB058723, and BC021209).

Multiple lines of evidence suggest that *RAI1* functions as a transcriptional regulator. An extended plant homeodomain (PHD) zinc finger, ZNF2 domain, is present in the carboxyl-terminus consisting of residues 1832-1903 (**Bi et al., 2004**). The PHD domain in *RAI1* is conserved in the trithorax family of nuclear proteins involved in the formation of a chromatin remodeling complex and in transcriptional regulation (**Milne et al., 2002; Nakamura et al., 2002**). *RAI1* and transcription factor 20 (*TCF20*), also named stromelysin1 platelet-derived growth factor (PDGF)-responsive element-binding protein (*SPBP*), likely evolved from a common ancestor gene. These two genes share similar genomic structure, closely related ZNF2 domains, and stretches of amino acid sequence with 50% or more identity (**Rekdal et al., 2000; Seranski et al., 2001**). TCF20 is a nuclear transcriptional cofactor that may stimulate activities of several transcription factors and contribute to attenuating and fine-tuning estrogen receptor α activity (**Rajadhyaksha et al., 1998; Lyngso et al., 2000; Rekdal et al., 2000; Gburcik et al., 2005**). Furthermore, Rai1 can be transported to the nucleus and has transactivation activity in its amino terminus according to in vitro transfection experiments (**Bi et al., 2005**).

In Northern blot analysis an approximately 8 Kb major transcript of human *RAI1* is ubiquitously expressed in all the tissues

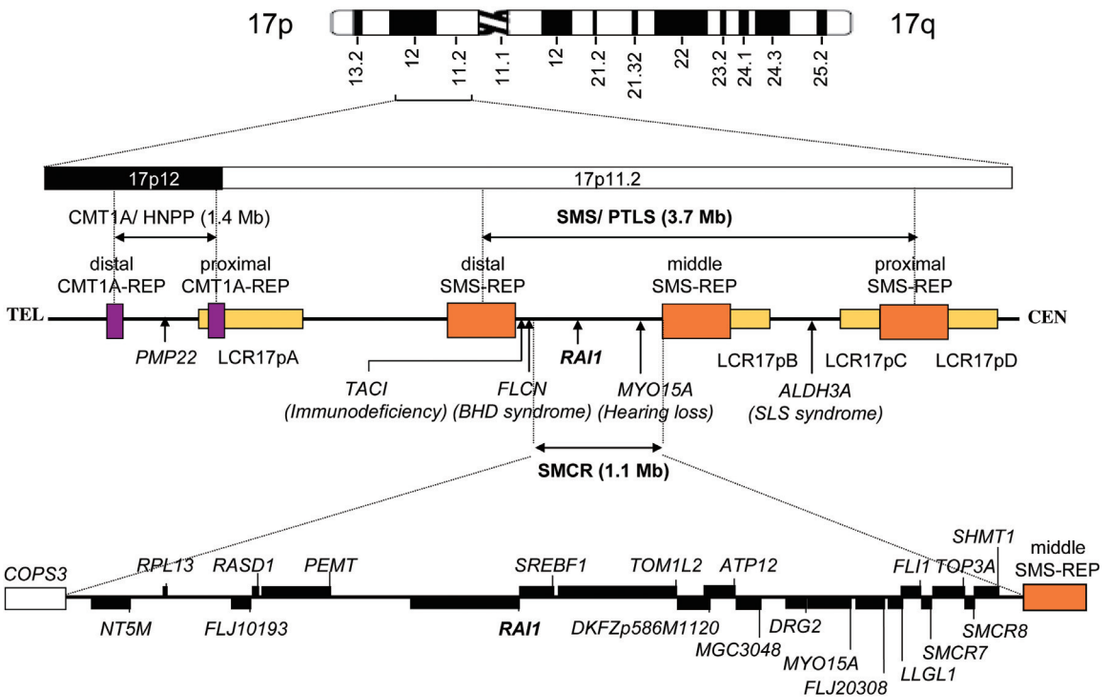

Figure 121–1. Schematic diagram of genomic architecture in chromosome 17p11.2-p12. The ideogram of human chromosome 17 is depicted above. The 3.7 Mb genomic interval in 17p11.2 that is commonly deleted in Smith–Magenis syndrome (SMS) or duplicated in Potocki-Lupski syndrome (PTLS) is flanked by two copies of LCRs "SMS-REPs" arranged in the same (or direct) orientation. A third copy is in the middle and is in reverse orientation. Two different LCRs "CMT1A-REPs" in 17p12 are located telomeric to the SMS region, mediating the 1.4 Mb duplication and deletion in Charcot–Marie–Tooth type 1A disease (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP), respectively. There are four additional >90 kb LCRs, LCR17pA, B, C, and D. The human disease genes located within this region are marked. Bottom shown are the twenty genes identified in the 1.1 Mb SMS critical region (SMCR).

studied (**Seranski et al., 2001; Toulouse et al., 2003**). Mouse *Rai1* (also named *GT1*) was first cloned by gene trapping when *Rai1* was up-regulated during neuron differentiation of mouse P19 embryonic carcinoma cells after RA treatment (**Imai et al., 1995**). In situ hybridization and immunohistochemistry showed that *Rai1* is expressed in multiple tissues and neuron-specifically in the adult mouse brain (**Imai et al., 1995**). We generated a *Rai1* null allele in mice carrying a *lacZ* reporter gene in the *Rai1* gene locus (**Bi et al., 2005, 2007**). Expression of *lacZ* in the heterozygous mice visualized by X-gal staining recapitulated the endogenous *Rai1* expression. Consistently, X-gal staining showed that in adult brain *Rai1* is expressed in the neurons predominantly in the hippocampus and the cerebellum. During embryogenesis, the expression of *Rai1* is mainly observed in epithelial cells such as the epithelium lining the olfactory pit and nasal process, otic vesicle, endoderm of bronchial arches, and apical ectodermal ridge (AER), gut, Rathke's pouch, and thyroid primordium. That *Rai1* is expressed predominantly in the primordia of many organs affected in SMS suggests that it is involved in the normal development and/or function of these organs.

CLINICAL DESCRIPTION

SMS is a clinically recognizable microdeletion syndrome with multiple congenital anomalies and mental retardation (MCA/MR), first described in 1982 (**Smith et al., 1982**). The spectrum of clinical features was delineated in 1986 (**Smith et al., 1986; Stratton et al., 1986**), and a multidisciplinary study was reported in 1996 (**Greenberg et al., 1996**). The most characteristic features of SMS are its specific neurobehavioral anomalies, disrupted sleep function, defined craniofacial anomalies, and brachydactyly, which distinguish this syndrome from other mental retardation syndromes with developmental delay (**Gropman et al., 2006**). Less common features include otolaryngologic abnormalities, hearing impairment, ophthalmologic anomalies, minor skeletal anomalies, obesity, and renal and cardiac anomalies. The clinical features frequently seen in SMS are summarized as Tables 121–2 and 121–3.

The facial appearance of SMS is quite distinctive and is characterized by a broad square-shaped face, broad nasal bridge with reduced nasal height, downturned mouth with fleshy and everted upper-lip with bulky philtral pillars. With progressing age, the facial features become more distinctive and coarse with increased jaw width and marked midface hypoplasia and prognathia, changing from micrognathia in infancy (**Allanson et al., 1999**). The SMS facial features can be quantified and discriminated from normal controls by three-dimensional facial morphology (**Hammond et al., 2005**).

Other common physical features are short stature, hoarse deep voice, dental anomalies, obesity, and dry skin. Minor skeletal anomalies include hand anomalies and scoliosis. Short and broad hands with brachydactyly are found in 85% of cases (**Greenberg et al., 1996; Schlesinger et al., 2003**), and reported digital anomalies are fifth finger clinodactyly, prominent finger pads, polydactyly (six digits), and syndactyly (**Kondo et al., 1991; Chen et al., 1996a; Mariannejensen and Kirchhoff, 2005**).

SMS patients exhibit both cognitive and maladaptive behaviors (Table 121–3). Self-injurious and stereotypical behaviors generally begin after 18 months of age. All patients have some level of learning difficulties and often severe speech impairment that can be out of proportion to other delays in development. Significant speech/expressive language delay and global motor delay of 2–24 months occur in over 90% of SMS patients (**Greenberg et al., 1996**). Most SMS patients function in the mild to moderate ranges of mental retardation. About 20% of patients reported a seizure history, and epileptiform electroencephalogram (EEG) patterns are not uncommon (27/31) (**Goldman et al., 2006**).

The self-injurious, maladaptive, ritualistic behaviors in SMS are distinct from and more severe than in other genetic syndromes (**Colley et al., 1990; Greenberg et al., 1991, 1996; Finucane et al., 2001; Clarke and Boer, 1998; Dykens and Smith, 1998; Smith et al., 1998a**). Maladaptive behaviors consist of frequent outbursts/temper tantrums, attention seeking, aggression, impulsivity, attention deficit,

disobedience with relative strengths in socialization, and relative weakness in daily living skills (**Madduri et al., 2006**). Frequently observed self-destructive behaviors are head banging, skin picking, nail biting, self-hitting, insertion of foreign objects into body orifices (polyembolokoilamania), and yanking out of finger and/or toe nails (onychotillomania) (**Greenberg et al., 1991, 1996**), which may be partially due to decreased sensitivity to pain. Stereotypic behaviors include spasmodic upper-body squeezing manifesting as self-hugging (**Finucane et al., 1994**) that is exacerbated by excitement, hand licking and page flipping (lick and flip) (**Dykens et al., 1997**), body rocking, and teeth grinding.

Table 121–1. Phenotypic Features: del(17)(p11.2p11.2) vs *RAI1* Mutation

	del(17)(p11.2p11.2)		*RAI1* Mutations	
	Common* %	Overall† %	Frequency††	%
Craniofacial				
Midface hypoplasia		93	10/13	77
Brachycephaly		89	10/13	77
Broad face		81	12/13	92
Downturned upper lip		73	11/13	85
Synophrys		62	3/10	30
Prognathia		52	9/10	90
Skeletal				
Brachydactyly		85	11/13	85
Short stature (<5th centile)	62	66	1/12	8
Scoliosis	60	61	4/12	33
Neurobehavioral				
Mental retardation	100‡	100‡	13/13	100
Sleep disturbance	100	100	11/11	100
Self-hugging		70–100	12/13	92
Self-injury		78–96	13/13	100
Seizures		19	3/13	23
Organ system and others				
Ophthalmologic abnormalities	92	91	7/10	70
Otolaryngologic abnormalities	91	90	9/10	90
Hearing impairment	72	67	2/12	17
Cardiac abnormality	39	45	1/12	8
Renal anomaly	15	19	0/10	0

*Reported in **Potocki et al., 2003** for patients with a SMS common deletion.
†Percentages are from **Chen et al., 1996a, Finucane et al., 2001,** and **Potocki et al., 2003** for patients with a deletion in 17p11.2.
‡From **Madduri et al., 2006**.
††Frequency based on data reported in **Slager et al., 2003; Bi et al., 2004, 2006,** and **Giriajan et al., 2005; 2006**.

Significant sleep disturbances are usually present in SMS patients when assessed by objective criteria (**Greenberg et al., 1991, 1996; Smith et al., 1998b**). SMS children and adults have difficulties falling asleep, frequent and prolonged nighttime awakenings, reduced rapid eye movement (REM) sleep, excessive daytime sleepiness, daytime napping, snoring, and bedwetting (**Greenberg et al., 1996; Smith et al., 1998b; Potocki et al., 2003**). The altered sleep pattern may be related to a shift in phase of the peak melatonin secretion from the night into the day documented in SMS individuals (**Potocki et al., 2000b; De Leersnyder et al., 2001b**).

Otolaryngologic and ophthalmologic defects are common. Most of the hearing loss in SMS is conductive possibly related to frequent chronic otitis media that often leads to multiple pressure equalizing (PE) tube placements. One patient with sensorineural hearing loss had a hemizygous missense mutation in *MYO15A*, a gene in the critical deletion interval responsible for the recessive deafness locus *DFNB3* (**Liburd et al., 2001**). The most common ocular findings are iris anomalies, microcornea, high myopia, and strabismus (**Finucane et al., 1993a; Chen et al., 1996b**). Cardiovascular abnormalities were reported in 27% of cases (**Greenberg et al., 1996**) and consist of ventricular septal defects (VSD), atrial septal defects (ASD), supravalvular aortic or pulmonic stenosis, mild tricuspid or mitral valve regurgitation, and total anomalous pulmonary venous return (**Myers and Challman, 2004**). SMS is sometimes misdiagnosed as velocardiofacial syndrome (VCFS) or DiGeorge syndrome because of these cardiac anomalies. Thirty-five percent of SMS patients have renal anomalies including duplication of the collecting system, unilateral renal agenesis, and ectopic kidney.

More than half of the SMS patients have hypercholesterolemia with their lipid values greater than the 95th centile for at least one of the following: total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) (**Smith et al., 2002**). The sterol regulatory element-binding protein-1 (*SREBF1*) gene is located within the SMCR. However, the heterozygous gene-disrupted mice were pheotypically normal. Clinical signs suggestive of peripheral neuropathy were found in 55% of patients and include decreased or absent deep tendon reflexes, decreased sensitivity to pain, flat (pes planus) or highly arched (cavus) feet, and decreased leg muscle mass (**Greenberg et al., 1991**). Nerve conduction velocities are normal in SMS. Other reported but less represented defects are hypothyroidism, mildly decreased immunoglobulins, obesity, and constipation.

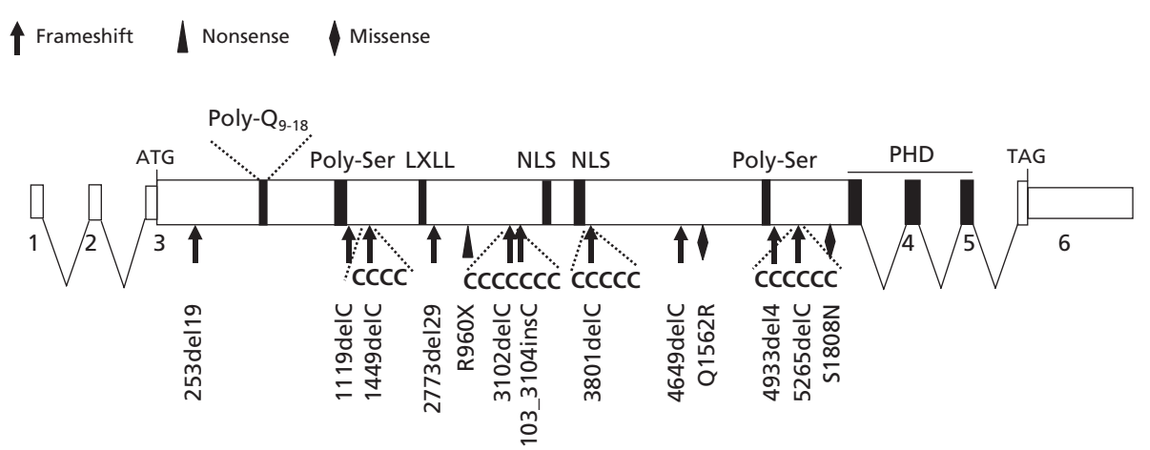

Figure 121–2. Gene structure of *RAI1* and point mutations found in SMS patients. Functional domains are indicated by black boxes including a poly-Q stretch encoded by polymorphic CAG repeats, two polyserine stretches, a nuclear hormone receptor-interacting domain containing a LXLL motif, two nuclear localization signals (NLS), and a plant homeodomain (PHD) zinc finger in the C terminus. Arrows depict frameshift mutations, arrowheads nonsense mutations, and diamonds missense mutations. The C-tracts that *RAI1* point mutations occurred in are indicated.

Table 121–2. Specification of Clinical Findings in SMS

Features	Proportion	Percentage	Reference
Craniofacial			
Midface hypoplasia	92/99	93	1
Brachycephaly	85/95	89	1
Broad nasal bridge	72/86	84	1
Broad face	43/53	81	1
Ear abnormalities	71/96	96	1
Tented mouth	48/66	73	1
Synophrys	25/40	62	1
Frontal bossing	51/90	57	1
Prognathia	43/83	52	1
Skeletal			
Brachydactly	82/96	85	1
Short stature	61/89	69	1
Scoliosis	22/52	42	1
Syndactyly	18/49	37	1
Pes planus/Pes cavus	11/23	47	2
Otolaryngologic	16/17	94	2
Hearing impairment	17/25	68	2
Hoarse, deep voice	53/66	80	1
Abnormal laryngoscopy	4/12	33	2
Ophthalmologic	23/27	85	2
Iris anomalies	19/28	67	3
Microcornea	14/28	50	3
Myopia	18/28	64	3
Strabismus	9/28	32	3
Cataracts	4/10	40	4
Retinal detachment	4/10	40	4
Ptosis	1/9	11	1
Ambylopia	1/9	11	1
Cardiovascular	20/70	28	1
Abnormal echocardiogram	5/12	41	2
Ventricular septal defect, VSD			
Atrial septal defect, ASD			
Mild regurgitation			
Tetralogy of Fallot			
Stenosis			
Mitral valve prolapse			
Pulmonary atresia			
Renal/urinary tract	12/43	27	1
Abnormal ultrasound	9/26	34	2
Duplication of the collection system			
Renal ectopia			
Unilateral renal agenesis			
Vesiculoureteral reflux and megaureter			
Ureteral vesicular obstruction			
Signs of peripheral neuropathy	17/31	54	5
Decreased deep tendon reflexes	10/16	62	5
Decreased sensitivity to pain	8/16	50	5
Other			
Obesity			
Low thyroxin (T4)	7/24	29	2
Low immunoglobulins	3/13	23	2

References: 1, **Chen et al., 1996a;** 2, **Greenberg et al., 1996;** 3, **Chen et al., 1996b;** 4, **Finucane et al., 1993a;** 5, **Greenberg et al., 1991**.

Duplications of 17p11.2 were mostly reported in isolated case reports or literature reviews consisting of a few duplications not molecularly defined **(Kozma et al., 1991; Roa et al., 1996)** and marker chromosomes **(Stankiewicz et al., 2001b; Shaw et al., 2004b; Yatsenko et al., 2005)**. A recent multidisciplinary study on 35 patients with the molecularly characterized 17p11.2 duplications, 22 of which have the common duplication, determined that duplication 17p11.2 syndrome is a distinct clinical entity that was referred to as the Potocki–Lupski syndrome **(Potocki et al., 2007)**. The key clinical findings in this study and reported in the original seven common duplication patients **(Potocki et al., 2000)** are summarized as Table 121-4. The features observed in >90% of PTLS patients are developmental delay, language impairment, cognitive impairment, poor feeding, hypotonia, and oral-pharyngeal dysphasia. The clinical features observed in patients with PTLS are distinct from those seen with SMS although cognitive and neurobehavioral abnormalities are present in both disorders. The PTLS patients lack the self-injurious and attention seeking behaviors found in most individuals with SMS. Instead, when evaluated by objective clinical assessment, the majority of them have autistic features such as decreased eye contact and motor mannerisms. Most PTLS patients have no facial abnormalities but can have a triangular face. The other clinical features present in over half of patients include sleep apnea, abnormal EEG, attention deficit, hypermetropia, and cardiovascular abnormalities.

IDENTIFICATION OF A MAJOR GENE AND MUTATIONAL SPECTRUM

The interstitial deletions in the SMS were originally identified by metaphase chromosome analysis (**Patil and Bartley, 1984; Smith et al., 1986; Stratton et al., 1986; Popp et al., 1987; Hamill et al.,**

Table 121–3. Neurobehavioral Phenotypes in SMS

Features	Percentage	Ref.
Developmental/cognitive profile		
Mental retardation (ranging 20–78)	100	1
Speech delay	96	1
Infantile hypotonia	51	1
Seizures	18	2
Abnormal EEG	52	2
Maladaptive behaviors		
Disobedience	94–100	3
Hyperactivity	94–100	3
Temper tantrums	94–100	3
Attention-seeking	94–100	3
Lability	89	3
Property destruction	86	3
Impulsivity	86	3
Argumentative	80	3
Nervousness	66	3
Physical aggression	57	3
Daytime wetting and soiling	54	3
Sleep disturbances		
Enuresis	82	4
Naps during day	82	4
Bedtime rituals	81	4
Snoring	69	4
Daytime drowsiness	68	4
Medication to facilitate sleep	59	4
Awaken for drink or bathroom	54	4
Self-injury/stereotypic behaviors behaviors		
Hand/wrist biting	93	5
Head banging	55	5
Self-slapping	62	5
Skin picking	52	5
Hair pulling	34	5
Onychotillomania	29–48	3, 5
Polyembolokoilamania	25–31	3, 5
Inserting hands into mouth	69	3
Inserting objects into mouth	54	3
Teeth grinding	54	3
Licking and page flipping	51	3
Self-hugging	46	3

References: 1, **Greenberg et al., 1996;** 2, **Goldman et al., 2006;** 3, **Dykens et al., 1998;** 4, **Smith et al., 1998b;** 5, **Finucane et al., 1994**.

Table 121–4. Clinical Features of Potocki–Lupski Syndrome

Features	Frequency*	%	Notes
Development and growth			
Developmental delay†	24/24	100	
Feeding difficulties†	18/19	95	
History of hypotonia†	19/21	90	
Gastroesophageal reflux	11/15	73	
Failure to thrive†	13/18	72	
Low birth weight	10/21	48	
Failure to progress at birth	7/18	39	And/or cesarean section
Gastrostomy tube	6/18	33	
Craniofacial/skeletal			
Scoliosis†	4/13	31	<10 degrees
Short stature†	5/21	24	
Microcephaly	2/10	20	
Neurobehavioral			
Mental retardation†	24/24	100	Variable, borderline to mild
Speech and language problems†	19/20	95	Language impairment, articulation difficulty
Autistic features†	10/12	83	
Abnormal EEG†	11/14	78	
Hyperactive or attention deficit†	5/7+	71	
Subjective sleep problems†	5/16	31	
Epilepsy†	1/20	5	
Organ system and others			
Oral-pharyngeal dysphasia	9/10	90	Swallow difficulty, bifid uvula
Sleep apnea	8/9	89	Central and/or obstructive
Dental anomalies†	6/7+	86	Malocclusion and crowded teeth
Hypermetropia††	9/15	60	
Cardiovascular defects†	6/11	55	Atrial septal defect, atrial dilatation, patent foramen ovale, dilated pulmonary annulus
CNS abnormality by MRI	7/14	50	Mild attenuation of corpus callosum, mild delay in myelination, prominence of semicircular canal and vestibule
Low total cholesterol and low LDL††	3/7	43	
Mildly low thyroxin†	2/7	28	Normal thyroid-stimulating hormone
Structural kidney defects†	2/13	15	Poor corticomedullar differentiation
Hearing loss†	1/16	6	Mild sensitivity loss in 20%

*From **Potocki et al., 2007**.
+From **Potocki et al., 2000**.
†Features that are also frequently present in SMS, but the severity and frequency may be different between SMS and PTLS.
††Features that are opposite to those in SMS.
Abbreviations: SMS, Smith–Magenis syndrome; PTLS, Potocki–Lupski syndrome

1988; Lockwood et al., 1988; Colley et al., 1990). DNA markers in chromosome 17p were then gradually developed (**Vance et al., 1989; Chance et al., 1990; McAlpine et al., 1990; Middleton-Price et al., 1990; Patel et al., 1990a, 1990b; Guzzetta et al., 1991, 1992; Raeymaekers et al., 1991; Vance et al., 1991**). Molecular analysis demonstrated that the majority of SMS patients have a common deletion interval spanning 4–5 Mb between marker *D17S58* proximally and cosmid cCI1798 distally (**Greenberg et al., 1991; Juyal et al., 1996a**). Three large copies of a complex LCR (SMS-REPs) were identified within the common deletion region (**Chen et al., 1997**; **Park et al., 2002**). The proximal SMS-REP (~256 Kb) and the distal copy (~176 Kb) are located in the same orientation, whereas the middle SMS-REP (~241 Kb) is inverted. The directly oriented proximal and distal copies of SMS-REP act as substrates for NAHR, resulting in deletions and the predicted reciprocal duplication (**Chen et al., 1997; Potocki et al., 2000a**; **Bi et al., 2003**). The SMS-REP LCRs are highly homologous (>98%) and contain at least 14 genes/pseudogenes each (**Park et al., 2002**). Other "SMS-REP-like" structures of approximately 11–30 Kb fragments, and often including the *TRE2/ubiquitin-specific protease 6 (USP6)* oncogene (**Paulding et al., 2003**), are present on chromosome 17 in multiple copies (**Park et al., 2002; Ou et al., 2006; Zody et al., 2006**).

About 70% of SMS patients have the common recurrent deletion that is approximately 3.7 Mb in size; about 5% have an uncommon, recurrent rearrangement of approximately 5 Mb (**Shaw et al., 2004a**); and 20% have unusual smaller or larger deletions ranging in size from approximately 1.5–9 Mb (**Greenberg et al., 1991; Trask et al., 1996; Juyal et al., 1996a; Chen et al., 1997; Potocki et al., 2003; Stankiewicz et al., 2003; Vlangos et al., 2005**). Many of the uncommon, nonrecurrent deletion breakpoints occurred in LCRs, indicating that higher-order genomic architecture involving LCRs plays a role in unusual deletions involving 17p (**Stankiewicz et al., 2003**). Some of the

unusual deletions (i.e., uncommon and nonrecurrent) were mediated by nonhomologous end-joining (NHEJ) (**Shaw and Lupski, 2005**), whereas others utilized repetitive sequences (e.g., Alu/Alu recombination) as homologous recombination substrates (**Shaw and Lupski, 2005**). Some deletions are part of complex chromosome rearrangements (**Yang et al., 1997**; **Park et al., 1998; Potocki et al., 1999**).

The critical SMS intervals were first narrowed and confined to an approximately 1.5 Mb region between *D17S29* and cCI1738 by using FISH and somatic cell hybrid mapping in 10 patients with a deletion distinct from the common deletion (**Juyal et al., 1996a; Elsea et al., 1997**). The SMCR was further narrowed to approximately 1.1 Mb flanked by the *COPS3* gene and the middle SMS-REP (**Bi et al., 2002**) and to an approximately 950 Kb interval independently (**Vlangos et al., 2003**). The first gene identified within the SMS common deletion region was *snU3* (**Chevillard et al., 1993**), and by 2002, more than 15 genes were mapped within the SMCR including *FLII* (**Chen et al., 1995**), *MFAP4* (**Zhao et al., 1995**), *cSHMT* (i.e., *SHMT1*) (**Elsea et al., 1995**), *COP9* (i.e., *COPS3*) (**Potocki et al., 1999**), *SREBF1*, and *MYO15.* A large number of expressed sequence tags (ESTs) with no homology to known genes were also identified (**Seranski et al., 1999; Bi et al., 2002**). A BAC/PAC contig was constructed spanning the SMS common deletion for complete DNA sequencing of this region (**Lucas et al., 2001; Bi et al., 2002**). Twenty genes were identified in the 1.1 Mb SMCR by homology search and gene prediction programs, 19 of which were conserved with the same order and orientation in the mouse genome (**Bi et al., 2002**). Interestingly, synteny breaks between human and mouse chromosomes were first observed to be coincident with LCRs in the SMS region (Fig. 121–3) (**Probst et al., 1999; Bi et al., 2002**). This is now well established for human chromosome 17 by direct genomic sequence comparisons with mouse chromosome 11, the first mouse chromosome with finished sequence (**Zody et al., 2006**).

Through direct DNA sequencing of candidate genes, mutations in the *RAI1* were identified in three phenotypic SMS patients without deletion detectable by FISH (**Slager et al., 2003**). Subsequently, ten more cases of *RAI1* point mutations were reported (**Bi et al., 2004, 2006; Girirajan et al., 2005, 2006**). All mutations are unique, located within exon 3, and arise de novo (Fig. 121–2). The 13 point mutations include ten frameshift, one nonsense, and two missense mutations. The patients with *RAI1* point mutations have the majority of SMS features including craniofacial, skeletal, and neurobehavioral abnormalities (Table 121–1). Thus, *RAI1* is the major causative gene for the expression of SMS clinical phenotypes. About 37% PTLS patients carry an uncommon non-recurrent duplication and more than half of the proximal breakpoints group at or near the pericentromeric region. The identification of a patient with the key phenotypic features of PTLS and carrying a small duplication helps narrow the critical region of PTLS to a 1.3-Mb interval containing 14 genes including *RAI1* (**Potocki et al., 2007**). It is likely that *RAI1* is also the gene responsible for the major clinical phenotypes in the PTLS based on the studies on mouse models (see section "Mutants in Orthologues").

Genes other than *RAI1* may also contribute to SMS especially for those features that appear to be absent in the patients with *RAI1* point mutations such as cardiovascular and renal anomalies. It is possible that halploinsufficiency of the other genes in the common deletion might influence penetrance and severity, as suggested by studies in mouse models (**Walz et al., 2003; Yan et al., 2004, 2007; Bi et al., 2005, 2007**). For example, *RASD1*, a gene located in the SMCR, may contribute to the sleep disturbance since it is a critical modulator in the circadian timekeeping system in mice (**Cheng et al., 2004**). Identification and phenotypic comparison of more patients with *RAI1* point mutations and patients with unusual deletions combined with studies of SMS models will help understand the potential roles of other genes within the SMCR in SMS.

A polymorphic CAG repeat in the *RAI1* gene encodes a polyglutamine stretch with sizes ranging from 9 to 18 in the normal population. The size of the polymorphic CAG repeat in *RAI1* has been associated with two neurological diseases. A study on 43 neuroleptic-responder schizophrenia patients and 63 nonresponder patients indicated that the neuroleptic responders have significantly shorter CAG repeats for the *hGT1* gene (i.e., *RAI1*) (**Joober et al., 1999**). CAG repeat length in

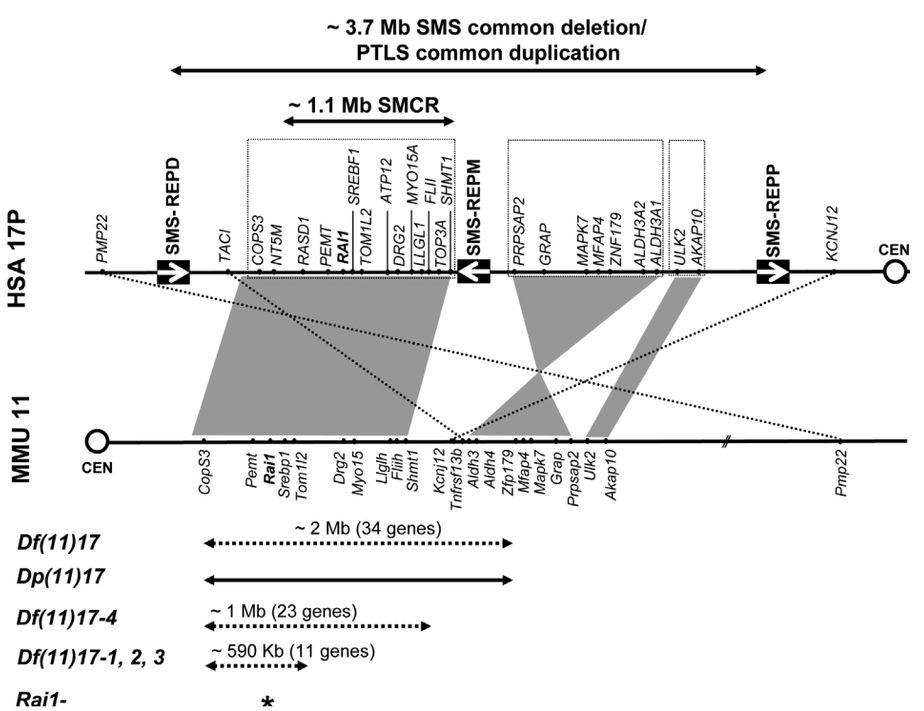

Figure 121–3. Comparison of the gene order in the human Smith–Magenis syndrome (SMS) common deletion region in 17p11.2 and its mouse syntenic region. Above are genes within the human SMS region. Black boxes represent the SMS-REPs with orientation indicated by arrows. Blocks of genes that exhibit linkage conservation (i.e., identical gene order) in humans and mice are boxed and connected via gray shading. At the bottom the regions deleted or duplicated in the SMS mouse models are indicated by double ended arrows with dotted lines for deletion and solid line for duplication.

RAI1 is also associated with age-at-onset variability in spinocerebellar ataxia type 2 (SCA2), one of a heterogeneous group of neurodegenerative disorders that is caused by the expansion of a polymorphic polyglutamine repeat (**Hayes et al., 2000**) in the ataxin-2 gene. However, no CAG repeat expansions have been reported as a causative factor for a specific phenotype including SMS nor is there any evidence that CAG variation contributes to SMS phenotypic variation (**Bi et al., 2006**).

Like many other syndromes due to gene dosage effects, the phenotype in SMS is quite variable. Different size of deletions contributes to phenotypic variation in SMS (**Trask et al., 1996; Natacci et al., 2000**). The extent of chromosomal deletion can be delineated by G-banding, FISH, pulsed-field gel electrophoresis (PFGE), and array comparative genome hybridization (aCGH). Patients with large deletions including the *PMP22* gene in chromosome 17p12 also have peripheral neuropathies manifested as HNPP in addition to SMS (**Trask et al., 1996**). Visceral anomalies occur with greater frequency in patients who have atypical deletions (**Potocki et al., 2003**). A multidisciplinary clinical evaluation of 39 SMS patients with the common deletion showed that even among the patients with deletions of identical size, the only constant objectively defined features are sleep disturbances, low adaptive functioning, and mental retardation (**Potocki et al., 2003**). A meta-analysis of 105 cases for the genotype and phenotype association was reported recently (**Edelman et al., 2007**). Patients with *RAI1* point mutation are less likely to have short stature, cardiac abnormalities, and hearing impairment. Comparison of phenotypic features of SMS patients with different molecular causes is shown in Table 121–1.

DIAGNOSIS, MANAGEMENT, AND COUNSELING

The birth incidence of SMS is reported to be approximately 1:25,000 with an equal sex ratio in Harris County, Texas, over a 2-year-period (**Greenberg et al., 1991**). This number is likely underestimated as delayed diagnosis is quite common due to the often subtle clinical features, particularly early in life. SMS patients are sometimes initially diagnosed with other mental retardation syndromes including Down syndrome (trisomy 21), fragile X-syndrome, DiGeorge syndrome and velocardiofacial syndrome, Prader–Willi syndrome (especially with obesity), and Williams syndrome. Many SMS children are given psychiatric diagnoses such as autism, attention deficit/hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), and mood disorder. Routine G-banded cytogenetic analysis and/or FISH testing using a probe covering the *RAI1* gene for a deletion in 17p11.2 can provide a definitive diagnosis of SMS. Small deletions might have been missed using some commercial probes developed before the identification of *RAI1* as the disease gene (**Vlangos et al., 2005**). For those patients with clinical features consistent with SMS but without deletion, DNA sequencing of the *RAI1* gene should be performed to evaluate for point mutations. Mosaicism for deletion 17p11.2 in peripheral blood lymphocytes and/or skin fibroblasts was also reported in patients with SMS manifestations (**Finucane et al., 1993b; Juyal et al., 1996b**). Interestingly, some cases being thought to be mosaic by G-banding of lymphocytes were shown not to be mosaic by FISH, probably because they had smaller deletions (**Juyal et al., 1995a, 1995b**). Molecular cytogenetic analysis is indispensable for the diagnosis of PTLS and most reported patients were initially identified by high resolution G-banded chromosome analysis and further confirmed by FISH analysis. However, array CGH has identified patients harboring the common or smaller duplication with a normal chromosome analysis. The implementation of array CGH in clinical genetics practice enables high sensitivity detection of duplication and deletion in this region and at the same time molecularly defining the involved genomic interval **(Shaw et al., 2004c; Lu et al., 2007).**

Almost all cases of SMS occurred sporadically, suggesting a low recurrent risk for parents. There is only one reported case of transmission of the deletion from a mother having mosaic 17p11.2 deletion (**Zori et al., 1993**). Parental balanced structural chromosome rearrangements such as 17p paracentric inversion (**Yang et al., 1997**) may increase the risk of deletion in their children. Prenatal testing is available using a combination of chromosome analysis and FISH on fetal cells from chorionic villus sampling (CVS) at 10–12 weeks' gestation or amniocentesis performed at about 15–18 weeks' gestation (**Fan and Farrell, 1994; Thomas et al., 2000**). Given its sporadic nature, the prenatal diagnosis may more likely be established by high resolution analysis of the human genome using aCGH (**Shaw et al., 2004c; Sahoo et al., 2006; Lu et al., 2007**).

Involvement of multiple systems in SMS means that newly diagnosed patients should have a multisystem screening for possible cardiac, renal, ophthalmologic, otolaryngologic, and skeletal anomalies (**Smith and Gropman, 2004**, http://www.genetests.org). Annual evaluation of these systems will facilitate early intervention. Better knowledge of the behavioral and emotional aspects of the complex genetic syndrome for the families and caregivers will make life easier. Maladaptive behaviors, in particular, aggression and attention problems, correlate with sleep disturbance (**Dykens and Smith, 1998**). Consistently, drug treatment to ameliorate sleep problems also has effects on cognitive and behavioral improvement. Two therapeutic trials have been performed by one group that showed that a combination of daytime dose of acebutolol, a selective β (1)-adrenergic antagonist which presumably blocks the endogenous abnormal circadian rhythmic release of melatonin, with an evening oral dose of melatonin restored the melatonin circadian rhythm reduced sleep disorders, and improved daytime behaviors (**De Leersnyder et al., 2001a, 2003**). Improved growth and better sleep quality have been reported with growth hormone (GH) replacement (**Itoh et al., 2004; Spadoni et al., 2004**).

MUTANTS IN ORTHOLOGUES

Mouse models have been a powerful tool for studying genomic disorders, such as DiGeorge syndrome and SMS (**Lindsay et al., 1999; Lindsay et al., 2001; Merscher et al., 2001; Walz et al., 2004b; Pentao, 2006**). The SMS common deletion is syntenic to the 32-34 cM region in mouse chromosome 11. Gene order and orientation in the SMS commonly deleted region, especially in the SMCR, is highly conserved between humans and mice (Fig. 121–3) (**Bi et al., 2002**), which makes it feasible to model SMS in mice. Orthologs of *RAI1* are present in primates, dog, rat, mouse, and chicken according to the NCBI database. In *Drosophila*, similarity was only found for the PHD domain. Murine Rai1 is a 1,890 amino acid protein that shares 81% identity and 86% similarity with human RAI1. The PHD domain, polyserine stretches, and bipartite nuclear signals are also present in mouse *Rai1*, with the exception that only two glutamines are encoded in the mouse genome instead of the polyglutamine stretch observed in humans. Several mouse models for the SMS and PTLS syndromes have been created (Fig. 121–3) and the features of these mouse lines are summarized in Table 121–5.

By chromosomal engineering a mouse model of SMS that carries an approximately 2 Mb deletion [*Df(11)17*] from the *Cops3* gene to the *Zfp179* gene was created (**Walz et al., 2003**). The deleted interval includes the majority of the mouse region syntenic to the SMS common deletion, including the complete SMCR. Animals that carry the chromosome engineered reciprocal duplication [*Dp(11)17*] were also constructed. The *Df(11)17/+* mice exhibited craniofacial abnormalities, marked obesity, seizures, abnormal circadian rhythm, and hypoactivity, which partially recapitulates the SMS phenotype (Table 121–5). The *Dp(11)17/+* mice were underweight and showed some behavioral abnormalities such as hyperactivity (**Walz et al., 2004a)**. Importantly, normalizing the gene dosage normalizes the phenotype. Compound heterozygous *Df(11)17/Dp(11)17* animals, that have a normal disomic or two copies for genes in the SMCR, had normal phenotypes including normal body weight and normal craniofacial appearance, and partially rescued behavioural abnormalities **(Walz et al., 2003, 2006)**. Therefore, the SMS phenotype is related to a gene dosage effect.

Four lines of mice [*Df(11)17-1, Df(11)17-2, Df(11)17-3*, and *Df(11)17-4*] were constructed using retrovirus-mediated chromosome engineering harboring smaller deletions of approximately 590 Kb in size covering eleven genes including *Rai1* **(Yan et al., 2004)** for the first three lines and 1 Mb for *Df(11)17-4* mice **(Yan et al., 2007)**. Both craniofacial abnormalities and obesity have been observed in the hemizygous mice, indicating that the smaller deletions contain the gene(s), most likely *Rai1*, causing craniofacial abnormalities and

Table 121–5. Mouse Models of Smith–Magenis and Potocki–Lupski Syndromes

Features		*Df(11)17/+* Δ*(Csn3−Zfp179)*	*Df(11)17−1/+* Δ*(Csn3−4933439F18Rik)*	*Rai1+/−*	*Rai1−/−*	*Dp(11)17/+ dup(Csn3−Zfp179)*	*Df(11)17/ Dp(11)17*	*Dp(11)17/ Rai1−*
Craniofacial abnormalities		+	+	+	+	−	−	−
Penetrance	mixed background	70%–80%	48%	18%	100%	NA	NA	NA
	Pure C57 BL/6 background	96%	100%	64%	NA	NA	NA	NA
Obesity		+	+	+	−	−	−	−
Underweight		−	−	−	Growth retardation	+	−	−
Reduced male fertility		+	−	−	+	−	NA	NA
T4 deficiency		+	NA	NA	NA	NA	NA	NA
Neurobehavioral abnormalities								
Overt seizures		+, 20%	NA	+, 2%	+, 30%	−	NA	NA
Abnormal EEG		+	NA	+	+	−	NA	NA
Abnormal circadian rhythm		+	NA	NA	NA	−	NA	NA
Impaired fear conditioning	Context-dependent	−	+	−	+	+	−	−
	Tone-dependant	−	+	−	+	−	−	−
Locomotor activity	Hypoactive	+	+	−	−	−	−	−
	Hyperactive	−	−	−	−	+	+	+

Note: Plus sign (+) = feature present; minus sign (-) = feature not present. "NA" means not assessed or not applicable. Without indication, mice were characterized under a C57BL6 and 129SvEv mixed background.

obesity. Similar abnormalities were also observed in the *Rai1*+/− mice. The vast majority of the *Rai1*−/− mutants were embryonic lethal and the few surviving *Rai1*−/− mice displayed malformations in both the craniofacial and the axial skeleton **(Bi et al., 2005)**. The craniofacial features were carefully studied by a combination of visual observation, skull measurements, and surface three-dimensional craniofacial scanning. In a mixed genetic background, the penetrance of the craniofacial phenotype was markedly reduced in mice with the smaller deletion when compared with larger deletion mice and it is further reduced in the *Rai1*+/− mice **(Yan et al., 2004; Bi et al., 2005)**. In a pure C57BL/6 background, the penetrance was markedly increased in both larger and smaller deletion strains and the *Rai1*+/− mice. Moreover, mice with the smaller deletion showed a penetrance similar to mice with the larger deletion and the *Rai1*+/− mice had a significantly reduced penetrance compared with the deletion strains **(Yan et al., 2007)**. These studies documented the influence of genetic background and deletion on craniofacial phenotype and suggested that the major modifying genetic element(s) resides within the 590 Kb genomic interval surrounding *Rai1*. Furthermore, these studies suggest potential trans regulatory effects perhaps analogoes to transvection **(Yan et al., 2007)**.

The notion that the *Rai1* is a critical regulator of neurobehavioral phenotype is supported by the studies on the mouse models **(Bi et al., 2007)**. The *Rai1* heterozygous mutant mice didn't display abnormal locomotor activity and/or learning deficits observed in the deletion mice and/or the duplication mice. However, *Rai1*+/− mice had an abnormal EEG and the few surviving *Rai1*−/− mice displayed severe neurobehavioral abnormalities including hind limb clasping, overt seizures, motor impairment, and context- and tone-dependant learning deficits. Additionally, X-gal staining of the *Rai1*+/− mice suggests predominant expression of *Rai1* in neurons of the hippocampus and the cerebellum.

Studies on *Dp(11)17* mice with a rescued disomic state of the *Rai1* gene have shed light on the role of *RAI1* in PTLS. Restoration of the normal disomic *Rai1* gene dosage in compound heterozygous mice carrying a *Dp(11)17* duplication along with a null allele of *Rai1* is sufficient to rescue the physical and behavioral phenotypes observed in *Dp(11)17*/+ mice **(Walz et al., 2006)**.

DEVELOPMENTAL PATHOGENESIS

Dosage insufficiency of the gene(s) in the SMS deleted region is responsible for the expression of clinical phenotypes in the SMS, as suggested by the studies in SMS mouse models. The mRNA transcribed from these truncation-carrying alleles in most patients with *RAI1* point mutations is likely either degraded through nonsense mediated decay (NMD) (**Mendell and Dietz, 2001**) or translated into a truncated nonfunctional protein. The dosage effect of the *RAI1* gene in both human and mice suggests that *RAI1* lies in a dosage-sensitive pathway that controls neuronal development and organogenesis. Genomic imprinting appears not to play a role in SMS, which was suggested by the random parental origin of deletion and the absence of any apparent parent of origin phenotypes (**Greenberg et al., 1991; Shaw et al., 2002**).

RAI1 is involved in retinoid signaling, in which RA concentration has to be precisely controlled. The expression of mouse Rai1 is up-regulated by a high concentration of RA in P19 embryonic carcinoma cells during its differentiation into neurons (**Imai et al., 1995**). An RA response element was found just upstream of exon 1 of the *RAI1* gene (**Toulouse et al., 2003**). Retinoid signaling has been implicated in many developmental processes mediated through multiple components from the enzymes that control the RA synthesis and degradation, the cytoplasmic RA-binding proteins, to the nuclear receptors that modulate gene transcription whose functions can be influenced through interactions with other proteins (**Ross et al., 2000**). Both human and mouse *RAI1* harbor a nuclear receptor interaction domain containing an LXLL motif that is found in all the coactivators interacting with retinoid receptors (**Bi et al., 2005**). *RAI1* may cooperate with retinoid receptors for the transduction of retinoid signaling. The only gene that is known to interact with *RAI1* is *TCF20*, a transcriptional cofactor (**Rekdal et al., 2000**). That TCF20 behaved as a repressor of activated estrogen receptor α hints that *RAI1* might be also involved in the regulation of hormone nuclear receptors. The PHD zinc finger, the nuclear localization, and the transactivation activity all suggest that *RAI1* functions as a transcriptional regulator possibly through formation of a chromatin remodeling complex. However, none of the target genes of *RAI1* are known.

Retinoid signaling regulates genes that control neuronal differentiation and is involved in the development of the central nervous system (**Maden, 2002**). Consistent with this, the *RAI1* gene functions in the nervous system, as indicated by the prominent feature of neurobehavioral abnormalities in SMS. The neuron-specific expression profile of *RAI1* also supports its functional involvement in neuronal development. *RAI1* is primarily expressed in neurons, and similar expression levels were shown in various subregions in both fetal and adult brains (**Seranski et al., 2001; Toulouse et al., 2003; Bi et al., 2003, 2007**). No expression was observed in the brain regions consisting predominantly

of glial cells such as the corpus callosum. Findings of structural brain anomalies are limited but consistent. Cranial computed tomography (CT) found ventriculomegaly and an enlarged posterior fossa in 9 of 25 SMS patients, although the clinical significance of this is not apparent (**Greenberg et al., 1996**). A significant bilateral decrease of gray matter concentration in the insula and lenticular nucleus of patients with SMS was reported by both three-dimensional magnetic resonance imaging (3D-MRI) and optimized VBM (Voxel-based morphometry) analysis on five boys (**Boddaert et al., 2004**). It is still unknown if these anatomical and functional anomalies are related to the behavioral features in SMS.

RAI1 is also involved in the formation of multiple systems other than the nervous system. The essential role of *Rai1* in embryonic development is indicated by the observation that the vast majority of the *Rai1* deficient mice died before birth (**Bi et al., 2005**). Obesity and similar craniofacial abnormalities were observed in different animal models (**Walz et al., 2003; Yan et al., 2004, 2007; Bi et al., 2005, 2007**), indicating that the normal dosage of *Rai1* is required for vertebrate homeostasis and skeletal development. The pathogenesis of structural malformations of the heart and kidney as well as the craniofacial, otolaryngologic, and ophthalmologic anomalies in SMS suggest that *RAI1* may contribute to the abnormal development of these systems and organs. Mouse *Rai1* is strongly expressed in organ primordia such as the otic vesicle, optic vesicle, thyroid primordium, and many others, implying that *Rai1* is required in the process of organogenesis. Major organ developmental abnormalities were not observed in all SMS mouse models. This lack of organ dysgenesis may relate to a genetic background effect as was observed for chromosome engineered mouse models of the DiGeorge/del22q11 syndrome wherein thymic and parathyroid anomalies were only observed in congenic genetic backgrounds but not in a mixed background (**Taddei et al., 2001**).

In conclusion, deletion and duplication of 17p11.2 in the genomic disorders SMS and PTLS, respectively, are stimulated and mediated by genomic structure involving LCRs. The syndromes result from rearrangements that represent the NAHR products of a reciprocal recombination event. *RAI1* is the major gene responsible for the majority of features in SMS and possibly in PTLS. *RAI1* functions as a transcriptional regulator in multiple systems including the nervous system, craniofacial development, and metabolic homeostasis.

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