Infantile Spinal Muscular Atrophy with Respiratory Distress Type 1 (SMARD1)

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Autosomal recessive spinal muscular atrophy with respiratory distress type 1 (SMARD1) is the second anterior horn cell disease in infants in which the genetic defect has been defined. SMARD1 results from mutations in the gene encoding the immunoglobulin μ-binding protein 2 (*IGHMBP2*) on chromosome 11q13. Our aim was to review the clinical features of 29 infants affected with SMARD1 and report on 26 novel *IGHMBP2* mutations. Intrauterine growth retardation, weak cry, and foot deformities were the earliest symptoms of SMARD1. Most patients presented at the age of 1 to 6 months with respiratory distress due to diaphragmatic paralysis and progressive muscle weakness with predominantly distal lower limb muscle involvement. Sensory and autonomic nerves are also affected. Because of the poor prognosis, there is a demand for prenatal diagnosis, and clear diagnostic criteria for infantile SMARD1 are needed. The diagnosis of SMARD1 should be considered in infants with non-5q spinal muscular atrophy, neuropathy, and muscle weakness and/or respiratory distress of unclear cause. Furthermore, consanguineous parents of a child with sudden infant death syndrome should be examined for *IGHMBP2* mutations.

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In 1974, Mellins and colleagues described two previously asymptomatic infants with an "unusual variant" of severe spinal muscular atrophy type 1 (SMA1). They presented with respiratory distress caused by diaphragmatic paralysis at the age of 1 and 2 months.[1] This distinguishes diaphragmatic SMA from classic SMA, in which paralysis of the diaphragm is not a presenting sign.[2–11] We mapped the gene locus of one form of diaphragmatic SMA with noncongenital onset of respiratory distress to chromosome 11q13-q21, referred to this disorder as spinal muscular atrophy with respiratory distress type 1 (SMARD1), and identified the responsible gene *IGHMBP2* which encodes immunoglobulin μ-binding protein 2.[12,13] In patients who had "severe infantile axonal neuropathy with respiratory failure" [13,14] or "early-onset severe axonal polyneuropathy with respiratory failure and autonomic involvement"[15] (this study), we also have identified *IGHMBP2* mutations. In addition, SMARD1 has been designated "distal hereditary motor neuronopathy type VI".[16] This nosological heterogeneity reflects not only confusion in terminology and the broad spectrum of clinical features in a previously undiagnosable neuropathy but may also mask a relatively high incidence of SMARD1. As in SMA1, the prognosis of SMARD1 is poor because of acute life-threatening respiratory dis-

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tress. Clearly, a better understanding of the spectrum of clinical symptoms in this disorder will facilitate the diagnosis of SMARD1. This is important in being able to offer accurate genetic counseling and to assist in the decision-making process for the initiation of mechanical ventilation of an affected infant. Here, we describe the clinical features of 29 infants affected with SMARD1 and 26 novel *IGHMBP2* mutations.

Subjects and Methods

DNA samples from 65 unrelated infants with SMA-like disease or neuropathy of unclear cause with respiratory distress were analyzed for mutations in the *IGHMBP2* gene. Details of the clinical findings in patients were documented according to a standard questionnaire. In all patients, a *SMN1* gene deletion was ruled out before our investigations. In 36 patients with a SMARD1-like phenotype including respiratory distress (male to female ratio 19:17) no mutations were found in the coding region or the exon–intron boundaries of the *IGHMBP2* gene. Another 29 infants (male to female ratio 15:14) showed *IGHMBP2* mutations, and mutations in six of these patients have been published previously.[13] In seven consanguineous SMARD1 families, one or more siblings were affected, and in one family the first two deceased infants had been suspected to be affected by sudden infant death syndrome. All parents provided written informed consent for participation of their child in this study and publication of results according to the Declaration of Helsinki.

Genetic Analysis

DNA was extracted from peripheral blood lymphocytes according to standard protocols. Polymerase chain reactions and sequencing analyses of the 15 exons including exon–intron boundaries of the *IGHMBP2* gene were performed as previously described.[13] Missense mutations were distinguished from polymorphisms by denaturing high-performance liquid chromatography analysis of 120 alleles from 60 unrelated individuals.

Accession numbers are as follows: OMIM, http://www.ncbi.nlm.nih.gov/Omim/searchomim.html, for *IGHMBP2* [*600502], SMA1 [#253300], and SMARD1 [#604320].

Results

Clinical Features of SMARD1 Infants

The main clinical features of the infants affected with SMARD1 can be subdivided systematically (Table 1).

PRENATAL FEATURES. In 23 of 24 SMARD1 patients, prenatal features of the disease were described retrospectively. Three quarters of the infants showed intrauterine growth retardation (birth weight below 10th percentile), and more than one third were born prematurely (<37 weeks gestational age) and/or showed decreased fetal movements.

RESPIRATORY SYSTEM. Life-threatening respiratory distress was the most prominent presenting symptom in infants affected with SMARD1, and inspiratory stridor and/or weak cry were its first indicators. All affected infants showed respiratory failure (Fig 1). In comparison with SMA1 patients who frequently have a bell-shaped thorax deformity due to intercostal muscle paralysis, SMARD1 patients showed eventration of the right or both hemidiaphragms without any thorax de-

Table 1. Symptoms of SMARD1 Infants and Age of Onset

Feature	No./Total No. (infants) (%)	Median (mo)	Interquartile Range	Range
Respiratory system				
Inspiratory stridor	7/14 (50)	0.5	2.8	0.0–5.1
Weak cry	21/21 (100)	1.0	2.6	0.0–5.6
Respiratory distress	29/29 (100)	3.0	3.2	0.1–12.0
Poor feeding	15/26 (58)	3.0	3.4	0.0–6.6
Respiratory failure	29/29 (100)	3.5	3.7	1.0–13.2
Neuromuscular system				
Foot deformities	19/22 (86)	1.5	6.3	0.0–24.3
Muscular hypotonia	22/27 (82)	1.8	6.0	0.0–10.1
Limb weakness distally marked	19/22 (86)	4.0	4.4	0.0–13.2
Tendon reflexes absent	18/21 (86)	4.0	3.8	0.0–42.6
Finger contractures	7/17 (41)	4.5	9.1	0.0–16.2
Cranial nerves				
Facial weakness	5/16 (31)	10.1	16.1	3.0–24.3
Tongue fasciculations	6/17 (35)	11.4	16.4	6.0–32.6
Sensory and autonomic nervous systems				
Decreased pain perception	3/11 (27)	6.6	—	5.0–10.1
Excessive sweating	7/12 (58)	5.0	1.0	3.0–68.2
Constipation	8/15 (53)	5.0	19.1	0.0–48.7
Bladder incontinence	5/10 (50)	12.0	10.2	2.0–16.2
Cardiac arrhythmia	5/7 (71)	—	—	—

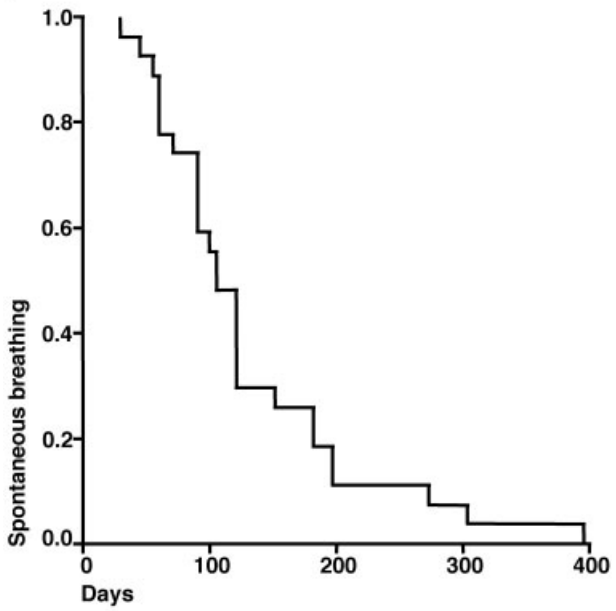

Fig 1. Kaplan–Meier analysis of overall sufficient spontaneous breathing in the study of SMARD1 infants. The latest time point, at which long-term artificial ventilation was initiated, was at day 395.

formity due to predominance of diaphragmatic paralysis (23 of 25 patients; Fig 2A).

NEUROMUSCULAR SYSTEM. Initially, affected infants showed weakness predominantly of distal muscles, usually starting in the lower limbs. Later, the upper limbs also were affected, and the progression led to a complete paralysis of limb and trunk muscles. As a result, infants developed foot deformities before finger contractures. Marked distal muscular weakness and atrophy with replacement by adipose tissue and no antigravity movements are characteristic features of hands and fingers (see Fig 2B). Corresponding to the clinical features, neurogenic changes in electromyography (22 of 25 patients), decrease in motor nerve conduction velocity (16 of 20 patients), and absent motor response after maximum stimulation (11 of 12 patients) were reported. In muscle biopsy specimens, neurogenic changes with fiber hypertrophy and atrophy were found (21 of 22 patients).

CRANIAL NERVES. Cranial nerve involvement was reported after permanent mechanical ventilation had been initiated and is not a presenting symptom in SMARD1.

SENSORY AND AUTONOMIC NERVOUS SYSTEMS. The same applies to the involvement of the sensory and autonomic nervous systems. Like in SMA, investigations

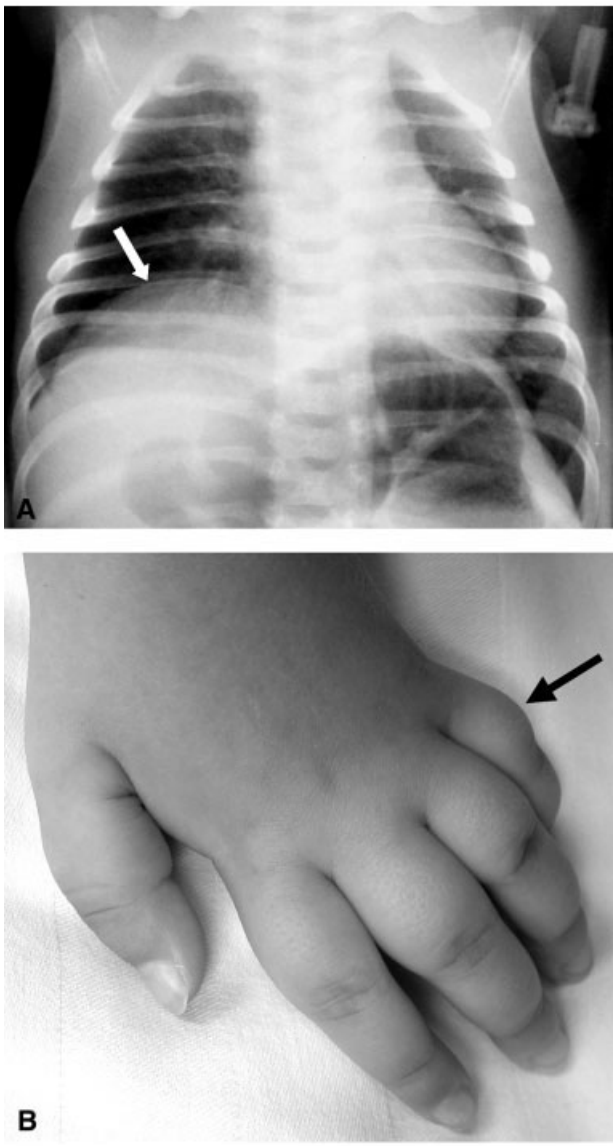

Fig 2. Features of infants with SMARD1. (A) Eventration of the right hemidiaphragm (arrow) *on chest x-ray indicated diaphragmatic paralysis in a 6-week-old girl. (B) No antigravity movements, marked muscle atrophy, and fatty pads* (arrow) *are characteristic features of hands and fingers in SMARD1 patients.*

of sural nerve biopsy specimens showed axonal degeneration (10 of 15 patients).

Genetic Results

Table 2 provides a list of the mutations in *IGHMBP2* of all 29 SMARD1 patients. Mutations in six patients have been previously published by our group.[13] Subsequently, we examined an additional 23 SMARD1 infants and found 26 novel mutations in the coding region of *IGHMBP2*, including 14 missense and 6 nonsense mutations, 4 frameshift and 1 in-frame dele-

Table 2. 1GHMBP2 *Mutations in 29 SMARD1 Infants (M:F = 15:14) Arranged according to Age at Onset of Respiratory Distress*

Patient (sex)	Geographic Origin	Age at Onset of Respiratory Distress (days)	Mutations	Amino Acid Substitutions	Class of Mutation	Exons
1(M)	Australia	3	1488C→A/1488C→A	C496X/C496X	Nonsense/nonsense	10/10
2(F)	Israel	21	114delA/114delA	—/—	Frameshift deletion/frameshift deletion	2/2
3(M)	Bangladesh	28	983delAAGAA/983delAAGAA	—/—	Frameshift deletion/frameshift deletion	7/7
4[a](M)	South Italy	30	1540G→A/1540G→A	E514K/E514K	Missense/missense	11/11
5(F)	Ghana	35	575T→C/1277T→C	L192P/L426P	Missense/missense	5/9
6(M)	Ghana	42	388C→T/1144G→A	R130X/E382K	Nonsense/missense	3/8
7[a](F)	Turkey	42	1738G→A/1738G→A	V580I/V580I	Missense/missense	12/12
8(M)	Austria	42	1714delAAG/2922T→G	K572del/D974E	In-frame deletion/missense	12/15
9(M)	Germany	45	2362C→T/—	R788X/—	Nonsense/—	13/—
10[a](F)	Lebanon	60	638A→G/638A→G	H213R/H213R	Missense/missense	5/5
11(M)	Germany	60	1082T→C/1730T→C	L361P/L577P	Missense/missense	8/12
12(F)	Australia	60	1488C→A/1808G→A	C496X/R603H	Nonsense/missense	10/13
13(M)	Australia	63	1488C→A/1748A→T	C496X/N583I	Nonsense/missense	10/12
14(F)	Germany	91	138T→A/1649insC	C46X/—	Nonsense/frameshift insertion	2/12
15(F)	Spain	91	439C→T/1488C→A	R147X/C496X	Nonsense/nonsense	3/10
16(M)	Germany	91	707T→G/1540G→A	L236X/E514K	Nonsense/missense	5/11
17(M)	U.K.	91	1488C→A/1488C→A	C496X/C496X	Nonsense/nonsense	10/10
18[a](F)	Germany	106	121C→T/675delT	Q41X/—	Nonsense/frameshift deletion	2/5
19[a,b](M)	Lebanon	106	707T→G/707T→G	L236X/L236X	Nonsense/nonsense	5/5
20(F)	Germany	106	707T→G/721T→C	L236X/C241R	Nonsense/missense	5/6
21(F)	Hungary	121	121delC/388C→T	—/R130X	Frameshift deletion/nonsense	2/3
22(F)	Belgium	121	983delAAGAA/—	—/—	Frameshift deletion/—	7/—
23(M)	Morocco	152	1000G→A/1000G→A	E334K/E334K	Missense/missense	7/7
24(M)	Turkey	152	1091T→C/2436delT	L364P/—	Missense/frameshift deletion	8/13
25[a](F)	Sicily	152	IVS13 + 1G→T/ IVS13+1G→T	—/—	Splice donor/splice donor	—/—
26(F)	Germany	167	1693G→A/1730T→C	D565N/L577P	Missense/missense	12/12
27[b](M)	Africa	182	1756G→T/1909C→T	G586C/R637C	Missense/missense	12/13
28(F)	Germany	182	439C→T/2362C→T	R147X/R788X	Nonsense/nonsense	3/13
29(M)	Australia	365	661A→G/1813C→T	T221A/R605X	Missense/nonsense	5/13

Nucleotide numbering refers to the translated part of the *IGHMBP2* mRNA beginning with A of ATG.

[a]Phenotypes of Patients 10 and 18 and *IGHMBP2* mutations of Patients 4, 7, 10, 18, 19, and 25 have been published previously.[12,13]
[b]Phenotypes of Patients 19 and 27 have been published previously.[14,15]

tions, and 1 frameshift insertion. The mutations are distributed over all exons of the gene except the 1st, 4th, and 14th (Fig 3). In two patients (Table 2, Patients 9 and 22), only one allele appeared to be mutated. Because only the coding region and the exon–intron boundaries of the *IGHMBP2* gene were analyzed, intron or promotor mutations of the second allele cannot be excluded.

Amino acids affected by missense mutations are conserved between human, mouse, rat, and golden hamster (data not shown). None of the missense mutations was detected in 120 alleles of 60 unaffected unrelated individuals, indicating that these mutations do not reflect common polymorphisms.

Discussion

Both infantile distal spinal muscular atrophy with respiratory distress type 1 (SMARD1) and infantile proximal spinal muscular atrophy type 1 (SMA1) are autosomal recessive disorders. They are characterized by degeneration of α-motoneurons in the anterior horns of the spinal cord, leading to neurogenic muscular atrophy with subsequent symmetrical muscle weakness of trunk and limbs in infancy.[1,2,4,5,7,8,12,17] Despite a substantial overlap in clinical features, the phenotypes of SMARD1 versus SMA1 infants can be distinguished.

In a retrospective study such as this, the findings on the age of onset cannot be regarded as definitive because not all infants were examined periodically from the time

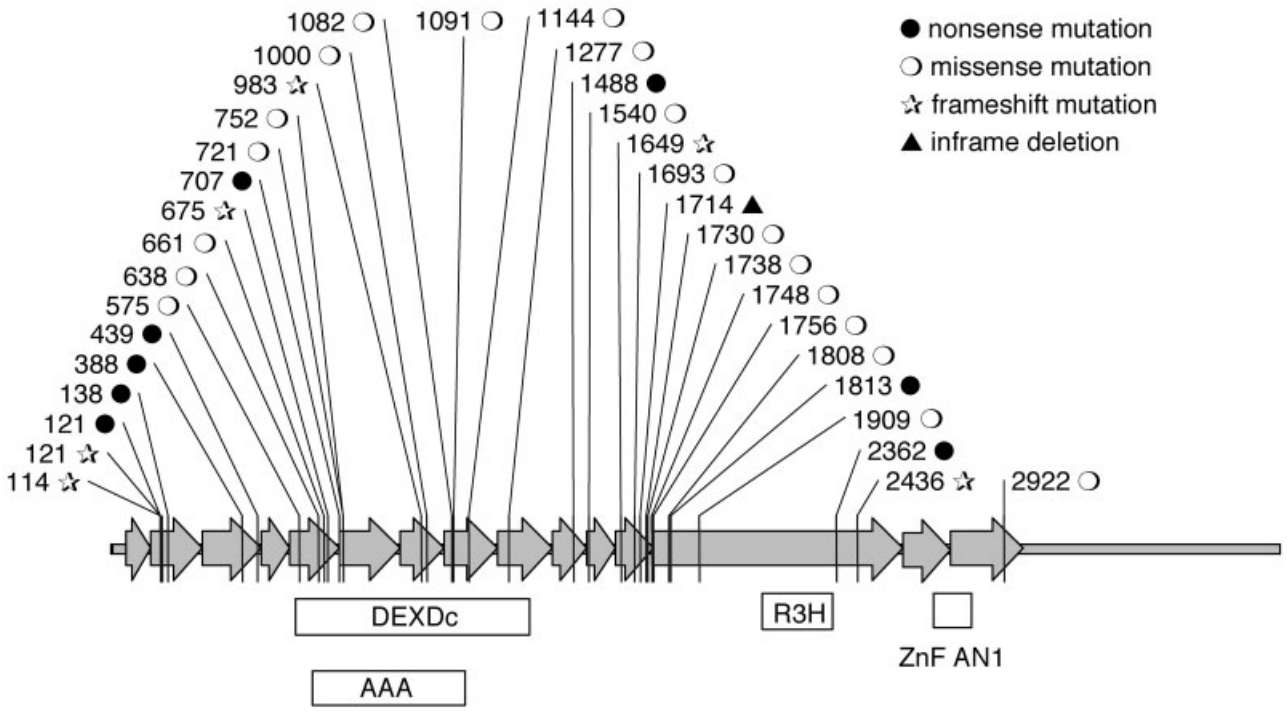

Fig 3. Position of mutations within the IGHMBP2 *protein. The coding region of the* IGHMBP2 *gene is drawn to scale. The nucleotide numbering refers to the translated part of the* IGHMBP2 *mRNA beginning with A of ATG. The exons are depicted as arrows. Most of the missense mutations occur within the DEXDc and/or AAA domains. A second hotspot is located between nucleotides 1693 and 1758. In this region, no specific functional domain has been identified so far. No mutations were located in the R3H and ZnF AN1 domains. DEXDc = DEAD-like helicases superfamily; AAA = ATPases associated with diverse cellular activities; R3H = putative single-stranded nucleic acids binding domain; ZnF AN1 = AN1-like zinc finger (simple modular architecture research tool; http://smart.embl-heidelberg.de). The single intron mutation (IVS13+1G→T, Patient 25, see Table 2) is not shown. The mutations at position nt752 and nt1730 have been described by Viollet and colleagues.*[23]

of birth. Nonetheless, prenatal features like intrauterine growth retardation were observed in almost all SMARD1 infants. This is in accordance with case reports on infantile diaphragmatic SMA.[1,3,7,8] It therefore is clear that a history of these problems is in keeping with this diagnosis and that features indicating such potential prenatal problems should be carefully assessed in pregnant women of affected families. In contrast with these less specific features, the onset of respiratory distress can be definitively recognized. Before the onset of frank respiratory distress, a weak cry and congenital foot deformities resulting from early involvement of the distal muscles of the lower limbs may have been noted. In other cases, respiratory failure appears without any indication of prior limb muscle weakness. The first presentation with respiratory failure may be mistaken for acute respiratory infection[3,4,7,8] or near-miss sudden infant death.[9] In one of our families, the first two affected siblings were reported to have died from sudden infant death syndrome. Later, the upper limbs are involved and muscle weakness rapidly progresses to generalized and symmetrical weakness of limb and trunk muscles.

Early involvement of the diaphragm and predominance of distal muscle weakness clearly distinguishes SMARD1 from SMA1. Essentially, in SMA1, symptoms manifest in reverse order. Infants with SMA1 will become floppy because of weakness of the proximal limb muscles and assume a frog leg position before they suffer from respiratory failure. In contrast with SMARD1, SMA1 infants have intercostal recessions and develop inefficient respiration due to paralysis of intercostal muscles.[17]

Although these clinical features may be discriminatory, indications of axonal type of degeneration as reported in SMARD1[14,15] also have been reported in SMA.[18–22] Not only the motor and sensory nervous systems but also the autonomic nervous system appears to be involved in SMARD1.[15]

SMARD1 is caused by mutations of the gene encoding immunoglobulin μ-binding protein 2 (*IGHMBP2*).[13] So far, nine *IGHMBP2* mutations in seven families have been reported.[13,23] The mutations previously described and those presented in this publication are distributed over 12 exons of *IGHMBP2* (see Table 2; Fig 3). Most of the missense mutations were found in a protein domain DEXDc that is common to DEAD box helicases.

A second hot spot is located between amino acids 565 and 586. The clustering of missense mutations in this area might indicate a fifth so far unidentified functionally important domain of the protein (see Fig 3). The localization and type of mutations could not be correlated to the severity of the clinical features.

In conclusion, spinal muscular atrophy with respiratory distress type 1 is characterized by diaphragmatic paralysis and peripheral neuropathy. The phenotype has some consistent features that should alert the clinician to the possibility of this diagnosis. Patients with non-5q SMA or unknown neuropathy and the consanguineous parents of a child with sudden infant death syndrome should be examined for *IGHMBP2* mutations.

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