Stüve-Wiedemann Syndrome: Update on Clinical and Genetic Aspects

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Abstract
Stüve-Wiedemann syndrome is a rare autosomal recessive disorder characterized by bowed long bones, joint restrictions, dysautonomia, and respiratory and feeding difficulties, leading to death in the neonatal period and infancy in several occasions. Since the first cases in 1971, much has been learned about this condition, including its molecular basis – mutations in the leukemia inhibitory factor receptor gene *(LIFR)* –, natural history and management possibilities. This review aims to highlight the clinical aspects, radiological features, molecular findings, and management strategies in Stüve-Wiedemann syndrome.   © 2016 S. Karger AG, Basel

In 1971, Stüve and Wiedemann described 2 sisters and a male cousin affected by a condition characterized by bowed legs and restricted joint movements, associated with other skeletal and craniofacial findings. All of them evolved with respiratory distress and died in the neonatal period. The authors recognized this condition as a distinct entity among the heterogeneous group of congenital bowing disorders. An autosomal recessive pattern of inheritance was suggested considering that there was recurrence in siblings and in a double first cousin.

The recognition of this disorder as a unique entity, later known as Stüve-Wiedemann syndrome (SWS), took several years to be achieved. Some overlapping characteristics between SWS and another specific bowing syndrome (campomelic dysplasia) described at the same time hampered the distinction. Nonetheless, experts in skeletal dysplasias recognized SWS and registered this condition in the classification of osteochondrodysplasias as a separate entity in 1992 [Spranger, 1992]. Campomelic dysplasia is acknowledged to be an autosomal dominant disorder caused by mutations in *SOX9* or by chromosome rearrangements that cause misregulation of *SOX9*.

Another challenging event that posed confusion in the characterization of SWS was the description of a severe subtype of Schwartz-Jampel syndrome (SJS). Al-Gazali et al. [1996] and Giedion et al. [1997] reported a lethal form of Schwartz-Jampel syndrome (SJS type 2), characterized by prenatal onset of hypokinesia, congenital contractures, feeding difficulties, early lethality and a distinct radiological pattern of congenital bowing of the long bones, myotonia and other skeletal abnormalities. The overlap of the clinical and radiological aspects in SJS type 2 and SWS let Cormier-Daire et al. [1998b] question if these syndromes were really distinct entities. Supporting this line of evidence, Superti-Furga et al. [1998] reviewed and compared the clinical and radiological aspects of SJS type

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2 and SWS and concluded that the similarities between these 2 entities were remarkable, and the only finding discordant was electromyographic myotonia. The authors favored the hypothesis that SJS type 2 and SWS were indeed a single disorder.

Dagoneau et al. [2004] identified the gene responsible for SWS. The authors analyzed previous individuals diagnosed as affected by SWS and SJS type 2 and demonstrated that both shared the same molecular basis, proving that the 2 disorders represent a single clinically and genetically homogeneous condition.

In the last nosology of skeletal dysplasias [Bonafe et al., 2015], SWS is classified in group 18, under the designation of campomelic dysplasia and related disorders. This group comprises conditions with bent-bone dysplasias, including campomelic dysplasia, SWS, both with known molecular basis, and the kyphomelic dysplasia, a probable heterogeneous disorder without a known genetic background.

Another hallmark of SWS is the presence of dysautonomic symptoms, which also allows this disorder to be classified in the group of ciliary neurotrophic factor (CNTF) receptor pathway – CNTF-receptor-related disorders – that comprises SWS, Crisponi syndrome and cold-induced sweating syndrome [Crisponi et al., 2007].

Prevalence

SWS is considered a rare disorder, whose prevalence is unknown. In the United Arab Emirates population, which is highly inbred and where termination of pregnancy is not accepted, the prevalence was estimated in 0.52/10,000 births [Al-Gazali et al., 2003a]. SWS has been described in different ethnic groups, including individuals from European countries [Wiedemann and Stüve, 1996; Cormier-Daire et al., 1998b; Dagoneau et al., 2004], Africa [Cormier-Daire et al., 1998b], North [Chen et al., 2001] and South America [Hatagami Marques et al., 2015], and the Middle East [Al-Gazali et al., 2003a; Dagoneau et al., 2004].

Clinical Findings, Course and Management

Even though SWS was initially described as a lethal condition, several long-term survivors have been reported in the literature, including adolescent individuals [Di Rocco et al., 2003; Morava et al., 2006; Gaspar et al., 2008; Palejwala et al., 2015] and an adult patient [Melone et al.,

2014]. Still, there is a high rate of mortality in this disorder, especially in the first few months of life, due to respiratory distress, difficulties with feeding and swallowing, or hyperthermic episodes. Different authors speculated about the underlying risk factors for the high mortality rates in SWS. Raas-Rothschild et al. [2003] described 2 siblings with SWS who died from severe pulmonary hypertension with medial hypertrophy of the pulmonary arterial wall, possibly related to the premature obliteration of the ductus arteriosus. The authors suggested that this cardiovascular abnormality could be the cause underlying the severe respiratory insufficiency in some individuals with SWS leading to early neonatal death. Guran et al. [2015] suggested that a central adrenal insufficiency could be responsible for sudden death in these affected individuals following inflammatory or stressful conditions, since the leukemia inhibitory factor receptor (LIFR) plays a role in the activation of the JAK/STAT pathway, participating in the transcriptional control of basal and stress-related adrenal steroidogenesis.

For the survivors, SWS continues to pose a high morbidity burden requiring specialized care, including several surgical procedures to correct the skeletal abnormalities. Although motor development is delayed, cognitive impairment is not a feature [Mikelonis et al., 2014].

Currently, there is no specific treatment for SWS, and management is directed towards the clinical manifestations. Bellais et al. [2010] used gentamicin to induce premature termination codon readthrough of LIFR mRNA in cultured skin fibroblasts of SWS patients with homozygous nonsense mutations. They were able to partially restore functional LIFR synthesis and stimulate the STAT3 pathway. Even though ototoxicity and nephrotoxicity are the main concerns for the drug gentamicin, the described strategy remains a promising specific therapeutic approach in the future for those who carry nonsense mutations.

Prenatal Abnormalities
The main ultrasound findings in SWS should be differentiated from other bent-bone skeletal dysplasias, such as campomelic, kyphomelic and diastrophic dysplasias [Farra et al., 2002; Begam et al., 2011]. The majority of the cases described in the literature in which the diagnosis of SWS was achieved in the prenatal period had a positive family history [Sigaudy et al., 1998; Catavorello et al., 2013].

A retrospective analysis of ultrasound findings in postnatal diagnosed SWS was conducted in a medicine fetal unit of a tertiary hospital in the United Arab Emirates during an 8-year period. Among the 10 fetuses with a

postnatal diagnosis of SWS, the authors observed the presence of a prenatal skeletal abnormality in 8 (80%) patients. The main prenatal ultrasound findings, observed mainly in the second trimester, were mild-to-moderate micromelia and bowing of the lower limb bones, affecting the tibia more than the femur, with relative sparing of the fibula and the upper limb bones, talipes and camptodactyly. They presented with normal scapulae as well as normal thoracic dimensions. In the third trimester, there were signs of intrauterine growth restriction with normal Doppler findings and oligohydramnios. The latter showed a variable onset, occurring between 28 and 36 weeks of gestation [Begam et al., 2011].

Facial Dysmorphisms

Although some mild dysmorphic features have been described by different authors [Cormier-Daire et al., 1998b; Gaspar et al., 2008], the most significant and frequent abnormalities, i.e. corneal opacities and smooth tongue, are caused by autonomic dysfunction; their management is described in the section Dysautonomia (see below).

Muscular and Skeletal Findings

The individuals affected by SWS present with short and bowed legs associated with joint restrictions, including camptodactyly, feet malposition, and knee and elbow extension-restricted mobility. With age, growth is impaired. There is progressive bowing of the long bones (fig. 1A, B) and destruction of the femoral head. Severe spinal deformities (fig. 1C, D) arise, along with osteoporosis and spontaneous fractures (fig. 1B) [Mikelonis et al., 2014]. At a later stage, luxations of the patellae occur [Gaspar et al., 2008; Jung et al., 2010].

Due to the progression of bowing of the lower limbs, some individuals with SWS may present with mobility problems. Gaspar et al. [2008] reported an SWS patient who gradually lost the ability to walk and became wheelchair dependent at 9 years of age. Another reported 9-year-old patient [Buonuomo et al., 2014] developed significant knee swelling due to monocytic synovial effusion and also was unable to walk.

In order to prevent the progressiveness of the skeletal abnormalities, orthopedic management should start early in the course of the disease. Even with careful surgical planning, patients may present recurrence of deformities and often have to undergo multiple procedures. When treating scoliosis, bracing is not always effective and surgical stabilization could be performed with a growing rod [Hassan et al., 2010; Wright et al., 2015]. Pizones et al. [2013] de-
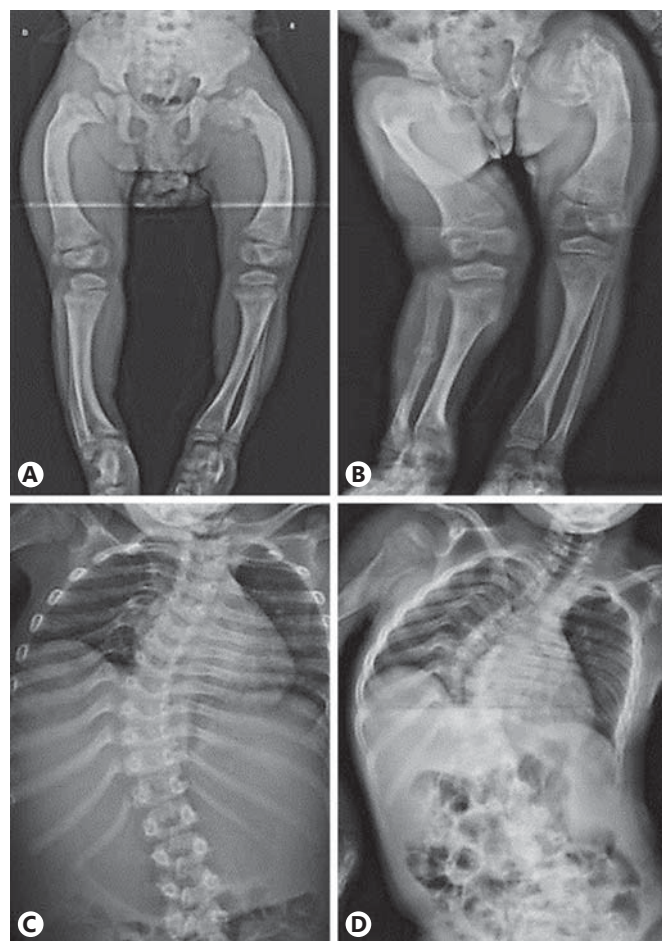

Fig. 1. Progression of the skeletal abnormalities in SWS in a 2-year period. **A, B** Progressive bowing of the long bones, with compromising of the femoral heads and fracture of the right fibula. Note the wide metaphyses, radiolucent lesions, and internal cortical thickening at the concavity of the bend of the long bones. **C, D** Progressive scoliosis.

scribed a delayed tetraparesis caused by cervical edema that was most likely secondary to ischemia in 2 SWS individuals following posterior spinal surgery for scoliosis. Although a partial recovery was observed in one patient, the other remained quadriplegic after conservative management. They emphasized that close surveillance should be maintained in these patients, since the neurological deficits can develop hours after the procedure.

Multiple osteotomies are performed to correct the bowing of the lower long bones [Hassan et al., 2010; Wright et al., 2015]. To reduce the number of surgical procedures, telescoping Fassier-Duval rods were recommended [Wright et al., 2015]. As these individuals show

decreased sensitivity to pain, Hassan et al. [2010] observed that the operated patients could walk earlier with the frames, which encouraged healing of the osteotomies, and that they tolerated removal of the frame and the pins as outpatients. Furthermore, spontaneous fractures, with little or no pain, have been described [Injarie et al., 2012].

Recurrent spontaneous fractures are another skeletal manifestation that also impacts the patients' quality of life [Gaspar et al., 2008; Corona-Rivera et al., 2009; Jung et al., 2010]. Treatment with bisphosphonates, calcium, vitamin D, and/or human growth hormone may be indicated to control osteoporosis and prevent further fractures [Corona-Rivera et al., 2009].

Histological analyses of the femoral metaphyses using hematoxylin-eosin-saffron staining showed an irregularity of the chondro-osseous junction with rare, thick and irregular primary trabeculae and an excess of osteoclastic resorption. Growth cartilage appeared normal, with relatively well-developed proliferative and hypertrophic zones [Cormier-Daire et al., 1998a].

Dysautonomia
Symptoms of dysautonomia include temperature dysregulation and sweating anomalies. Temperature instability remains, and there is excessive and sometimes paradoxical sweating [Mikelonis et al., 2014].

Since one of the characteristic manifestations of SWS is bouts of hyperthermia, the concern of a possible increased risk for malignant hyperthermia during anesthesia was raised. However, Hassan et al. [2010] reported a total of 26 general anesthetic procedures in 5 patients with no events of hyperthermia. Bonthuis et al. [2009] reported the use of sevoflurane with no complications in 6 anesthetic procedures in the same patient. SWS individuals also present with reduced pain sensation and reduced or absent patellar reflex [Mikelonis et al., 2014].

There are signs of a reduced corneal reflex and decreased sensation in the eye, together with alacrima or hypolacrimation, and an absent or severely reduced blinking reflex, causing recurrent keratitis with corneal opacities and ulcerations. Corneal scarring and a compromised ocular surface can cause stimulus deprivation amblyopia in children with SWS [Injarie et al., 2012].

The eyes should receive early protection against repeated trauma and sunlight exposure [Gaspar et al., 2008; Catavorello et al., 2013]. Injarie et al. [2013] recommended that frequent follow-up and detailed attention not only to the ocular surface but also to accurate refraction, which must be done every 3 months in children younger than 8 years, should be performed in order to achieve an accept-able development of vision. To improve ocular surface lubrication, conservative procedures, such as the use of artificial drops during the day and ointment at night, the use of punctual plug advices or surgical procedure (punctual occlusion) to increase the tear reservoir and therefore reduce the need for artificial tears, may be implemented. To reduce the surface area exposed to drying and minor trauma, lateral tarsorrhaphy could be applied, and if the corneal pathology is central or paracentral, optical iridectomy has been performed to increase retinal stimulation [Injarie et al., 2013].

The tongue should be protected in young children; special appliances can be used to cover the teeth to avoid tongue biting [Akawi et al., 2012].

Swallowing disorders are probably related to pharyngoesophageal dyskinesia due to an abnormal autonomic control of the anterior rami of cervical roots C1–C5 [Corona-Rivera et al., 2009]. Attention to the swallowing problems is required to prevent pulmonary aspirations. This vigilance should continue for the first 5 years of life [Corona-Rivera et al., 2009]; however, Akawi et al. [2012] recommended that the families should be alerted that even later the patient can have swallowing problems and choking. In general, the swallowing difficulties improve during the second or third year of life [Corona-Rivera et al., 2009; Catavorello et al., 2013]. Nasogastric tube feeding and/or gastrostomy are sometimes required to prevent aspirations and proper feeding [Corona-Rivera et al., 2009; Hatagami Marques et al., 2015; Knipe et al., 2015].

Hyperthermic episodes in SWS individuals might be linked to emotional/environmental triggering factors [Jung et al., 2010]; thus, these factors should be controlled if possible. SWS is one of the monogenic genetic syndromes in which bouts of high fever in the neonatal period represent an intrinsic risk to sudden death [Cormier-Daire et al., 1998b; Jung et al., 2010; Rigante, 2012].

Radiological Findings
Short and bowed long bones, especially femora and tibiae, with internal cortical thickening at the concavity of the bend, are the hallmark of the skeletal abnormalities. Long bones of the upper limbs may present with minimal bowing. Other findings include wide metaphyses, radiolucent lesions with abnormal trabeculation and slightly irregular margins. Mineralization is generally reduced, and signs of fractures and/or healed fracture are seen (fig. 1A, B). The elbow and knee joints appear deformed, fingers and feet are malpositioned, and scoliosis is observed (fig. 1C, D). The femoral head is compromised (fig. 1A, B).

Less frequent skeletal abnormalities described are: dolichocephalic configuration of the cranium, squared jaw, with hypoplastic ramus; poor ossification of the vertebral bodies, with pronounced anterior notch and slight flattening of the cervical spine, with mild beaking; shallow acetabula, small ilia and broad pubic and ischial bones/puboischial synchondrosis in the pelvis, and widening of the anterior ends of the ribs/thin ribs [Wiedemann and Stüve, 1996; Cormier-Daire et al., 1998a; Al-Gazali et al., 2003b].

Genetic Aspects

Autosomal Recessive Monogenic Disorder

Since the first descriptions of the disorder, an autosomal recessive mode of inheritance was suggested for SWS, based on recurrence of the disease in siblings and the presence of consanguinity in several cases. This pattern of inheritance was confirmed by the discovery of variants in both copies of *LIFR* in patients with SWS [Dagoneau et al., 2004].

Dagoneau et al. [2004] used a homozygosity-mapping strategy to unravel the gene responsible for SWS. The authors analyzed 11 families with SWS (10 consanguineous families and 1 nonconsanguineous family) and found linkage of the disease gene to chromosome 5p13.1. Among the several putative disease genes within the candidate region, *LIFR* was considered a good candidate, since the LIFR is able to bind multiple cytokines. Furthermore, *Lifr*$^{-/-}$ mice present bone compromise, characterized by a reduction of fetal bone volume, with an increased number of osteoclasts, besides reduction of astrocyte numbers in spinal cord and brain, and perinatal death.

LIFR and Its Product

LIFR is composed of 20 exons and encodes a 1097-amino acid transmembrane protein, a cytokine receptor, containing 8 distinct domains in its extracellular segment. These domains can be subclassified as 2 cytokine-binding modules, separated by an immunoglobin-like domain, followed by 3 fibronectin type-III domains at the membrane-proximal end. It has to be considered that following the extracellular domain, the transmembrane domain and the cytoplasmic domain operate [Dagoneau et al., 2004; Nicola and Babon, 2015].

Functional LIFRs are found in different organs, including the liver, bone, uterus, kidney, and the central nervous system. LIFR binds with low affinity to several IL-6 family members, including LIF, oncostatin-M (OSM), cardiotrophin-1 (CT-1), CNTF, and cardiotrophin-like cytokine factor 1 (CLCF-1).

The binding of LIF to its receptor (LIFR) results in JAK1 becoming catalytically active. JAK1 then initiates a cascade of tyrosine phosphorylation that stimulates the JAK/STAT, MAP-kinase and PI3-kinase signaling pathways, known to play a role in differentiation, survival and self-renewal. The contributions, both quantitatively and qualitatively, of the JAK/STAT, MAP-kinase and PI3-kinase pathways following LIF stimulation are often cell-type specific [Mikelonis et al., 2014; Nicola and Babon, 2015].

The loss-of-function mutations in *LIFR* compromise the signaling of the different cytokines that bind this receptor, leading to the phenotype observed in SWS. As LIFR is widely expressed, the signs and symptoms present in SWS could depend on which cytokines are involved and their signaling, as described below, with emphasis in bone remodeling [Mikelonis et al., 2014]:

1. Smooth tongue: fungiform papillae do not develop in the absence of LIF and CNTF signaling;
2. Cardiovascular phenotype: LIF and CT-1 downstream signaling act in sympathetic neurons;
3. Dysphagia and respiratory problems: OSM and CT-1, as well as CLCF-1/ cytokine receptor-like factor 1 (CRLF-1), play a role in motor neurons, including the nucleus ambiguous that innervates the esophagus, pharynx, larynx, and coordinates swallowing;
4. Short stature: impairment of CNTF signaling could be responsible for this characteristic, once *Cntf* knockout mice display a short bone phenotype;
5. Paradoxical sweating: dysautonomic symptoms are caused by a lack of CLCF-1/CRLF-1 signaling;
6. Skeletal abnormalities: LIF and CT-1 play a role in bone resorption. Osteoblasts express high-affinity receptors for LIF, and LIF enhances the differentiation of bone marrow stromal cells to the osteoblast lineage, while also inhibiting differentiation towards adipocytes. LIF inhibits the expression of sclerostin in osteocytes, which is a potent inhibitor of bone formation by osteoblasts. Osteoclasts do not express LIFR or produce LIF, suggesting that LIF effects on these cells at the growth plate are indirectly mediated through osteoblasts and osteocytes via the induction of receptor activator of nuclear factor kappa-B ligand (RANKL) production. RANKL is the primary mediator of osteoclast formation, function and survival. In animal models, *Lifr*$^{-/-}$ mice showed dramatic bone loss. Thus, loss of LIF and CT-1 signaling in SWS, due to the absence of a functional LIFR, most likely contributes to osteopenia and bone-specific traits seen in this syndrome [Mikelonis et al., 2014; Nicola and Babon, 2015].

Table 1. Mutations in *LIFR* identified in SWS

Exon	Nucleotide change	Amino acid change	Alleles, n
3	c.144_145dup	p.Ala49Glyfs*6	2
3	c.170del	p.Thr57Ilefs*54	2
3	c.171_174del	p.Asn58Ilefs*52	3
3	c.189G>A	p.Trp63*	1
3	c.194G>C	p.Cys65Ser	2
IVS3	c.257+1G>T	splicing	2
4	c.380dup	p.Asn128Lysfs*2	1
6	c.653dup	p.Glu219Glyfs*3	10
7	c.756dup	p.Lys253*	8
7	c.845T>C	p.Ile282Thr	1
7	c.875T>C	p.Leu292Pro	1
9	c.1122_1291del	p.Phe375Leufs*14	1
9	c.1231_1234del	p.Asn411Leufs*13	1
9	c.1252C>T	p.Arg418*	2
IVS10	c.1438-4A>G	splicing	1
IVS11	c.1601-1G>A	splicing	2
12	c.1621dup	p.Thr541Asnfs*8	2
13	c.1789C>T	p.Arg597*	11
13	c.1865C>T	p.Ala622Val	1
14	c.2013dup	p.Met672Tyrfs*12	1
15	c.2074C>T	p.Arg692*	8
16	c.2170C>G	p.Pro724Ala	2
16	c.2275dup	p.Tyr759Leufs*14	2
16	c.2336G>T	p.Gly779Val	1
17	c.2434C>T	p.Arg812*	4
17	c.2472_2476del	p.Ser824Argfs*41	2
15–20	c.2065+1418_*2384del	deletion	2

The missense mutations c.194G>C and c.2170C>G were present in 2 patients with partial SWS phenotype.

Variants in LIFR in SWS

All the variants in *LIFR* described in patients with SWS in the literature are depicted in table 1. The nomenclature used to describe these variants is recommended by HGVS (Human Genome Variation Society), with REFSeq accession numbers NM_002310.5 and NG_011817.1, for variants in coding sequence and splicing junction, respectively.

Twenty-five different variants in *LIFR* have been described in typical SWS patients: 11 frameshift, 6 nonsense, 4 missense, 3 splicing, and 1 deletion (table 1). In addition, a recurrent frameshift variant (c.653dup) and a nonsense mutation (c.2074C>T) were identified in families from the United Arab Emirates and Turkey respectively, indicating a founder effect in these regions [Dagoneau et al., 2004; Yeşil et al., 2014].

Analyses of *LIFR* RNA transcripts by RT-PCR in fibroblasts of SWS patients showed a weak signal or no signal. Moreover, binding experiments using iodinated LIF revealed that the affected individuals failed to express high-affinity LIFRs, and the activation of JAK/STAT signaling was hampered, showing no phosphorylation of STAT3. These findings suggested that null *LIFR* mutations in SWS induce instability of *LIFR* transcripts, with the generation of a markedly truncated protein [Dagoneau et al., 2004].

Two descriptions of patients harboring a partial SWS phenotype, lacking the typical shortening and bowing of the long bones, were reported recently [Melone et al., 2014; Elsaid et al., 2016]. In both cases, one isolated and one familial, the patients harbored missense, non-truncating mutations in both alleles, which alter LIFR glycosylation. It is possible to speculate that a residual protein function and a specific tissue threshold could explain the lack of the typical shortening and bowing of the long bones in these affected individuals.

Nonclassical Pattern of Inheritance

A 33-year-old woman showing a partial phenotype of SWS, in which the typical skeletal findings – shortening and bowing of the long bones – were lacking, harbored a homozygous missense mutation in *LIFR* (p.Pro724Ala). Genome-wide SNP arrays, including parental samples, revealed a complete maternal isodisomy for chromosome 5. In vitro studies confirmed that the mutation p.Pro724Ala alters the receptor glycosylation and *LIFR* function, compromising STAT3 phosphorylation in Hep3B cells transfected with the Pro724Ala mutation, compared to control cells [Melone et al., 2014].

Genetic Heterogeneity

Jung et al. [2010] reported 4 patients without mutations in *LIFR*. The phenotype of these 4 individuals was typical of SWS, with lower limb bowing and dysautonomic symptoms in all 4 of them, joints restriction in 3, and scoliosis in 2. In these individuals, activation of the JAK/STAT3 pathway upon phosphorylation by LIF in skin fibroblasts was normal, and mutations in another gene – *CRLF* – were not found. The authors compared the clinical findings of the negative *LIFR* individuals with the 6 other positive patients displaying long-term survival that were also evaluated and concluded that there was no difference between the groups. Thus, the analysis supported the clinical homogeneity of SWS, despite genetic heterogeneity.

Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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