

REVIEW

Open Access

# Stüve-Wiedemann syndrome: LIFR and associated cytokines in clinical course and etiology

Dawn Mikelonis, Cheryl L Jorcyk, Ken Tawara and Julia Thom Oxford\*

## Abstract

Stüve-Wiedemann syndrome (STWS; OMIM #610559) is a rare bent-bone dysplasia that includes radiologic bone anomalies, respiratory distress, feeding difficulties, and hyperthermic episodes. STWS usually results in infant mortality, yet some STWS patients survive into and, in some cases, beyond adolescence. STWS is caused by a mutation in the leukemia inhibitory factor receptor (*LIFR*) gene, which is inherited in an autosomally recessive pattern. Most *LIFR* mutations resulting in STWS are null mutations which cause instability of the mRNA and prevent the formation of LIFR, impairing the signaling pathway. LIFR signaling usually follows the JAK/STAT3 pathway, and is initiated by several interleukin-6-type cytokines. STWS is managed on a symptomatic basis since there is no treatment currently available.

**Keywords:** Stüve-Wiedemann syndrome, Leukemia inhibitory factor receptor, LIF, LIFR

## Introduction

### History

Stüve-Wiedemann syndrome (STWS) was first described in 1971, presenting in two sisters with congenital bowing of the tibia and femur, abnormally positioned feet, and camptodactyly. Both patients experienced respiratory distress and consequently died within a few days of birth. One of the patients also suffered from deglutination difficulty and hyperthermia. Stüve and Wiedemann suspected that the syndrome had autosomal recessive inheritance since the patients were sisters [1,2]. Although the prognosis of STWS remains poor, recent reports show that some STWS patients survive at least into early adolescence [3,4], and beyond.

### Classification

Surviving STWS patients were found to be phenotypically identical to Schwartz-Jampel syndrome type 2 (SJS2) survivors. Therefore, SJS2 and STWS are now considered to be the same disorder, and the title “Schwartz-Jampel Syndrome type 2” has been dropped [5,6]. Both SJS2 and STWS have been linked to a mutation of the leukemia inhibitory factor receptor (*LIFR*) gene on chromosome 5p13.1 [7].

STWS includes autonomic nerve dysfunction [3], and the related ciliary neurotrophic factor receptor (*CNTFR*) gene has also been linked to autonomic nervous system dysfunction [8]. Therefore, STWS is also included in the family of *CNTFR* pathway-related disorders [9]. This classification exemplifies the clinical overlaps between STWS, Crisponi syndrome, which includes facial weakness, feeding difficulties, camptodactyly and hyperthermia in infancy followed by scoliosis, and cold-induced sweating in adolescence, and cold-induced sweating syndrome (CISS) [9,10]. However, the skeletal features of STWS allow it to also be classified within the group of bent-bone dysplasias [11].

STWS is found across multiple ethnic groups in multiple regions of the world including North America, Europe, and the Middle East [7,12,13]. However, STWS appears to be more common in the United Arab Emirates [14], as well as in Oman and Yemen [12,15].

### Clinical manifestations

STWS is a rare autosomal recessive bent-bone dysplasia (OMIM #601559). It is characterized by bowing of the long bones with cortical thickening and rarefaction, wide and blurred margins of the metaphyses, contracture and limited mobility of elbows and knees, osteopenia, flared iliac wings, hypoplasia of the lower ilia, and an abnormal trabecular shape [1,7,13,16]. Additional features include camptodactyly, contracture of fingers, and symptoms of

\* Correspondence: joxford@boisestate.edu  
Boise State University, Department of Biological Sciences, Biomolecular Research Center, 1910 University Drive, Boise State University, Boise ID 83725, USA

dysautonomia (Table 1). Figure 1 shows an individual at ten months of age, who was later diagnosed with STWS. Most individuals suffering from STWS do not survive beyond the first few months of life due to respiratory distress, difficulties with feeding and swallowing, or hyperthermic episodes [1,7,10,12,13,17-19]. Patients that do survive show an improvement in prognosis as a normal breathing rhythm is established and the ability to swallow is gained, yet difficulties with swallowing can still occur later in childhood [13].

With age, there is progressive bowing of the long bones with tubulation of diaphyses, rarefaction and striation of metaphyses, and destruction of the femoral heads [12]. Severe spinal deformities arise, along with streaky osteoporosis and spontaneous fractures. The

joints are prominent and show restricted mobility. Temperature instability remains, and there is excessive, and sometimes paradoxical sweating. Other signs of dysautonomia persist, such as a smooth tongue, absent corneal and patellar reflexes, and reduced pain sensation. Physical growth and motor development is delayed, but intelligence is normal [7,12,13].

In some cases, it is possible to predict the presence of STWS before birth via ultrasound. Prenatal symptoms can sometimes be seen in the late second- or third trimester. The prenatal symptoms of STWS include oligohydramnios, intrauterine growth restriction despite normal Doppler findings about the umbilical artery, camptodactyly, bowing of the lower bones affecting the tibia more than the femur, and micromelia [20].

**Table 1 Diagnostic characteristics of STWS**

Organ system	Neonatal	Childhood	Treatment	Reference
<b>Embryonic</b>	Oligohydramnios			[20]
	Intrauterine growth restriction; low birth weight, length and head circumference	Growth retardation		[1,2,20]
<b>Skeletal</b>	Micromelia, bowing of the long bones with cortical thickening, wide metaphyses, and abnormal trabeculae	Progressive bowing of the long bones with continued radiologic abnormalities		[1,2,7,12,13,19,55]
	Camptodactyly	Camptodactyly		[1,2]
	Scoliosis	Scoliosis	Corrective surgery	[7,12,13]
	Osteopenia or osteoporosis	Osteopenia or osteoporosis	Bisphosphonates, calcium, vitamin D, human growth hormone, surgery and physical therapy	[11,13,18]
	Facial anomalies	Facial anomalies Spontaneous fractures Prominent joints with restricted mobility	Corrective surgery	[18] [7,12,13,119]
<b>Muscular</b>	Hypotonia, Contractures			[19]
<b>Pulmonary</b>	Respiratory distress	Respiratory distress improves		[1,2]
	Pulmonary hypoplasia			[20]
<b>Cardiovascular</b>	Pulmonary hypertension			[79-81]
<b>Gastrointestinal</b>	Dysphagia	Dysphagia improves	Intubation, nasogastric tube feeding, gastrostomy	[12,13]
<b>Nervous system</b>	Hyperthermic episodes	Temperature instability		[1,2]
	Excessive sweating	Excessive and paradoxical sweating		[9]
	Absent corneal and patellar reflexes	Absent corneal and patellar reflexes		[7,12,13]
	Hypolacrimation	Hypolacrimation	artificial tear drops and ointments, lacrimal punctum dilation	[17,120,121]
		Delayed motor development Reduced pain sensation Smooth tongue		[7,12,13]
<b>Ocular</b>	Corneal opacities	Corneal opacities	Keratotomy	[17,120]
<b>Endocrine system</b>	Ectopic thyroid Hypothyroidism			[18]

Open cells in the table indicate no available treatment. Some features generally improve over time (i.e., respiratory distress and dysphagia), while other features become progressively worse (i.e., bowing of the long bones).



**Figure 1** Image of STWS patient at 10 months of age. Facial features and contracture of fingers are evident. Patient carries two mutations in the *LIFR* gene; 1) a duplication of 22 nucleotides within exon 4, causing a frameshift predicted to result in a premature stop codon following five unique amino acids, and 2) a deletion of nine nucleotides within exon 12, resulting in the deletion of three amino acids at the protein level. Both mutations occur within the region of the gene encoding the extracellular domain. The mutation resulting in the premature stop codon is anticipated to result in mRNA instability, and it is therefore likely to result in a null mutation. These mutations are unique, having not been previously described. Photograph printed with permission from patient, now age 23.

## Genetic etiology

### Genetic mutations responsible for STWS

Dagoneau et al. determined that the leukemia inhibitory factor receptor (*LIFR*) gene on chromosome 5p13.1 is responsible for STWS [7]. Their findings were reinforced by the observation that *LIFR*<sup>-/-</sup> mice have reduced fetal bone volume, an increased number of osteoclasts, reduced numbers of astrocytes in the spinal cord and brain, and perinatal death [21]. The mouse phenotype is considered to be similar to that of STWS [7]. Furthermore, most patients with STWS have a mutation within the *LIFR* gene [20]. Many STWS patients in the United Arab Emirates have an identical frameshift mutation in the *LIFR* gene that results in a premature stop codon [20].

The mutated *LIFR* gene is inherited in an autosomal recessive pattern. The mutations reported have been either missense or nonsense mutations, with the majority being nonsense mutations within the exons encoding the extracellular domain [7]. Fourteen distinct null mutations were observed in 19 families, most of which resulted in premature stop codons which altered the stability of the mRNA, resulting in an absence of the

*LIFR* protein and impairment of the *LIFR* signaling pathway [7]. The *LIFR* gene has 19 exons and normally encodes a transmembrane protein which is 1,097 amino acids long [7,22,23].

### Genetic variability

Interestingly, not all patients who are diagnosed with STWS have an identified *LIFR* mutation [13,19]. The gene(s) responsible for the STWS phenotype in these exceptional cases have not been identified. This variability suggests that modifier genes may play a role in STWS, as well [13]. Other genes within the candidate region (chromosome 5p13.1 from locus D5S194 to D5S1457) mapped by Dagoneau et al. included *FLJ39155* (EGFLAM or Pikachurin, a proteoglycan), disabled-2 (*DAB2*), complement 9 (*C9*), Fyn-binding protein (*FYB*), and oncostatin M receptor (*OSMR*) [7]. While these genes may play a role as disease modifiers or may be potential candidates for those cases of STWS that are not linked to a mutation in *LIFR*, to date, limited information exists to support the likelihood of the involvement of these genes in skeletal, respiratory or neurological symptoms associated with the syndrome. For example, a neurologic function has been described for the *FLJ39155* locus. *FLJ39155* gene product has been localized to the synaptic cleft of the photoreceptor ribbon synapse and gene disruption experiments demonstrated the necessity of this protein for proper synaptic signal transmission and visual function [24]. Knockout of this gene selectively disrupts synaptogenesis between photoreceptor and bipolar cells. Additionally, micro-duplications of the short arm of chromosome 5 that include the 5p13.1 region have been linked to neurologic symptoms [25]. This region includes the genes *FYB*, *C9*, and *DAB-2*.

Respiratory function has been associated with *DAB-2*. *DAB-2* is a clathrin-associated sorting protein (CLASP) that contributes to clathrin recruitment, vesicle formation, and cargo selection. In the lungs, cystic fibrosis transmembrane conductance regulator, a cAMP-activated chloride channel expressed in the apical plasma membrane of human airway epithelial cells, is endocytosed in a *DAB-2*-dependent manner [26]. *DAB-2* also plays a role in bone morphogenetic protein signaling [27] and nerve cell differentiation [28].

Complement C9 may play a role in skeletal development through its function during endochondral ossification [29], and in respiratory function [30], and has been implicated in demyelination diseases [31]. *FYB* has been linked to osteoclastogenesis [32] and lung physiology [33]. Additionally, a neurologic function has been described for *FYB* through an association with hereditary motor-sensory neuropathy [34].

*OSMR* plays a key role in bone homeostasis as demonstrated by the *OSMR*<sup>-/-</sup> mouse, which exhibits an osteopetrotic phenotype due to an effect on osteoclast

differentiation [35,36]. OSMR has also been implicated in the respiratory system [37], and the nervous system [38], as well as metabolic symptoms such as mature-onset obesity, severe hepatic steatosis, and insulin resistance [39]. Other proteins that play an essential role in the LIFR pathway as ligands or as competing receptor, such as the cytokine receptor-like factor 1 (CRLF1), cardiotrophin-like cytokine factor 1 (CLCF1), and ciliary neurotrophic factor (CNTF) may play a role in STWS [13] and are discussed in more detail below.

## The LIFR protein and its signaling pathway

### The LIFR protein

The LIFR protein (also called glycoprotein-190; gp 190) is composed of a signal peptide followed by three main domains. The extracellular domain (45-833aa) includes two cytokine receptor homology domains (CRH1 and CRH 2), one Ig-like domain (Ig), and one type III fibronectin domain with three modules (FNIII). Following the extracellular domain is the transmembrane domain (TM; 834-858aa), and finally the cytoplasmic domain (CD; 859-1097aa; Figure 2).

### The LIFR signaling pathway

LIFR binds with low affinity to several IL-6 family members, including leukemia inhibitory factor (LIF), oncostatin-M (OSM), cardiotrophin-1 (CT-1, also abbreviated as CTF-1), ciliary neurotrophic factor (CNTF), and cardiotrophin-like cytokine factor 1 (CLCF-1, also abbreviated as CLC) (Figure 3) [40-43]. Both LIF and OSM can bind to the LIFR. LIF binds to LIFR $\beta$ , which then recruits gp130 for higher affinity and cell signaling [23]. In contrast, OSM binds gp130 with low affinity but has little to no biological activity unless a second receptor chain is recruited, either the LIFR $\beta$  or the more highly specific OSMR $\beta$  [44-47]. CT-1 binds to gp130 and LIFR [48], while CNTF first binds to ciliary neurotrophic factor receptor (CNTFR $\alpha$ ) before recruiting LIFR. [49] Cardiotrophin-like cytokine factor 1 (CLCF-1) forms a heterodimer with either cytokine receptor-like factor 1 (CRLF1) or soluble ciliary neurotrophic factor receptor (sCNTFR) and competes for this same receptor complex (Figure 3; [13,50-52]).

When a cytokine binds to LIFR (primarily through the fibronectin type III domain), LIFR associates with glycoprotein 130 (gp130), and the addition of gp130 creates a high-affinity complex [53]. The dimerization of LIFR and gp130 causes cytoplasmic JAK to be phosphorylated at the tyrosine 705 residue. JAK then phosphorylates tyrosine residues on the intercellular domains of gp130 and LIFR [54,55]. In turn, STAT3 proteins are phosphorylated [54]. STAT3 then forms a homodimer and moves to the nucleus, where it binds to cytokine-responsive elements and ultimately activates gene transcription (Figure 3) [55-57]. Alternatively, LIFR binding can stimulate JAK/STAT1 in a similar manner [56,57]. To a lesser extent, the SHP2/RAS/MAPK pathway can also be activated (Figure 3) [55,58,59]. LIFR is also present in a soluble form, which binds to LIF in a competitive manner, so that LIF cannot exert its effects on cells [60]. In some cell types, after signaling is completed, LIFR is internalized through endocytosis and degraded [61-63].

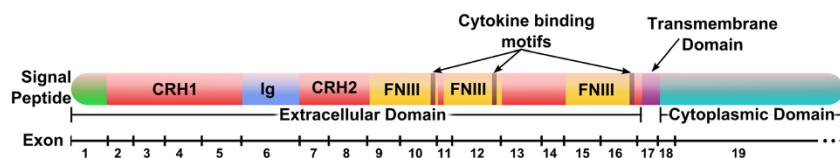
## LIFR ligands linked to neonatal development

### Leukemia inhibitory factor receptor ligands: bone remodeling, neuronal development, and myoblast differentiation

LIF is a pleiotropic cytokine, secreted by a variety of cell types, including epithelial and stromal cells of the endometrium [64], osteoblasts [65,66], bone marrow stromal cells, fibroblasts, astrocytes, heart myoblasts, T lymphocytes, monocytes, and thymic epithelial cells among others [67].

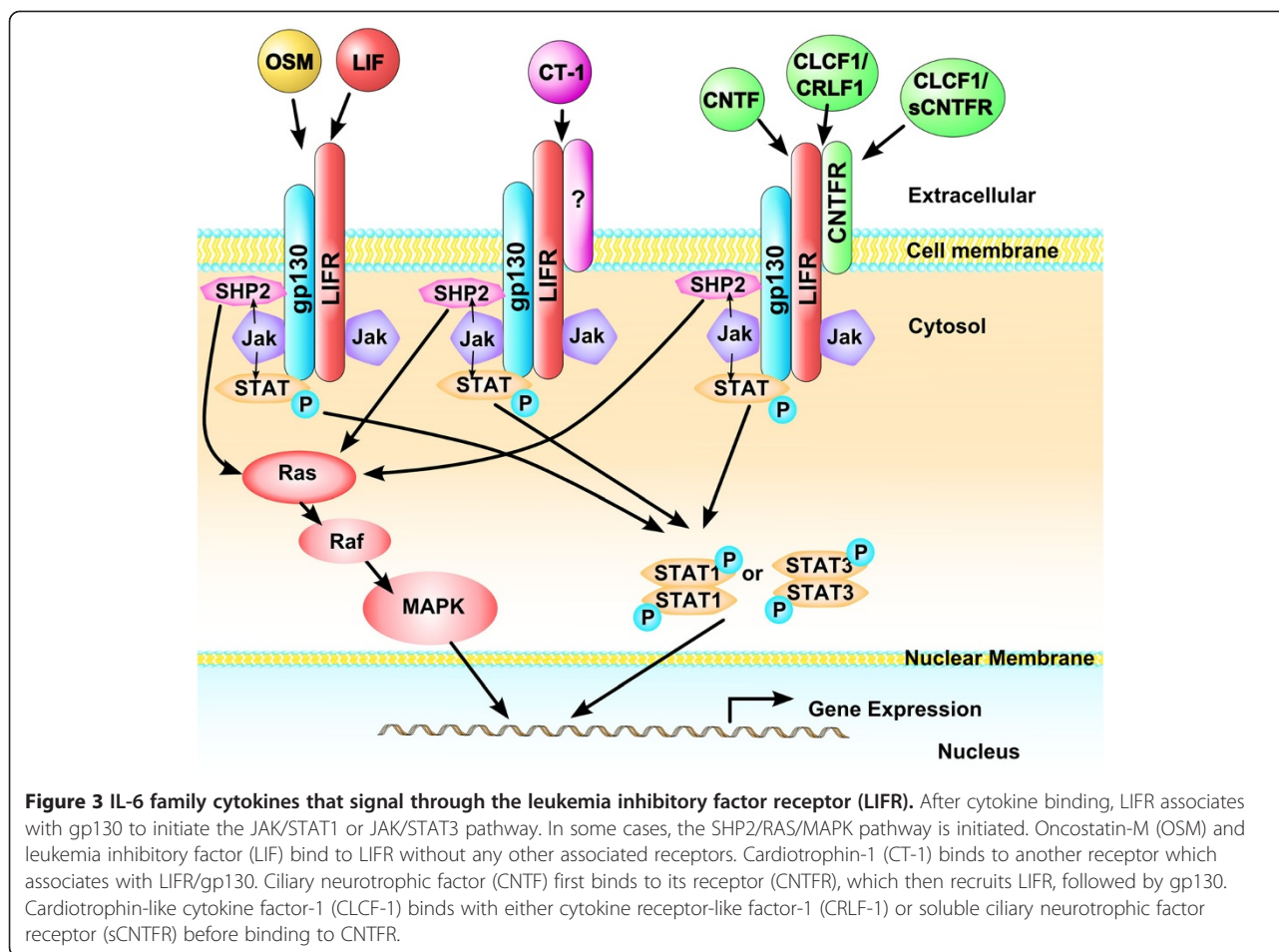
The traits of the *Lif* knockout mice that are shared with STWS include giant osteoclasts [68] and some loss of motor neurons [69]. Giant osteoclasts are the result of interactions between FRA2 and c-JUN with LIF [68]. On the other hand, some have argued that there is no severe neuronal dysfunction in *Lif*<sup>-/-</sup> mice [70].

LIF and CT-1 play a role in bone resorption. LIF and CT-1 were found to stimulate the proliferation and differentiation of both osteoblasts and osteoclasts [71-75]. Specifically, LIF and CT-1 stimulate osteoclast formation by enhancing the expression of RANKL (receptor activator of nuclear factor kappa-B ligand). RANKL is the primary mediator of osteoclast formation, function, and survival.



**Figure 2** The LIFR protein with domains and exons shown. The numbers indicate the location of the 19 exons (figure not to scale). The domains (CRH1, Ig, CRH2, FNIII, TD and CD) are illustrated within their corresponding region of the protein (extracellular, transmembrane, or cytoplasmic). SP: signal peptide; CRH: cytokine receptor homology domain; Ig: Ig-like domain; FNIII: type III fibronectin domain; TM: transmembrane domain; CD: cytoplasmic domain.





**Figure 3 IL-6 family cytokines that signal through the leukemia inhibitory factor receptor (LIFR).** After cytokine binding, LIFR associates with gp130 to initiate the JAK/STAT1 or JAK/STAT3 pathway. In some cases, the SHP2/RAS/MAPK pathway is initiated. Oncostatin-M (OSM) and leukemia inhibitory factor (LIF) bind to LIFR without any other associated receptors. Cardiotrophin-1 (CT-1) binds to another receptor which associates with LIFR/gp130. Ciliary neurotrophic factor (CNTF) first binds to its receptor (CNTFR), which then recruits LIFR, followed by gp130. Cardiotrophin-like cytokine factor-1 (CLCF-1) binds with either cytokine receptor-like factor-1 (CRLF-1) or soluble ciliary neurotrophic factor receptor (sCNTFR) before binding to CNTFR.

Hence, RANKL plays a role in the reduction of bone density, volume and strength. *Ct-1* knockout mice showed osteopenia at the neonatal stage. Taken together, loss of LIF and CT-1 signaling in STWS due to the absence of a functional LIFR most likely contributes to osteopenia and bone-specific traits seen in STWS.

LIF also acts as a neurotrophic factor [76]. The smooth tongue phenotype seen in STWS is due to a lack of fungiform papillae. Fungiform papillae do not develop in the absence of LIF and CNTF signaling that cannot be mediated by the mutated *LIFR* gene [77]. Furthermore, LIF and CNTF are known to stimulate cholinergic differentiation in sympathetic neurons, inducing choline acetyltransferase gene expression, which in turn promotes the survival of cholinergic neurons [78]. Similarly, LIF and CT-1 are important for the cholinergic transdifferentiation of cardiac sympathetic neurons. Hence, it is likely that a lack of LIF and CT-1 downstream signaling leads to the cardiovascular phenotype seen in STWS [79-81]. LIF also has neuromodulatory roles in the respiratory airways [82]. Table 2 summarizes the relationship between STWS symptoms and the loss of specific cytokine signaling that cannot be

**Table 2 Stüve-Wiedemann syndrome (STWS) with the corresponding molecular etiology**

STWS phenotype	Cytokine	Reference
Smooth tongue	LIF, CNTF	[7,77]
Osteopenia	LIF, OSM, CT-1	[58,68,89,99]
Cardiovascular malfunctions	LIF, CT-1	[79-81,94,99]
Paradoxical sweating	CLCF1/CRLF1	[9,13,106]
Dysphagia	CT-1?, OSM?, CLCF1/CRLF1?	[20,70,107,108]
Respiratory distress	CT-1?, OSM?	[82]
Short stature	CNTF	[58,70,89,100]

Each of the cytokines signal through the leukemia inhibitory factor receptor (LIFR). In STWS, the *LIFR* gene is mutated, and due to the mutation, cytokine signaling is blocked, and the corresponding manifestations of STWS occur. Only symptoms for which the mechanism has been explored are listed. Those followed by a question mark are still under considerable speculation. LIF: leukemia inhibitory factor; CNTF: ciliary neurotrophic factor; OSM: oncostatin-M; CT-1: cardiotrophin-1; CLCF1: cardiotrophin-like cytokine factor-1; CRLF1: cytokine receptor-like factor-1.

mediated by LIFR due to a mutated *LIFR* gene and absence of LIFR protein.

LIF induces skeletal muscle satellite cells to proliferate via the JAK2-STAT3 pathway [83,84]. Satellite cells are quiescent resident multipotential cells that are essential for muscle growth and hypertrophy, and are recruited for muscle growth, regeneration, and repair of injured muscles. LIF is able to both promote or inhibit myoblast differentiation, depending upon conditions [83,85], and acts as a survival factor for myoblasts [86]. Thus, the lack of LIF downstream signaling resulting from an absence of LIFR in STWS may be a contributing factor in the muscular symptoms associated with STWS.

#### **Oncostatin-M (OSM): bone and motor neuron development**

OSM shares similarities with LIF. For example, both are able to induce the differentiation of myeloid leukemia cells to macrophage-like cells in mice [87]. LIF and OSM are located near each other on chromosome 22, and their arrangements suggest that LIF and OSM may be the result of a gene duplication event of an ancestral gene [88].

OSM, CT-1, and to a lesser extent, LIF, are involved in bone formation *in vitro* and *in vivo* [58,89]. OSM can bind to either OSMR:gp130 or LIFR:gp130 heterodimeric receptors. The effect of OSM on bone formation depends on which receptor complex it acts through. When OSM acts through LIFR:gp130 receptor complex, it promotes bone formation by inhibiting sclerostin, for example. Conversely, when OSM acts through OSMR:gp130 receptor complex, it promotes bone resorption by stimulating RANKL production and osteoclast formation [71,90,91]. Therefore, in STWS, the lack of OSM signaling through LIFR:gp130 receptor complex is not able to contribute positively to bone formation, and, in addition, OSM signaling mediated by OSMR:gp130 promotes bone resorption, thus playing a role in osteopenia.

The number of motor neurons in the facial nucleus, lumbar spinal cord, and nucleus ambiguus are severely reduced in mice that do not express LIFR. Importantly for STWS, the nucleus ambiguus innervates the esophagus, pharynx, larynx, and coordinates swallowing. The nucleus ambiguus is responsible for initiating the respiratory rhythm. LIF and CNTF enhance the differentiation and survival of motor neurons, yet Li et al. found that mice deficient in CNTF do not show a decrease in motor neurons, and that mice deficient in LIF do not show any severe neuronal defects. Therefore, Li et al. demonstrated that the reduction in motor neurons seen in STWS is due to the inability of OSM and CT-1 to signal through the mutated LIFR [70]. Taken together, OSM and CT-1 are the most likely LIFR ligands responsible for the respiratory distress and dysphagia seen in STWS. Others have argued that the respiratory distress

of STWS may be secondary to myotonia instead of pulmonary hypoplasia [20].

#### **Cardiotrophin-1 (CT-1): heart, motor neurons, and airway smooth muscle**

CT-1, along with LIF, was shown to play an important role in the cholinergic transdifferentiation of cardiac sympathetic neurons in rodents [79,92]. Specifically, CT-1 reduced the number of preganglionic sympathetic neurons, which are important for inducing heart rate, ventricular pressure, and contractility [93]. CT-1 is also known to induce cardiac myocyte hypertrophy and vascular smooth muscle cell proliferation *in vitro* [80]. Therefore, the lack of CT-1 signaling in STWS may play a role in the cardiovascular phenotype [94]. CT-1 was also found to play a role in motor neuron survival [95]. As indicated above, CT-1 plays essential roles in bone and skeletal development. Additionally, a role for CT-1 in airway smooth muscle cells has been identified [96,97]. Therefore, an absence of CT-1 signaling in STWS may contribute to the respiratory phenotype of STWS.

#### **Ciliary Neurotrophic Factor (CNTF): motor neuron survival and contribution to short stature**

CNTF was first isolated from chick eyes, where it helped the survival of embryonic ciliary ganglia [98]. CNTF is expressed in the developing nervous system, particularly in the motor neurons, and it plays a role in motor neuron survival [70].

STWS includes low birth weight and length, delayed growth, and short stature [13,20]. While one symptom of STWS may be dwarfism, since *LIFR*<sup>-/-</sup> mice exhibit dwarfism [89,99], the short stature within the trunk region seen in STWS may, in part, be secondary to progressive scoliosis, however this would not explain the reduction in leg length [13]. Relevant to both explanations, CNTF is expressed in chondrocytes, the cells that are responsible for longitudinal bone growth at the growth plate [89,100]. LIF and CT-1 are also expressed in chondrocytes [101,102], however LIF and CT-1 do not induce chondrogenesis [89]. A short bone phenotype is seen in *Cntf* knockout mice [100]. Therefore, impairment of CNTF signaling in the absence of a functional LIFR in STWS is the most likely cause of the short stature phenotype observed in STWS.

#### **Cardiotrophin-like Cytokine Factor-1 (CLCF-1): autonomic functioning**

Crisponi syndrome and cold-induced sweating syndrome share some features with STWS, such as feeding difficulties, trismus, paradoxical sweating (i.e., sweating with low body temperatures; [9,20]), and hyperthermic episodes [10]. Crisponi syndrome is now considered to be the same disorder as cold-induced sweating syndrome

[103], and cold-induced sweating syndrome is caused by mutations in the *CLCF-1* or *CRLF-1* genes [9]. CLCF-1 binds with either CRLF-1 (cytokine receptor-like factor-1) or sCNTFR (soluble ciliary neurotrophic factor receptor) and then competes with CNTF (ciliary neurotrophic factor) for the receptor complex composed of CNTFR, LIFR and gp130 (Figure 3; [51,104,105]). Therefore, it seems that the dysautonomic symptoms seen in STWS are caused by a lack of CLCF-1/CRLF-1 signaling due to a mutated *LIFR* gene [13,21]. Adding to this evidence, in mice, *Clcf-1/Crlf-1* appears to be responsible for cholinergic differentiation of neurons innervating sweat glands [106].

Mice lacking *Crlf-1*, *Cntfr* and *Clcf-1* are unable to suckle and die shortly after birth [107]. These mice also have a reduced number of motor neurons in the facial nucleus [108]. Therefore, a lack of CLCF-1/CRLF-1 signaling is the best candidate for the dysphagia and facial muscle contractions seen in STWS.

### **A note about bowing of the long bones**

#### **Myotonia and mechanical forces May play a role**

The etiology for each of the major STWS symptoms discussed thus far has been on a cellular level. However mechanical forces also may play an important role in STWS. Congenital bowing of the long bones is a hallmark feature of STWS [1], but it is not unique to STWS and manifests in other syndromes including type IX Ehlers-Danlos syndrome, Campomelic Displasia, Larsen syndrome and other conditions. [109-112]. Some have suggested that prenatal bowing of the long bones results from the mechanical forces of imbalanced muscles acting on structurally weak bones *in utero* [113-115]. Begam et al. found that prior to birth, patients with STWS have myotonia [20], which could produce imbalanced muscular force. Other studies also noted myotonia as a symptom [16,116,117]. Therefore, bowing of the long bones in STWS may be due to mechanical forces acting on bones that are weakened by inadequate signaling.

### **Managing Stüve-Wiedemann syndrome**

There are no treatments available for STWS at this time. However, aminoglycosides are capable of inducing the read-through of premature stop codons. Since premature stop codons are present in many *LIFR* mutations associated with STWS, the aminoglycoside gentamycin was tested on fibroblast cultures from STWS patients. High doses of gentamycin restored lost JAK/STAT signaling. Although high doses of gentamycin are nephro- and ototoxic *in vivo*, perhaps a similar treatment modality should be explored further [55].

Currently, STWS is managed symptomatically, with prevention of lung aspirations being a top priority [12]. Since STWS patients are unable to maintain a respiratory

rhythm or swallow during the first year of life, oftentimes, intubation, nasogastric tube feeding and/or gastrostomy are necessary [118]. Although swallowing abilities generally improve over time [13], it is recommended that caretakers are vigilant while the patient is eating for at least the first five years of life as aspiration and choking can still occur later in childhood [18]. Furthermore, children with STWS have been noted to bite their tongue and cause damage. This can be prevented by using an appliance to cover the teeth to prevent tongue damage until the child gains enough self-awareness to limit unintentional tongue biting [118].

Osteopenia or osteoporosis in STWS may be treated using bisphosphonates with calcium, 1,25 OH vitamin D and/or human growth hormone [18]. Surgery is often necessary to improve other bone malformations [13,119], and physical therapy may also be helpful [118].

In STWS, it is important to protect the eyes from damage, including sunlight, to prevent visual loss. Once ocular issues arise (e.g., corneal opacities, hypolacrimation and impaired pupillary function), a balanced approach is recommended [120]. The results of corneal transplantation in children with anesthetic corneas are poor [121]. However, corneal opacities can be corrected with keratectomy procedures [17]. For hypolacrimation, the frequent use of artificial tear drops and ointment at night are recommended. Additionally, lacrimal punctum dilation and punctual plugs can be implemented to encourage the accumulation of a tear reservoir. Tarsorrhaphies can be performed to help protect the cornea from exposure. Tropicamide eye drops are used to help dilate the pupil. If tropicamide fails, iridectomies are recommended [120].

Prior to surgery, physicians and STWS patients and families should be advised of certain complications which may occur with STWS. Specifically, some have argued that anesthesia increases the risk of malignant hyperthermia in STWS [122,123]. However, others have recently argued against this claim [17]. Additionally, tetraplegia was reported in two STWS patients within 40 hours of an otherwise uneventful thoracolumbar scoliosis corrective surgery. Pizones et al. therefore recommended close monitoring after spinal surgery regardless of the course of the surgery. The first symptom of delayed tetraplegia in these cases was acute severe neck pain [4].

### **Future directions**

#### **More information about etiology**

Although most reported cases of STWS are associated with a mutation in the *LIFR* gene [7], there are some diagnosed cases of STWS in which the patient does not have a *LIFR* mutation [13]. These cases should be explored further. It is possible that those patients were misdiagnosed, as STWS shares many traits with other syndromes [10,20,99]. However, it is also very likely that



other genes play a role in STWS [13]. Identical frame-shift mutations in the *LIFR* gene in different individuals have also been reported to show differing outcomes or severity [7].

Even in the cases where LIFR signaling is known to be the root cause of STWS, connections between signaling and symptoms have not been fully elucidated. It is known that many cytokines have redundant roles. It is likely to expect that the cytokines interact with one another, and that other proteins involved in STWS indirectly will be discovered with additional research.

### Improving outcomes

It has been noted that STWS patients who survive the first year of life show an improvement in their ability to swallow and regulate breathing [13]. This is a crucial improvement, as feeding difficulties, respiratory failure and hyperthermic episodes are the most frequently cited causes of early death in STWS [6,7,10]. However, it appears that the reason behind this improvement has not yet been explored on a physiological level, or on a molecular level. It would be interesting to learn what causes this shift in STWS phenotypes over time, and what causes these serious symptoms to occasionally return to cause unexpected death. Furthermore, this knowledge could have important implications in the development of treatments which are currently unavailable.

### Conclusions

STWS is a rare bent-bone dysplasia with dysautonomic manifestations that is generally caused by the autosomal recessive inheritance of a mutated *LIFR* gene. The symptoms of STWS are the result of a lack of LIFR signaling, although the exact mechanisms remain unclear for most phenomena. There is currently no treatment available for STWS. Instead, symptoms are managed accordingly. Although STWS is a rare condition, the prognosis remains poor and there are many unanswered questions regarding its pathology. Therefore, further research is needed to provide a better mechanistic understanding as well as to make progress toward novel therapies that take advantage of what we do know about the targeted manipulation of specific signaling pathways.

### Consent

Written informed consent was obtained from the patient, who is now if legal age, for the publication of this report and any accompanying images.

### Abbreviations

CLCF-1 or CLC: Cardiotrophin-like cytokine factor-1; CNTF: Ciliary neurotrophic factor; CNTFR: Ciliary neurotrophic factor receptor; CRLF1: Cytokine receptor-like factor 1; CT-1 or CTF1: Cardiotrophin 1; LIF: Leukemia inhibitory factor; LIFR: Leukemia inhibitory factor receptor; OSM: Oncostatin-M; OSMR: Oncostatin-M receptor; sCNTFR: Soluble ciliary neurotrophic factor receptor; STWS: Stüve-Wiedemann syndrome; JSJ2: Schwartz-Jampel syndrome type 2.

### Competing interests

There are no conflicts of interest to declare.

### Authors' contributions

DM and JTO contributed to the conceptual design. DM carried out data collection. KT designed the review figures. DM created the first draft, which was revised critically by JTO, CJ, and KT. CJ and KT provided analysis and interpretation of information related to IL-6 family members. JTO provided analysis and interpretation related to skeletal development. All authors read and approved the final manuscript.

### Acknowledgements

Research reported in this publication was supported by an Institutional Development Award (IDeA) from the National Center for Research Resources and the National Institute of General Medical Sciences of the National Institutes of Health under grant numbers P20 RR016454 and P20 GM103408, and the Department of Biological Sciences (B451).

Received: 23 November 2013 Accepted: 6 March 2014

Published: 12 March 2014

### References

1. Stuve A, Wiedemann HR: Congenital bowing of the long bones in two sisters. *Lancet* 1971, **2**:495.
2. Wiedemann H, Stueve A: Stüve-Wiedemann syndrome: update and historical footnote. *Am J Med Genet* 1996, **63**:12–16.
3. Rocco MD, Stella G: Long-term survival in Stuve-Wiedemann syndrome: a neuro-myo-skeletal disorder with manifestations of dysautonomia. *Am J Med Genet* 2003, **118A**:362–368.
4. Pizones J, Sponseller PD, Izquierdo E, Sanz E, Sanchez-Martinez F, Alvarez P, Zuniga L: Delayed tetraplegia after thoracolumbar scoliosis surgery in Stuve-Wiedemann syndrome. *Spine Deform* 2013, **1**:72–78.
5. Chen E, Cotter P: Characterization of a long-term survivor with Stüve-Wiedemann syndrome and mosaicism of a supernumerary marker chromosome. *Am J Med Genet* 2001, **101**:240–245.
6. Superti-Furga A, Tenconi R: Schwartz-Jampel syndrome type 2 and Stüve-Wiedemann syndrome: a case for "Lumping". *Am J Med Genet* 1998, **78**:150–154.
7. Dagoneau N, Scheffer D, Huber C, Al-Gazali LI, Di Rocco M, Godard A, Martinovic J, Raas-Rothschild A, Sigaudy S, Unger S, Nicole S, Fontaine B, Taupin J-L, Moreau J-F, Superti-Furga A, Le Merrer M, Bonaventure J, Munnich A, Legeai-Mallet L, Cormier-Daire V: Null Leukemia Inhibitory Factor Receptor (*LIFR*) Mutations in Stüve-Wiedemann/Schwartz-Jampel Type 2 Syndrome. *Am J Hum Genet* 2004, **74**:298–305.
8. Dagoneau N, Bellais S, Blanchet P: Mutations in Cytokine Receptor-Like Factor 1 (*CRLF1*) Account for Both Crisponi and Cold-Induced Sweating Syndromes. *Am J Hum Genet* 2007, **80**:966–970.
9. Crisponi L, Crisponi G, Meloni A: Crisponi Syndrome Is Caused by Mutations in the *CRLF1* Gene and Is Allelic to Cold-Induced Sweating Syndrome Type 1. *Am J Hum Genet* 2007, **80**:971–981.
10. Rigante D: Are there febrile diseases with a risk of sudden death in children? *Arch Dis Child* 2012, **97**:180.
11. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, Mortier G, Mundlos S, Nishimura G, Rimoin DL, Robertson S, Savarirayan R, Sillence D, Spranger J, Unger S, Zabel B, Superti-Furga A: Nosology and classification of genetic skeletal disorders: 2010 revision. *Am J Med Genet A* 2011, **155A**:943–968.
12. Al-Gazali LI, Ravenscroft A, Feng A, Shubbar A, Al-Saggaf A, Haas D: Stüve-Wiedemann syndrome in children surviving infancy: clinical and radiological features. *Clin Dysmorphol* 2003, **12**:1–8.
13. Jung C, Dagoneau N, Baujat G, Merrer M, David A, Rocco M, Hamel B, Megarbane A, Superti-Furga A, Unger S, Munnich A, Cormier-Daire V: Stuve-Wiedemann syndrome: long-term follow-up and genetic heterogeneity. *Clin Genet* 2010, **77**:266–272.
14. Al-Gazali L, Ali BR: Mutations of a country: a mutation review of single gene disorders in the United Arab Emirates (UAE). *Hum Mutat* 2010, **31**:505–520.
15. Koul R, Al-Kindy A, Mani R, Sankhla D, Al-Futaisi A: One in three: congenital bent bone disease and intermittent hyperthermia in three siblings with stuve-wiedemann syndrome. *Sultan Qaboos Univ Med J* 2013, **13**:301–305.
16. Cormier-Daire V, Munnich A, Lyonnet S, Rustin P, Delezoide AL, Maroteaux P, Le Merrer M: Presentation of six cases of Stüve-Wiedemann syndrome. *Pediatr Radiol* 1998, **28**:776–780.



17. Bonthuis D, Morava E: **Stuve Wiedemann syndrome and related syndromes: case report and possible anesthetic complications.** *Paediatr Anesth* 2009, **19**:212–217.
18. Corona-Rivera JR, Cormier-Daire V, Dagoneau N, Coello-Ramírez P, López-Marure E, Romo-Huerta CO, Silva-Baez H, Aguirre-Salas LM, Estrada-Solorio MI: **Abnormal oral-pharyngeal swallowing as cause of morbidity and early death in Stuve-Wiedemann syndrome.** *Eur J Med Genet* 2009, **52**:242–246.
19. Kaissi A, Rumppler M, Csepan R, Grill F, Klaushofer K: **Congenital contractures and distinctive phenotypic features consistent with Stuve-Wiedemann syndrome in a male infant.** *Cases J* 2008, **1**:121.
20. Begam M a, Alsafi W, Bekdache GN, Chedid F, Al-Gazali L, Mirghani HM: **Stuve-Wiedemann syndrome: a skeletal dysplasia characterized by bowed long bones.** *Ultrasound Obstet Gynecol* 2011, **38**:553–558.
21. Ware CB, Horowitz MC, Renshaw BR, Hunt JS, Liggitt D, Koblar SA, Gliniak BC, McKenna HJ, Papayannopoulou T, Thoma B: **Targeted disruption of the low-affinity leukemia inhibitory factor receptor gene causes placental, skeletal, neural and metabolic defects and results in perinatal death.** *Development* 1995, **121**:1283–1299.
22. Tomida M, Gotoh O: **Structure of the gene encoding the human differentiation-stimulating factor/leukemia inhibitory factor receptor.** *J Biochem* 1996, **120**:201–205.
23. Gearing DP, Thut CJ, VandeBos T, Gimpel SD, Delaney PB, King J, Price V, Cosman D, Beckmann MP: **Leukemia inhibitory factor receptor is structurally related to the IL-6 signal transducer, gp130.** *EMBO J* 1991, **10**:2839–2848.
24. Sato S, Omori Y, Katoh K, Kondo M, Kanagawa M, Miyata K, Funabiki K, Koyasu T, Kajimura N, Miyoshi T, Sawai H, Kobayashi K, Tani A, Toda T, Usukura J, Tano Y, Fujikado T, Furukawa T: **Pikachurin, a dystroglycan ligand, is essential for photoreceptor ribbon synapse formation.** *Nat Neurosci* 2008, **11**:923–931.
25. Kluger G, Koehler U, Neuhann TM, Pieper T, Staudt M, von Stülpnagel C: **Generalized epilepsy in two patients with 5p duplication.** *Neuropediatrics* 2013, **44**:225–229.
26. Cihil KM, Ellinger P, Fellows A, Stolz DB, Madden DR, Swiatecka-Urban A: **Disabled-2 protein facilitates assembly polypeptide-2-independent recruitment of cystic fibrosis transmembrane conductance regulator to endocytic vesicles in polarized human airway epithelial cells.** *J Biol Chem* 2012, **287**:15087–15099.
27. Kim J-D, Kang H, Larrivée B, Lee MY, Mettlen M, Schmid SL, Roman BL, Qyang Y, Eichmann A, Jin S-W: **Context-dependent proangiogenic function of bone morphogenetic protein signaling is mediated by disabled homolog 2.** *Dev Cell* 2012, **23**:441–448.
28. Huang C-H, Cheng J-C, Chen J-C, Tseng C-P: **Evaluation of the role of Disabled-2 in nerve growth factor-mediated neurite outgrowth and cellular signalling.** *Cell Signal* 2007, **19**:1339–1347.
29. Andrades JA, Nimni ME, Becerra J, Eisenstein R, Davis M, Sorgente N: **Complement proteins are present in developing endochondral bone and may mediate cartilage cell death and vascularization.** *Exp Cell Res* 1996, **227**:208–213.
30. Wimmers K, Khoa DVA, Schütze S, Murani E, Ponsuksili S: **The three-way relationship of polymorphisms of porcine genes encoding terminal complement components, their differential expression, and health-related phenotypes.** *BMC Proc* 2011, **5 Suppl** 4:S19.
31. Liu WT, Vanguri P, Shin ML: **Studies on demyelination in vitro: the requirement of membrane attack components of the complement system.** *J Immunol* 1983, **131**:778–782.
32. Kim HS, Kim DK, Kim AR, Mun SH, Lee SK, Kim JH, Kim YM, Choi WS: **Fyn positively regulates the activation of DAP12 and FcγR-mediated costimulatory signals by RANKL during osteoclastogenesis.** *Cell Signal* 2012, **24**:1306–1314.
33. Kim AN, Jeon W-K, Lim K-H, Lee H-Y, Kim WJ, Kim B-C: **Fyn mediates transforming growth factor-beta1-induced down-regulation of E-cadherin in human A549 lung cancer cells.** *Biochem Biophys Res Commun* 2011, **407**:181–184.
34. Nevsimalová S, Prazák J, Herzog P, Seemanová E: **Duffy locus linkage and HLA antigens in hereditary motor-sensory neuropathy.** *Schweiz Arch Neurol Psychiatr* 1991, **142**:19–29.
35. Tanaka M, Hirabayashi Y, Sekiguchi T, Inoue T, Katsuki M, Miyajima A: **Targeted disruption of oncostatin M receptor results in altered hematopoiesis.** *Blood* 2003, **102**:3154–3162.
36. Walker EC, McGregor NE, Poulton IJ, Solano M, Pompolo S, Fernandes TJ, Constable MJ, Nicholson GC, Zhang J-G, Nicola NA, Gillespie MT, Martin TJ, Sims NA: **Oncostatin M promotes bone formation independently of resorption when signaling through leukemia inhibitory factor receptor in mice.** *J Clin Invest* 2010, **120**:582–592.
37. Chen D, Chu C-Y, Chen C-Y, Yang H-C, Chiang Y-Y, Lin T-Y, Chiang I-P, Chuang D-Y, Yu C-C, Chow K-C: **Expression of short-form oncostatin M receptor as a decoy receptor in lung adenocarcinomas.** *J Pathol* 2008, **215**:290–299.
38. Morikawa Y: **Oncostatin M in the development of the nervous system.** *Anat Sci Int* 2005, **80**:53–59.
39. Komori T, Tanaka M, Senba E, Miyajima A, Morikawa Y: **Lack of oncostatin M receptor β leads to adipose tissue inflammation and insulin resistance by switching macrophage phenotype.** *J Biol Chem* 2013, **288**:21861–21875.
40. Gough NM, Gearing DP, King JA, Willson TA, Hilton DJ, Nicola NA, Metcalf D: **Molecular cloning and expression of the human homologue of the murine gene encoding myeloid leukemia-inhibitory factor.** *Proc Natl Acad Sci U S A* 1988, **85**:2623–2627.
41. Malik N, Kallestad JC, Gunderson NL, Austin SD, Neubauer MG, Ochs V, Marquardt H, Zarling JM, Shoyab M, Wei CM: **Molecular cloning, sequence analysis, and functional expression of a novel growth regulator, oncostatin M.** *Mol Cell Biol* 1989, **9**:2847–2853.
42. Pennica D, Swanson TA, Shaw KJ, Kuang WJ, Gray CL, Beatty BG, Wood WI: **Human cardiotrophin-1: protein and gene structure, biological and binding activities, and chromosomal localization.** *Cytokine* 1996, **8**:183–189.
43. Stöckli KA, Lottspeich F, Sendtner M, Masiakowski P, Carroll P, Götz R, Lindholm D, Thoenen H: **Molecular cloning, expression and regional distribution of rat ciliary neurotrophic factor.** *Nature* 1989, **342**:920–923.
44. Liu J, Modrell B, Aruffo A, Scharnawske S, Shoyab M: **Interactions between oncostatin M and the IL-6 signal transducer, gp130.** *Cytokine* 1994, **6**:272–278.
45. Gearing DP, Bruce AG: **Oncostatin M binds the high-affinity leukemia inhibitory factor receptor.** *New Biol* 1992, **4**:61–65.
46. Gearing DP, Comeau MR, Friend DJ, Gimpel SD, Thut CJ, McGourty J, Brasher KK, King JA, Gillis S, Mosley B: **The IL-6 signal transducer, gp130: an oncostatin M receptor and affinity converter for the LIF receptor.** *Science* 1992, **255**:1434–1437.
47. Mosley B, De Imus C, Friend D, Boiani N, Thoma B, Park LS, Cosman D: **Dual oncostatin M (OSM) receptors. Cloning and characterization of an alternative signaling subunit conferring OSM-specific receptor activation.** *J Biol Chem* 1996, **271**:32635–32643.
48. Wollert KC, Taga T, Saito M, Narazaki M, Kishimoto T, Glembocki CC, Vernallis AB, Heath JK, Pennica D, Wood WI, Chien KR: **Cardiotrophin-1 activates a distinct form of cardiac muscle cell hypertrophy. Assembly of sarcomeric units in series VIA gp130/leukemia inhibitory factor receptor-dependent pathways.** *J Biol Chem* 1996, **271**:9535–9545.
49. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F: **Principles of interleukin (IL)-6-type cytokine signalling and its regulation.** *Biochem J* 2003, **374**:1–20.
50. Port MD, Laszlo GS, Nathanson NM: **Transregulation of leukemia inhibitory [corrected] factor receptor expression and function by growth factors in neuroblastoma cells.** *J Neurochem* 2008, **106**:1941–1951.
51. Elson GC, Lelièvre E, Guillet C, Chevalier S, Plun-Favreau H, Froger J, Suard I, de Coignac AB, Delneste Y, Bonnefoy JY, Gauchat JF, Gascan H: **CLF associates with CLC to form a functional heteromeric ligand for the CNTF receptor complex.** *Nat Neurosci* 2000, **3**:867–872.
52. Stahl N, Yancopoulos GD: **The tripartite CNTF receptor complex: activation and signaling involves components shared with other cytokines.** *J Neurobiol* 1994, **25**:1454–1466.
53. Giese B, Roderburg C, Sommerauer M, Wortmann SB, Metz S, Heinrich PC, Müller-Newen G: **Dimerization of the cytokine receptors gp130 and LIFR analysed in single cells.** *J Cell Sci* 2005, **118**:5129–5140.
54. Kunisada K, Hirota H, Fujio Y, Matsui H, Tani Y, Yamauchi-Takahara K, Kishimoto T: **Activation of JAK-STAT and MAP kinases by leukemia inhibitory factor through gp130 in cardiac myocytes.** *Circulation* 1996, **94**:2626–2632.
55. Bellais S, Goff C, Dagoneau N, Munnich A, Cormier-Daire V: **In vitro read-through of termination codons by gentamycin in the Stuve-Wiedemann Syndrome.** *Eur J Hum Genet* 2010, **18**:130–132.
56. Sriram K, Benkovic SA, Hebert M, Miller DB, O'Callaghan JP: **Induction of gp130-related cytokines and activation of JAK2/STAT3 pathway in**

- astrocytes precedes up-regulation of glial fibrillary acidic protein in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of neurodegeneration: key signaling pathway for ast. *J Biol Chem* 2004, **279**:19936–19947.
57. Sekimoto T, Imamoto N, Nakajima K, Hirano T, Yoneda Y: Extracellular signal-dependent nuclear import of Stat1 is mediated by nuclear pore-targeting complex formation with NPI-1, but not Rch1. *EMBO J* 1997, **16**:7067–7077.
58. Sims NA, Jenkins BJ, Quinn JMW, Nakamura A, Glatt M, Gillespie MT, Ernst M, Martin TJ: Glycoprotein 130 regulates bone turnover and bone size by distinct downstream signaling pathways. *J Clin Invest* 2004, **113**:379–389.
59. Schiemann WP, Bartoe JL, Nathanson NM: Box 3-independent signaling mechanisms are involved in leukemia inhibitory factor receptor alpha- and gp130-mediated stimulation of mitogen-activated protein kinase. Evidence for participation of multiple signaling pathways which converge at Ras. *J Biol Chem* 1997, **272**:16631–16636.
60. Zhang JG, Zhang Y, Owczarek CM, Ward LD, Moritz RL, Simpson RJ, Yasukawa K, Nicola NA: Identification and characterization of two distinct truncated forms of gp130 and a soluble form of leukemia inhibitory factor receptor alpha-chain in normal human urine and plasma. *J Biol Chem* 1998, **273**:10798–10805.
61. Blanchard F, Duplomb L, Wang Y, Robledo O, Kinzie E, Pitard V, Godard A, Jacques Y, Baumann H: Stimulation of leukemia inhibitory factor receptor degradation by extracellular signal-regulated kinase. *J Biol Chem* 2000, **275**:28793–28801.
62. Blanchard F, Wang Y, Kinzie E, Duplomb L, Godard A, Baumann H: Oncostatin M regulates the synthesis and turnover of gp130, leukemia inhibitory factor receptor alpha, and oncostatin M receptor beta by distinct mechanisms. *J Biol Chem* 2001, **276**:47038–47045.
63. White UA, Stephens JM: Neurotrophin activates STAT3 independent of LIFR activation in adipocytes. *Biochem Biophys Res Commun* 2010, **395**:48–50.
64. Lindhard A, Bentin-Ley U, Ravn V, Islin H, Hviid T, Rex S, Bangsbo S, Sørensen S: Biochemical evaluation of endometrial function at the time of implantation. *Fertil Steril* 2002, **78**:221–233.
65. Allan EH, Hilton DJ, Brown NA, Evelyn RS, Yumita S, Metcalf D, Gough NM, Ng KW, Nicola NA, Martin TJ: Osteoblasts display receptors for and responses to leukemia-inhibitory factor. *J Cell Physiol* 1990, **145**:110–119.
66. Jay PR, Centrella M, Lorenzo J, Bruce AG, Horowitz MC: Oncostatin-M: a new bone active cytokine that activates osteoblasts and inhibits bone resorption. *Endocrinology* 1996, **137**:1151–1158.
67. Gough NM, Williams RL: The pleiotropic actions of leukemia inhibitory factor. *Cancer Cells* 1989, **1**:77–80.
68. Bozec A, Bakiri L, Hoebertz A, Eferl R, Schilling AF, Komnenovic V, Scheuch H, Priemel M, Stewart CL, Amling M, Wagner EF: Osteoclast size is controlled by Fra-2 through LIF/LIF-receptor signalling and hypoxia. *Nature* 2008, **454**:221–225.
69. Bugga L, Gadiant RA, Kwan K, Stewart CL, Patterson PH: Analysis of neuronal and glial phenotypes in brains of mice deficient in leukemia inhibitory factor. *J Neurobiol* 1998, **36**:509–524.
70. Li M, Sendtner M, Smith A: Essential function of LIF receptor in motor neurons. *Nature* 1995, **378**:724–727.
71. Palmqvist P, Persson E, Conaway HH, Lerner UH: IL-6, Leukemia Inhibitory Factor, and Oncostatin M Stimulate Bone Resorption and Regulate the Expression of Receptor Activator of NF- $\kappa$ B Ligand, Osteoprotegerin, and Receptor Activator of NF- $\kappa$ B in Mouse Calvariae. *J Immunol* 2002, **169**:3353–3362.
72. Ruan M, Pederson L, Bradley EW, Bamberger A-M, Oursler MJ: Transforming growth factor- $\beta$  coordinately induces suppressor of cytokine signaling 3 and leukemia inhibitory factor to suppress osteoclast apoptosis. *Endocrinology* 2010, **151**:1713–1722.
73. Malaval L, Aubin JE: Biphasic effects of leukemia inhibitory factor on osteoblastic differentiation. *J Cell Biochem Suppl* 2001, **Suppl 36**:63–70.
74. Walker EC, McGregor NE, Poulton IJ, Pompolo S, Allan EH, Quinn JMW, Gillespie MT, Martin TJ, Sims NA: Cardiotrophin-1 is an osteoclast-derived stimulus of bone formation required for normal bone remodeling. *J Bone Miner Res* 2008, **23**:2025–2032.
75. Richards CD, Langdon C, Deschamps P, Pennica D, Shaughnessy SG: Stimulation of osteoclast differentiation in vitro by mouse oncostatin M, leukaemia inhibitory factor, cardiotrophin-1 and interleukin 6: synergy with dexamethasone. *Cytokine* 2000, **12**:613–621.
76. Majumder A, Banerjee S, Harrill JA, Machacek DW, Mohamad O, Bacanamwo M, Mundy WR, Wei L, Dhara SK, Stice SL: Neurotrophic effects of leukemia inhibitory factor on neural cells derived from human embryonic stem cells. *Stem Cells* 2012, **30**:2387–2399.
77. Gardiner J, Barton D, Vanslambrouck JM, Braet F, Hall D, Marc J, Overall R: Defects in tongue papillae and taste sensation indicate a problem with neurotrophic support in various neurological diseases. *Neuroscientist* 2008, **14**:240–250.
78. Nawa H, Nakanishi S, Patterson PH: Recombinant cholinergic differentiation factor (leukemia inhibitory factor) regulates sympathetic neuron phenotype by alterations in the size and amounts of neuropeptide mRNAs. *J Neurochem* 1991, **56**:2147–2150.
79. Kanazawa H, Ieda M, Kimura K, Arai T, Kawaguchi-Manabe H, Matsuhashi T, Endo J, Sano M, Kawakami T, Kimura T, Monkawa T, Hayashi M, Iwanami A, Okano H, Okada Y, Ishibashi-Ueda H, Ogawa S, Fukuda K: Heart failure causes cholinergic transdifferentiation of cardiac sympathetic nerves via gp130-signaling cytokines in rodents. *J Clin Invest* 2010, **120**:408–421.
80. Pennica D, King KL, Shaw KJ, Luis E, Rullamas J, Luoh SM, Darbonne WC, Knutzon DS, Yen R, Chien KR: Expression cloning of cardiotrophin 1, a cytokine that induces cardiac myocyte hypertrophy. *Proc Natl Acad Sci USA* 1995, **92**:1142–1146.
81. Turnley AM, Bartlett PF: Cytokines that signal through the leukemia inhibitory factor receptor-beta complex in the nervous system. *J Neurochem* 2000, **74**:889–899.
82. Knight DA, D'Aprile AC, Spalding LJ, Goldie RG, Thompson PJ: Leukaemia inhibitory factor (LIF) upregulates excitatory non-adrenergic non-cholinergic and maintains cholinergic neural function in tracheal explants. *Br J Pharmacol* 2000, **130**:975–979.
83. Spangenburg EE, Booth FW: Multiple signaling pathways mediate LIF-induced skeletal muscle satellite cell proliferation. *Am J Physiol Cell Physiol* 2002, **283**:C204–C211.
84. Megeney LA, Perry RL, LeCouter JE, Rudnicki MA: bFGF and LIF signaling activates STAT3 in proliferating myoblasts. *Dev Genet* 1996, **19**:139–145.
85. Jo C, Kim H, Jo I, Choi I, Jung S-C, Kim J, Kim SS, Jo SA: Leukemia inhibitory factor blocks early differentiation of skeletal muscle cells by activating ERK. *Biochim Biophys Acta* 2005, **1743**:187–197.
86. Hunt LC, Tudor EM, White JD: Leukemia inhibitory factor-dependent increase in myoblast cell number is associated with phosphatidylinositol 3-kinase-mediated inhibition of apoptosis and not mitosis. *Exp Cell Res* 2010, **316**:1002–1009.
87. Rose TM, Bruce AG: Oncostatin M is a member of a cytokine family that includes leukemia-inhibitory factor, granulocyte colony-stimulating factor, and interleukin 6. *Proc Natl Acad Sci U S A* 1991, **88**:8641–8645.
88. Rose TM, Lagrou MJ, Fransson I, Werelius B, Delattre O, Thomas G, Jong PJ, Todaro GJ, Dumanski JP: The genes for oncostatin M (OSM) and leukemia inhibitory factor (LIF) are tightly linked on human chromosome 22. *Genomics* 1993, **17**:136–140.
89. Sims NA, Walsh NC: GP130 cytokines and bone remodelling in health and disease. *BMB Rep* 2010, **43**:513–523.
90. Bolin C, Tawara K, Sutherland C, Redshaw J, Aranda P, Moselhy J, Anderson R, Jorczyk CL: Oncostatin m promotes mammary tumor metastasis to bone and osteolytic bone degradation. *Genes Cancer* 2012, **3**:117–130.
91. Brounais B, Chipoy C, Mori K, Charrier C, Battaglia S, Pilet P, Richards CD, Heymann D, Rédini F, Blanchard F: Oncostatin M induces bone loss and sensitizes rat osteosarcoma to the antitumor effect of Midostaurin in vivo. *Clin Cancer Res* 2008, **14**:5400–5409.
92. Martinou JC, Martinou I, Kato AC: Cholinergic differentiation factor (CDF/LIF) promotes survival of isolated rat embryonic motoneurons in vitro. *Neuron* 1992, **8**:737–744.
93. Oberle S, Schober A, Meyer V, Holtmann B, Henderson C, Sendtner M, Unsicker K: Loss of leukemia inhibitory factor receptor beta or cardiotrophin-1 causes similar deficits in preganglionic sympathetic neurons and adrenal medulla. *J Neurosci* 2006, **26**:1823–1832.
94. Gritman K, Winkle DM, Lorentz CU, Pennica D, Habecker BA: The lack of cardiotrophin-1 alters expression of interleukin-6 and leukemia inhibitory factor mRNA but does not impair cardiac injury response. *Cytokine* 2006, **36**:9–16.
95. Pennica D, Arce V, Swanson TA, Vejsada R, Pollock RA, Armanini M, Dudley K, Phillips HS, Rosenthal A, Kato AC, Henderson CE: Cardiotrophin-1, a cytokine present in embryonic muscle, supports long-term survival of spinal motoneurons. *Neuron* 1996, **17**:63–74.

96. Zhou D, Zheng X, Wang L, Stelmack G, Halayko AJ, Dorscheid D, Bai TR: **Expression and effects of cardiotrophin-1 (CT-1) in human airway smooth muscle cells.** *Br J Pharmacol* 2003, **140**:1237–1244.
97. Zheng X, Zhou D, Seow CY, Bai TR: **Cardiotrophin-1 alters airway smooth muscle structure and mechanical properties in airway explants.** *Am J Physiol Lung Cell Mol Physiol* 2004, **287**:L1165–L1171.
98. Barbin G, Manthorpe M, Varon S: **Purification of the chick eye ciliary neurotrophic factor.** *J Neurochem* 1984, **43**:1468–1478.
99. Akawi NA, Ali BR, Al-Gazali L: **Stüve-Wiedemann syndrome and related bent bone dysplasias.** *Clin Genet* 2012, **82**:12–21.
100. McGregor NE, Poulton IJ, Walker EC, Pompolo S, Quinn JMW, Martin TJ, Sims NA: **Ciliary neurotrophic factor inhibits bone formation and plays a sex-specific role in bone growth and remodeling.** *Calcif Tissue Int* 2010, **86**:261–270.
101. Grimaud E, Blanchard F, Charrier C, Gouin F, Redini F, Heymann D: **Leukaemia inhibitory factor (lif) is expressed in hypertrophic chondrocytes and vascular sprouts during osteogenesis.** *Cytokine* 2002, **20**:224–230.
102. Sheng Z, Pennica D, Wood WI, Chien KR: **Cardiotrophin-1 displays early expression in the murine heart tube and promotes cardiac myocyte survival.** *Development* 1996, **122**:419–428.
103. Herholz J, Meloni A, Marongiu M, Chiappe F, Deiana M, Herrero CR, Zampino G, Hamamy H, Zalloum Y, Waaler PE, Crisponi G, Crisponi L, Rutsch F: **Differential secretion of the mutated protein is a major component affecting phenotypic severity in CRLF1-associated disorders.** *Eur J Hum Genet* 2011, **19**:525–533.
104. Sims NA: **gp130 Signaling in bone cell biology: multiple roles revealed by analysis of genetically altered mice.** *Mol Cell Endocrinol* 2009, **310**:30–39.
105. Rousseau F, Chevalier S, Guillet C, Rapon E, Diveu C, Froger J, Barbier F, Grimaud L, Gascan H: **Ciliary neurotrophic factor, cardiotrophin-like cytokine, and neuropoietin share a conserved binding site on the ciliary neurotrophic factor receptor alpha chain.** *J Biol Chem* 2008, **283**:30341–30350.
106. Stanke M, Duong CV, Pape M, Geissen M, Burbach G, Deller T, Gascan H, Otto C, Parlato R, Schütz G, Rohrer H: **Target-dependent specification of the neurotransmitter phenotype: cholinergic differentiation of sympathetic neurons is mediated in vivo by gp 130 signaling.** *Development* 2006, **133**:141–150.
107. Alexander WS, Rakar S, Robb L, Farley A, Willson TA, Zhang JG, Hartley L, Kikuchi Y, Kojima T, Nomura H, Hasegawa M, Maeda M, Fabri L, Jachno K, Nash A, Metcalf D, Nicola NA, Hilton DJ: **Suckling defect in mice lacking the soluble haemopoietin receptor NR6.** *Curr Biol* 1999, **9**:605–608.
108. Forger NG, Prevette D, deLapeyrière O, Bovis B, Wang S, Bartlett P, Oppenheim RW: **Cardiotrophin-like cytokine/cytokine-like factor 1 is an essential trophic factor for lumbar and facial motoneurons in vivo.** *J Neurosci* 2003, **23**:8854–8858.
109. Cormier-Daire V, Geneviève D, Munnich A, Merrer M: **New insights in congenital bowing of the femora.** *Clin Genet* 2004, **66**:169–176.
110. Sartoris DJ, Luzzatti L, Weaver DD, Macfarlane JD, Hollister DW, Parker BR: **Type IX Ehlers-Danlos syndrome. A new variant with pathognomonic radiographic features.** *Radiology* 1984, **152**:665–670.
111. Farra C, Piquet C, Guillaume M, D'Ercole C, Philip N: **Congenital bowing of long bones: prenatal ultrasound findings and diagnostic dilemmas.** *Fetal Diagn Ther* 2002, **17**:236–239.
112. Bicknell LS, Farrington-Rock C, Shafeghati Y, Rump P, Alanay Y, Alembik Y, Al-Madani N, Firth H, Karimi-Nejad MH, Kim CA, Leask K, Maisenbacher M, Moran E, Pappas JG, Prontera P, de Ravel T, Fryns J-P, Sweeney E, Fryer A, Unger S, Wilson LC, Lachman RS, Rimoin DL, Cohn DH, Krakow D, Robertson SP: **A molecular and clinical study of Larsen syndrome caused by mutations in FLNB.** *J Med Genet* 2007, **44**:89–98.
113. Angle C: **Congenital bowing and angulation of long bones.** *Pediatrics* 1954, **13**:257–268.
114. Austin G, Gold R, Mirra J: **Long-limbed campomelic dwarfism. A radiologic and pathologic study.** *Am J Dis Child* 1980, **134**:1035–1042.
115. Spranger J, Hall B: **Spectrum of Schwartz-Jampel syndrome includes micromelic chondrodysplasia, kyphomelic dysplasia, and Burton disease.** *Am J Med Genet* 2000, **94**:287–295.
116. Gaspar IM, Saldanha T, Cabral P, Vilhena MM, Tuna M, Costa C, Dagoneau N, Daire VC, Hennekam RCM: **Long-term follow-up in Stüve-Wiedemann syndrome: a clinical report.** *Am J Med Genet A* 2008, **146A**:1748–1753.
117. Giedion A: **Heterogeneity in Schwartz-Jampel chondrodystrophic myotonia.** *Pediatr Radiol* 1997, **27**:454.
118. Catavorello A, Vitale SG, Rossetti D, Caldaci L, Panella MM: **Case report of prenatal diagnosis of Stüve-Wiedemann Syndrome in a woman with another child affected too.** *J Prenat Med* 2013, **7**:35–38.
119. Shea KG, Apel PJ, Hutt NA, Guarino J: **Valgus slipped capital femoral epiphysis without posterior displacement: two case reports.** *J Pediatr Orthop B* 2007, **16**:201–203.
120. Injarie A, Narang A, Idrees Z, Saggat A, Nischal K: **Ocular treatment of children with Stüve-Wiedemann Syndrome.** *Cornea* 2012, **31**:269–272.
121. Bonini S, Rama P, Olzi D, Lambiasi A: **Neurotrophic keratitis.** *Eye (Lond)* 2003, **17**:989–995.
122. Seay AR, Ziter FA: **Malignant hyperpyrexia in a patient with Schwartz-Jampel syndrome.** *J Pediatr* 1978, **93**:83–84.
123. Fowler W, Layzer R, Taylor R, Eberle E, Sims G, Munsat T, Philippart M, Wilson B: **The Schwartz-Jampel syndrome. Its clinical, physiological and histological expressions.** *J Neurol Sci* 1974, **22**:127–146.

doi:10.1186/1750-1172-9-34

**Cite this article as:** Mikelonis et al.: Stüve-Wiedemann syndrome: LIFR and associated cytokines in clinical course and etiology. *Orphanet Journal of Rare Diseases* 2014 **9**:34.

**Submit your next manuscript to BioMed Central and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at  
www.biomedcentral.com/submit

