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Neuropathies of Stüve-Wiedemann Syndrome due to mutations in leukemia inhibitory factor receptor (LIFR) gene

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ABSTRACT

Stüve-Wiedemann syndrome (STWS; OMIM #610559) is a rare disease that results in dysfunction of the autonomic nervous system, which controls involuntary processes such as breathing rate and body temperature. In infants, this can result in respiratory distress, feeding and swallowing difficulties, and hyperthermic episodes. Individuals may sweat excessively when body temperature is not elevated. Additionally, individuals have reduced ability to feel pain and may lose reflexes such as the corneal reflex that normally causes one to blink, and the patellar reflex resulting in the knee-jerk. STWS usually results in infant mortality, yet some STWS patients survive into early adulthood. STWS is caused by a mutation in the leukemia inhibitory factor receptor (LIFR) gene, which is inherited in an autosomal-recessive pattern. Most LIFR mutations resulting in STWS cause instability of the mRNA due to frameshift mutations leading to premature stop codons, which prevent the formation of LIFR protein. STWS is managed on a symptomatic basis as no treatment is currently available.

Introduction

Stüve-Wiedemann syndrome (STWS) was first described in 1971 in two sisters with congenital bowing of the tibia and femur. While both patients experienced respiratory distress and died within a few days, one also suffered from hyperthermia[1,2]. Although the prognosis of STWS remains poor today, recent reports show that some STWS patients survive into adulthood[3,4]. STWS patients are phenotypically identical to Schwartz-Jampel syndrome type 2 (SJS2) patients[5,6], and both SJS2 and STWS have been linked to a mutation of the leukemia inhibitory factor receptor (*LIFR*) gene on chromosome 5p13.1, and SJS2 and STWS are now considered the same syndrome[7]. STWS is found across multiple ethnic groups in multiple regions of the world including North America, Europe, and the Middle East[7,8-12].

The skeletal features of STWS place it within the bent-bone dysplasias[13], 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[1,7,9,14]. Progressive bowing of the long bones, severe spinal deformities, osteoporosis and spontaneous fractures occur. Joints may be prominent with restricted mobility. While skeletal features are important, skeletal symptoms will not be the focus of this review, and we will restrict our discussion to nervous system symptoms.

Clinical manifestations

Many individuals with STWS do not survive beyond the first few months of life due to respiratory distress, difficulties with feeding and swallowing, and hyperthermic episodes[1,7-9,15-17]. 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 [9]. Temperature instability is accompanied by excessive and 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[7-9]. The smooth tongue phenotype seen in STWS is due to a lack of fungiform papillae, normally found on the upper surface of the tongue. The inner structural connective tissue of fungiform papillae is highly innervated and provides the ability to distinguish taste. Taste bud development and maintenance is strictly dependent on the innervation during early postnatal development, and fungiform papillae do not develop when innervation is obstructed[18]. Additionally, fungiform papillae do not develop in the absence of a functional LIFR or signaling by LIF and CNTF[19]. Lack of fungiform papillae is both a structural and a neurological pathology of STWS. A smooth tongue due to their absence is a key indicator of the role LIFR plays in normal neuronal development of taste buds, and an important symptom that STWS patients encounter.

Genetic etiology

The mutated *LIFR* gene is inherited in an autosomal recessive pattern. The mutations reported to date have been missense or nonsense mutations, with the majority of mutations occurring within the exons encoding the extracellular domain[7]. The *LIFR* gene has 20 exons, 19 of which encode amino acids of this transmembrane protein which is 1,097 amino acids long[7,20,21].

Mouse genetic models have informed us of phenotypes resembling STWS. LIFR null mice display a strikingly similar phenotype consistent with STWS patients[22]. The number of motor neurons in the facial nucleus, lumbar spinal cord, and nucleus ambiguous are severely reduced in mice that do not express LIFR[23]. Importantly for STWS, the nucleus ambiguus innervates the esophagus, pharynx, larynx, and coordinates swallowing and is responsible for initiating the respiratory rhythm.

Genetic Variability

Although not all STWS patients have an identified *LIFR* mutation[9,17], other genes responsible for the STWS phenotype have not been identified. Additional genes within the chromosomal region 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. 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[24]. DAB-2 also plays a role in bone morphogenetic protein signaling[25] and nerve cell differentiation[26]. Additionally, a neurologic function has been described for *FYB* through an association with hereditary motor-sensory neuropathy[27]. OSMR, like LIFR, is able to bind to glycoprotein (gp)130 to form heterodimers within the plasma membrane. *OSMR* has also been implicated in the respiratory system[28], and the nervous system[29], as well as metabolic symptoms such as mature-onset obesity, severe hepatic steatosis, and insulin resistance[30].

OSMR plays a key role in bone homeostasis as demonstrated by the *OSMR*($^{-/-}$) mouse, which exhibits an osteopetrotic phenotype due to an effect on osteoclast differentiation[31,32]. The *OSMR* ($^{-/-}$) mouse however, does not display the autonomic manifestations seen in STWS patients, suggesting that loss of *OSMR* by itself would not result in STWS. Therefore, the presence of *OSMR* within the candidate region is likely due to gene duplication and its presence within the candidate region is probably coincidence.

Proteins that play an essential role in the LIFR signaling pathway as ligands or as competing receptor, such as the cytokine receptor-like factor 1 (CRLF1), cardiotrophin-like cytokine factor 1 (CLCF1), neuropoietin (NP), and ciliary neurotrophic factor (CNTF) may play a role in the neuronal symptoms of STWS[9] and are discussed in more detail.

The lifr protein and signaling

The LIFR Protein

The LIFR protein (glycoprotein-190; gp190) 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). The transmembrane domain (TM; 834-858aa) is located between the extracellular domain and the cytoplasmic domain (CD; 859-1097aa) (Figure 1).

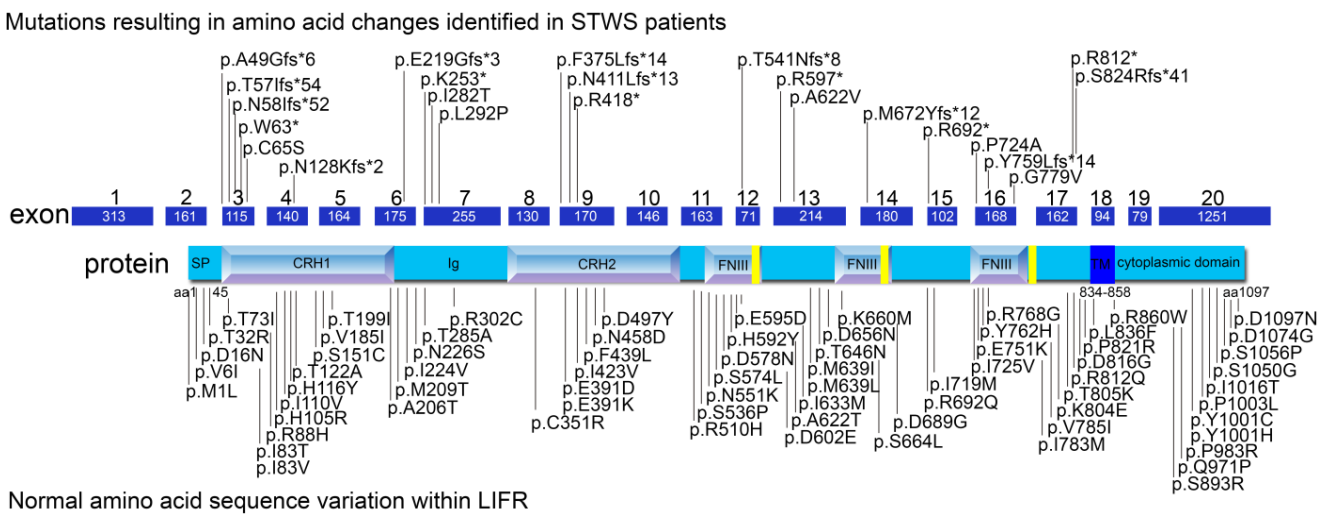

Figure 1. Known mutations in LIFR and normal sequence variants of LIFR. The LIFR protein is encoded by 19 exons within a 20 exon mRNA. The domains are illustrated within their corresponding region of the protein. SP: signal peptide; CRH1 and CRH2: cytokine receptor homology domains 1 and 2, Ig: Immunoglobulin-like domain; FNIII: fibronectin type III domain (433-530; 541-623; 729-821); TM: transmembrane domain (834-858); CD: cytoplasmic domain. Mutations observed in STWS patients are illustrated above the gene model[86] and the normal variations within the LIFR gene are indicated below the gene model[87]. Currently, no pattern has emerged for the symptoms experienced by STWS patients and their specific mutation.

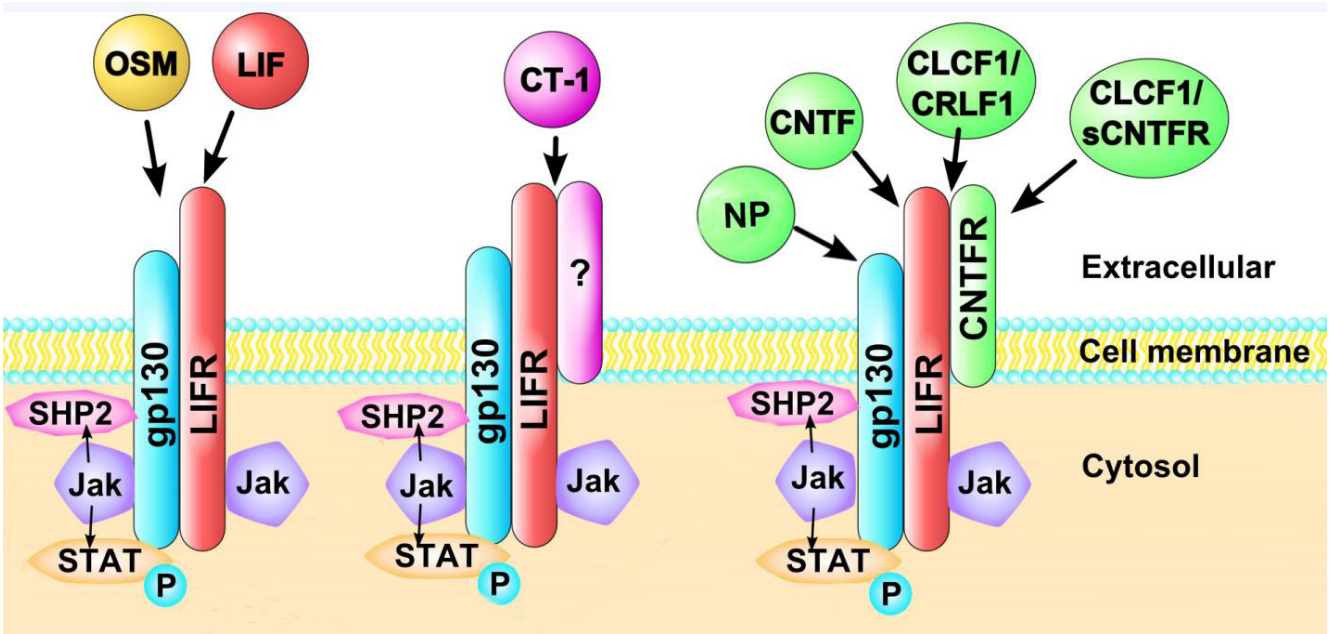

Figure 2. Cytokines interacting with LIFR. Leukemia inhibitory factor (LIF), oncostatin-M (OSM), cardiotrophin-1 (CT-1), ciliary neurotrophic factor (CNTF), neuropoietin (NP), and cardiotrophin-like cytokine factor 1 (CLCF-1/CRLF1 or a soluble form sCNTRF) bind to LIFR-containing heterodimeric receptors. LIFR can associate with other receptor subunits including gp130 and CNTFR. OSM and LIF interact with LIFR in association with gp130. CT-1 associates with LIFR with gp130 and potentially other receptor subunits. CNTF interacts with LIFR in association with gp130 and CNTFR, as does CLCF-1/CRLF1, NP and sCRLF1. Additionally, binding may occur in a competitive fashion with other cytokines, increasing the complexity of signaling through LIFR.

The LIFR Signaling Pathway

LIFR binds with low affinity to several IL-6 cytokine family members, including leukemia inhibitory factor (LIF), oncostatin-M (OSM), cardiotrophin-1 (CT-1, also abbreviated as CTF-1), ciliary neurotrophic factor (CNTF), neuropoietin (NP also abbreviated CTF2 in mouse, and CTF2P in human), and cardiotrophin-like cytokine factor 1 (CLCF-1, also abbreviated as CLC)[33-36] (Figure 2). Both LIF and OSM bind to the LIFR. LIF binds to LIFRβ, which then recruits gp130 for higher affinity and cell signaling[21]. In contrast, OSM binds gp130 with low affinity but has little to no biological activity unless a second receptor chain is recruited, either the LIFRβ or the more highly specific OSMRβ[37-40]. CT-1 binds to gp130 and LIFR[41], while CNTF first binds

STWS phenotype	Cytokine
Smooth tongue	LIF, CNTF
Osteopenia	LIF, OSM, CT-1
Cardiovascular malfunctions	LIF, CT-1
Paradoxical sweating	CLCF1/CRLF1
Dysphagia	CT-1?, OSM?, CLCF1/CRLF1?
Respiratory distress	CT-1?, OSM?
Short stature	CNTF

Table 1: LIFR ligand and associated symptoms
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. Neuropoietin is not included in the table.

to ciliary neurotrophic factor receptor (CNTFRα) before recruiting LIFR[42]. NP signals through a receptor complex comprising CNTFRα, gp130, and LIFR[43]. 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[9,44-46]. CNTF, LIF, and NP may be responsible for neuronal development and survival, as CTNF possesses neurotrophic activity and can enhance precursor self-renewal and expansion of neuronal stem cells[47,48]. CTNF and LIF may play a role in motor neuron innervation[49-51] and NP can sustain *in vitro* survival of embryonic motor neurons and can increase the proliferation of neural precursors[52] (Table 1).

Lifr ligands linked to neuronal development

Leukemia Inhibitory Factor

LIF is a pleiotropic cytokine, secreted by a variety of cell types, including epithelial and stromal cells[53], osteoblasts[54,55], bone marrow stromal cells, fibroblasts, astrocytes, heart myoblasts, T lymphocytes, monocytes, and thymic epithelial cells among others[56].

LIF acts as a neurotrophic factor[57] and may play a role in motor neuron innervation[49-51]. LIF is known to stimulate cholinergic differentiation in sympathetic neurons, inducing choline acetyltransferase gene expression, which in turn promotes the survival of cholinergic neurons[58]. Similarly, LIF is important for the cholinergic transdifferentiation of cardiac sympathetic neurons. Hence, it is likely that a lack of LIF downstream signaling leads to the cardiovascular phenotype seen in STWS[59-61]. LIF also has neuromodulary roles in the respiratory airways[62]. LIF enhances the differentiation and survival of motor neurons.

Oncostatin-M (OSM)

OSM shares similarities with LIF, as both are able to induce the differentiation of myeloid leukemia cells to macrophage-like cells in mice[63]. 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[64].

The reduction in motor neurons seen in STWS is due in part to the inability of OSM to signal through the mutated LIFR[23]. OSM is likely to be one of the LIFR ligands responsible for the respiratory distress and dysphagia seen in STWS.

Cardiotrophin-1 (CT-1)

CT-1 plays an important role in the cholinergic transdifferentiation of cardiac sympathetic neurons in rodents[59,65]. Specifically, CT-1 loss reduced the number of preganglionic sympathetic neurons, which are important for inducing heart rate, ventricular pressure, and contractility[66]. CT-1 is also known to induce cardiac myocyte hypertrophy and vascular smooth muscle cell proliferation *in vitro*[60]. Therefore, the lack of CT-1 signaling in STWS may play a role in the cardiovascular phenotype[67] and in motor neuron survival[68]. A role for CT-1 in airway smooth muscle cells has been identified[69,70], and therefore, an absence of CT-1 signaling in STWS may contribute to the respiratory phenotype of STWS. Similarly, CT-1 is important for the cholinergic transdifferentiation of cardiac sympathetic neurons. Hence, it is likely that a lack of CT-1 downstream signaling leads to the cardiovascular phenotype seen in STWS[59-61]. The reduction in motor neurons seen in STWS is due in part to the inability of CT-1 to signal through the mutated LIFR[23]. CT-1 is likely to be responsible for the respiratory distress and dysphagia seen in STWS.

Ciliary Neurotrophic Factor (CNTF)

STWS includes autonomic nerve dysfunction[3], and ciliary neurotrophic factor receptor (*CNTFR*) gene has also been linked to autonomic nervous system dysfunction[71,72]. CNTF is expressed in the developing nervous system, particularly in the motor neurons, and it plays a role in motor neuron survival[23]. CNTF are known to stimulate cholinergic differentiation in sympathetic neurons, inducing choline acetyltransferase gene expression, which in turn promotes the survival of cholinergic neurons[58]. CNTF enhances the differentiation and survival of motor neurons. Mice deficient in CNTF do not show a decrease in motor neurons.

Neuropoietin (NP; CTF2; CTF2P)

Neuropoietin is encoded by the CTF2 gene in the mouse and CTF2P in human. The approved name is cardiotrophin 2, pseudogene in humans. It was described in 2004 by Derouet and colleagues[52], located on mouse chromosome 7 (choromosome 16 in humans) in close proximity to

the cardiotrophin-1 gene. NP or CTF2, is predominantly expressed in mouse neuroepithelia during embryonic life, acts through a receptor complex comprising CNTFRα component, gp 130, and LIF receptor. Like CNTF, it promotes the survival of embryonic motor neurons and could increase the proliferation of neural precursor cells. Interestingly, the human gene has evolved into a pseudogene due to an 8 base pair deletion causing a disruption in the reading frame. This suggests that signaling via CNTF can compensate in the absence of a functional CTF2 in humans. While NP (CTF2) plays key roles in other mammals, it does not play a role in the symptoms of STWS.

NP is highly expressed in embryonic neuroepithelia and in the retina. NP can sustain the *in vitro* survival of embryonic motor neurons and could increase the proliferation of neural precursors. NP induces neuroepithelial cells to differentiate into astrocytes, and does so in coordination with bone morphogenetic protein 2 (BMP2)[43,52,73].

Cardiotrophin-like Cytokine Factor-1 (CLCF-1)

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[72]), and hyperthermic episodes[74]. Crisponi syndrome is now considered to be the same disorder as cold-induced sweating syndrome[75], and cold-induced sweating syndrome is caused by mutations in the *CLCF-1* or *CRLF-1* genes. 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[43,45,76]. Therefore, it is likely that the dysautonomic symptoms seen in STWS are caused by a lack of CLCF-1/CRLF-1 signaling due to a mutated *LIFR* gene. Additionally, Clcf-1/Crlf-1 is responsible for cholinergic differentiation of neurons innervating sweat glands[77].Mice lacking Crlf-1, Cntfr and Clcf-1 are unable to suckle and die shortly after birth[78]. These mice also have a reduced number of motor neurons in the facial nucleus[79]. Therefore, a lack of CLCF-1/CRLF-1 signaling leads to dysphagia and facial muscle contractions observed in STWS.

Future directions

Although most reported cases of STWS are associated with a mutation in the *LIFR* gene, some diagnosed cases do not have a demonstrable mutation in the *LIFR* gene. Although it is possible that those patients were misdiagnosed, as STWS shares many traits with other syndromes, it is also very likely that other genes play a role in STWS. Identical frameshift mutations in the *LIFR* gene in different individuals have also been reported to show differing outcomes or severity.

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. As many cytokines possess redundant roles, it is likely that there is overlap in function. Additional proteins involved in STWS will likely be discovered as additional research is carried out.

The future holds promise for potential new treatments for STWS. In the case where a single mutation causes STWS, gene editing technologies such as CRISPR/Cas9 may be used to directly modify and correct the STWS associated change in the genome[80]. If successful, correcting the LIFR gene could result in the expression of a normal and functional LIFR protein. Antisense mediated exon skipping may also be a useful strategy in cases where exons encode independently folding domains within the protein or where the remaining domain can still fold stably and correctly and carry out the function of the normal protein[81]. Exon skipping strategies may be especially applicable in cases where a mutation causes a change in reading frame, and skipping of an exon will restore the proper reading frame. Many of the identified disease causing mutations are nonsense mutations, introducing a premature stop codon within the coding regions, resulting in the production of a truncated protein or alternatively, mRNA template degradation. It may be possible to promote read-through of premature stop codons using aminoglycoside antibiotic treatment[82-84] that influences the fidelity of the stop codon recognition by changing the conformation of the rRNA. 5-(fluorophenyl)-1,2,4-oxadiazolyl-benzoic acid has also been suggested to suppress nonsense mutations by read-through and is being considered for the treatment of cystic fibrosis and may also be applicable for STWS nonsense mutations[85].

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. 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.

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