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INVITED REVIEW

Crisponi/cold-induced sweating syndrome: Differential diagnosis, pathogenesis and treatment concepts

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Abstract

Crisponi/cold-induced sweating syndrome (CS/CISS) is an autosomal recessive disease characterized by hyperthermia, camptodactyly, feeding and respiratory difficulties often leading to sudden death in the neonatal period. The affected individuals who survived the first critical years of life, develop cold-induced sweating and scoliosis in early childhood. The disease is caused by variants in the *CRLF1* or in the *CLCF1* gene. Both proteins form a heterodimeric complex that acts on cells expressing the ciliary neurotrophic factor receptor (CNTFR). CS/CISS belongs to the family of "CNTFR-related disorders" showing a similar clinical phenotype. Recently, variants in other genes, including *KLHL7*, *NALCN*, *MAGEL2* and *SCN2A*, previously linked to other diseases, have been associated with a CS/CISS-like phenotype. Therefore, retinitis pigmentosa and Bohring-Optiz syndrome-like (*KLHL7*), Congenital contractures of the limbs and face, hypotonia, and developmental delay syndrome (*NALCN*), Chitayat-Hall/Schaaf-Yang syndrome (*MAGEL2*), and early infantile epileptic encephalopathy-11 syndrome (*SCN2A*) all share an overlapping phenotype with CS/CISS, especially in the neonatal period. This review aims to summarize the existing literature on CS/CISS, focusing on the current state of differential diagnosis, pathogenesis and treatment concepts in order to achieve an accurate and rapid diagnosis. This will

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improve patient management and enable specific treatments for the affected individuals.

KEYWORDS
Cold-induced sweating, Crisponi syndrome, *CRLF1*, *CLCF1*, *KLHL7*, *MAGEL2*, *NALCN*, *SCN2A*

1 | INTRODUCTION

Crisponi syndrome (CS, MIM#601378) was firstly described in Sardinian families and although some phenotypic overlap existed with other phenotypes, the syndrome was hypothesized to be a unique entity and a new syndrome.[1] Later on, Accorsi et al[2] and Nannenberg et al[3] reported further patients with an identical phenotype, and suggested to name the entity Crisponi syndrome. CS is a rare recessively inherited disease with a high neonatal lethality. The principal clinical symptoms are recurrent periods of hyperthermia, camptodactyly, feeding and respiratory difficulties induced by abnormal paroxysmal contractions of the facial and oropharyngeal muscles. Some CS individuals survive the first year of life and often display a spontaneous improvement of feeding difficulties and hyperthermia.[1,4] However, these individuals develop scoliosis, sometimes mild psychomotor retardation as well as cold-induced sweating combined with massively elevated plasma noradrenaline (NA) levels in early childhood.[5] Cold-induced sweating syndrome type 1 (CISS1) was initially described in two siblings at the age of 20 and 21 years.[6] They showed cold-induced sweating at ambient temperatures lower than 20°C. A retrospective study revealed that most of the patients showed crises of hyperthermia, respiratory difficulties or contractions of facial and oropharyngeal muscles in infancy, typical symptoms of CS.[7] Scoliosis as well as other dysmorphic features are additional symptoms of this syndrome. Both, CS and CISS1 are caused by variants in the *cytokine receptor like factor 1* (*CRLF1*) gene, coding for a ligand of the ciliary neurotrophic factor receptor (CNTFR).[4,8,9] Genetic and functional studies on altered CRLF1 indicated that CS and CISS1 are two occurrences of the same disorder. Thus, CS is considered as the infantile presentation of CISS1.[10,11] CS/CISS1 belongs to the family of "CNTFR-related disorders" with overlapping clinical features including cold-induced sweating syndrome type 2 (CISS2, MIM#610313) and Stüve-Wiedemann Syndrome (STWS, MIM#601559). CS/CISS2 is caused by variants in *cardiotrophin-like cytokine factor 1* (*CLCF1*),[7,12,13] and STWS by variants in *leukemia inhibitory factor receptor* (*LIFR*).[14] The combination of typical clinical CS/CISS symptoms and the detection of disease-associated variants in *CRLF1* or *CLCF1* are the prerequisites for diagnosis.

The differential diagnosis in CS/CISS has rapidly changed with the use of next generation-based sequencing techniques. Variants in genes others than those related to the family of "CNTFR-related disorders" have been recently found to be associated with a CS/CISS-like phenotype. In 2016, disease causing variants in *kelch like family member 7* (*KLHL7*) were detected in individuals with a CS/CISS-like phenotype associated with retinitis pigmentosa (RP).[15] Recently, additional genes have been identified to be mutated in five other individuals with a CS/CISS-like phenotype, namely *sodium leak channel, non-selective* (*NALCN*), *MAGE family member L2* (*MAGEL2*) and *sodium voltage-gated channel alpha subunit 2* (*SCN2A*).[16] These genes are involved in the pathogenesis of other disorders with a dominant/de novo hereditary pattern. In this respect, whole exome sequencing disclosed unpredicted differential diagnoses in people with a CS/CISS-like phenotype, suggesting a high phenotypic overlap particularly in the neonatal period among the associated syndromes including congenital contractures of the limbs and face, hypotonia, and developmental delay (CLIFAHDD, MIM#616266), Schaaf-Yang (SHFYNG, MIM#615547), and early infantile epileptic encephalopathy-11 (EIEE11, MIM#613721) syndromes. Thus, the diagnosis is rather difficult and strengthening the importance of the molecular diagnostic confirmation.[16]

2 | CLINICAL DIAGNOSIS OF CS/CISS1

CS/CISS1 is characterized by a variety of symptoms and presents directly after birth with recurrent periods of hyperthermia up to 42°C occurring without infection and an exaggerated startle response associated with orofacial/laryngeal muscular manifestations (Figure 1).[1] These include paroxysmal contractions of the facial and oropharyngeal muscles, puckering of the lips, restricted jaw movements, laryngospasm, cyanosis, difficulties in swallowing and an excessive salivation in response to handling or crying. However, in relaxing or sleeping periods these symptoms are absent (Figure 1, Video S1).[1] Combined with the failure to suckle paroxysmal contractions result in serious feeding difficulties usually requiring the procedure of nasogastric or percutaneous endoscopic gastrostomy (PEG) feeding.[1,4] The mechanism underlying respiratory difficulties in CS/CISS is unclear. However, CS/CISS1-related respiratory difficulties in association with fever crises can lead to seizures and sudden death. Further typical clinical features are camptodactyly, a round face with chubby cheeks, trismus, depressed nasal bridge, high arched palate, hypertonia of neck muscles, foot anomalies as well as dehydration (Figure 2). Although most of the CS/CISS1 individuals decease in the first year of life (60% in our Sardinian cohort), a few of them survive past infancy, when most of the fatal infantile problems suddenly diminished. They show a spontaneous improvement of hyperthermia and facial contractions. However, thermoregulatory problems persist and at the age of about 3 years, they develop profuse sweating on the upper body, face and arms at ambient temperatures below 20°C, associated to a

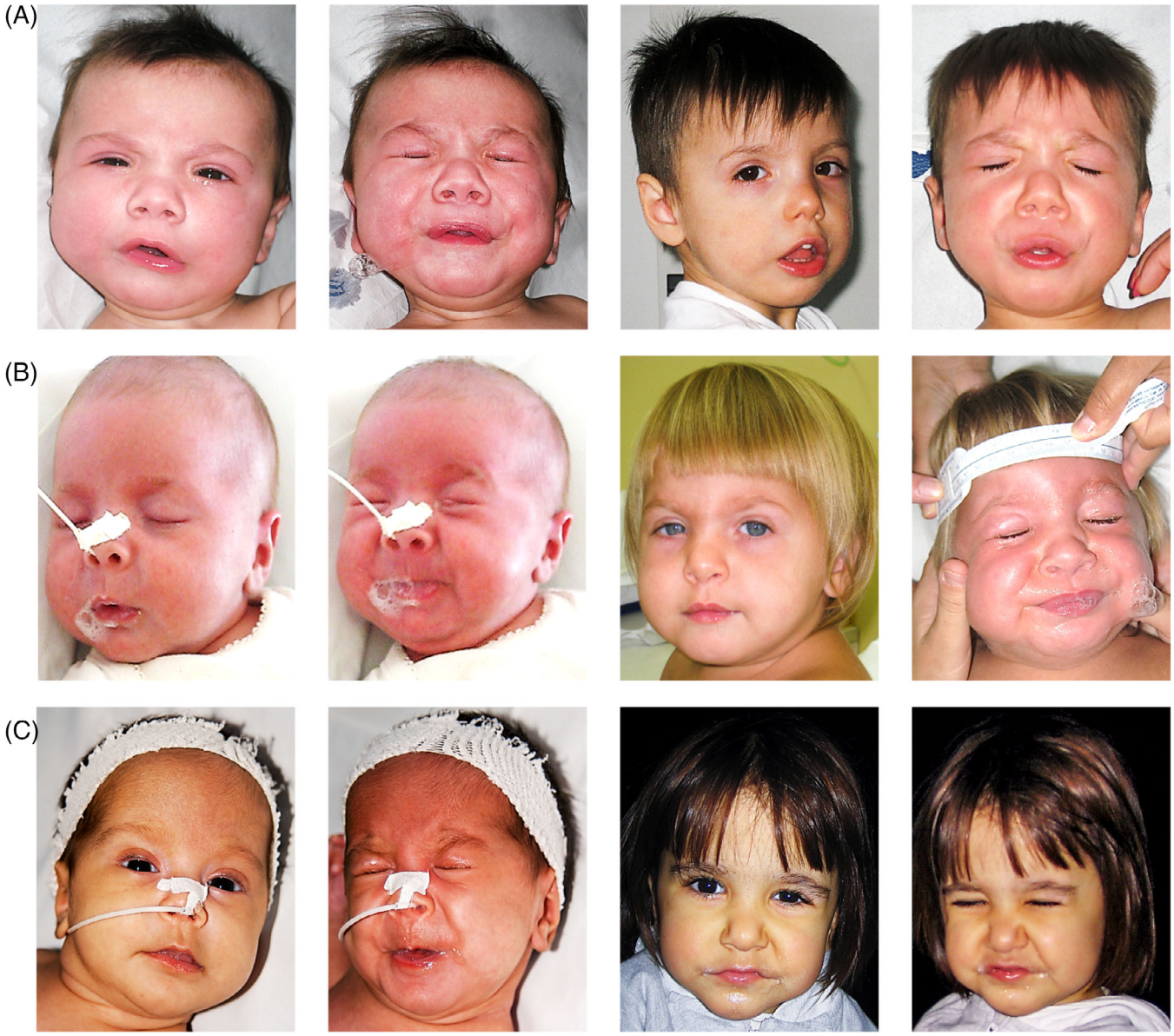

FIGURE 1 Typical features of CS/CISS1 individuals. Three Sardinian CS/CISS1 cases (A-C) during the neonatal period and infancy showing a normal facial expression when relaxed or sleeping and a distinctive paroxysmal contraction of the facial and oropharyngeal muscles with puckering of the lips and an excessive salivation in response to handling or crying. This feature is maintained during growth

massive increase of plasma NA levels. Profuse sweating can also occur in a state of nervousness or through the consumption of sweets.[11,12] In contrast to the cold-induced sweating, CS/CISS1 individuals show minimal sweating at hot environmental temperatures, which results in overheating.[11] Piras et al[17] classified CS/CISS1 in three groups with different severity based on the presence of four distinct disease symptoms, namely hyperthermia and feeding difficulties in infancy, scoliosis and cold-induced sweating in childhood/adolescence: (1) mild phenotype: cold-induced sweating and scoliosis in adolescence but no periods of hyperthermia or feeding difficulties in infancy; (2) intermediate phenotype: episodes of hyperthermia or feeding difficulties within the first year of life and scoliosis and cold-induced sweating later; and (3) severe phenotype: episodes of hyperthermia and feeding difficulties in infancy, scoliosis and cold-induced sweating in childhood/adolescence.

3 | MOLECULAR DIAGNOSIS OF CS/CISS

A definite diagnosis of CS/CISS depends on clinical findings as well as the identification of disease-causing variants in the associated genes. Approximately 95% of the molecularly tested and so far in the literature reported cases of CS/CISS can be explained by variants in *CRLF1* (CS/CISS1). The remaining cases can be explained by variants in *CLCF1* (CS/CISS2). In our internal cohort, 60% of CS/CISS cases present homozygous or compound heterozygous disease-associated

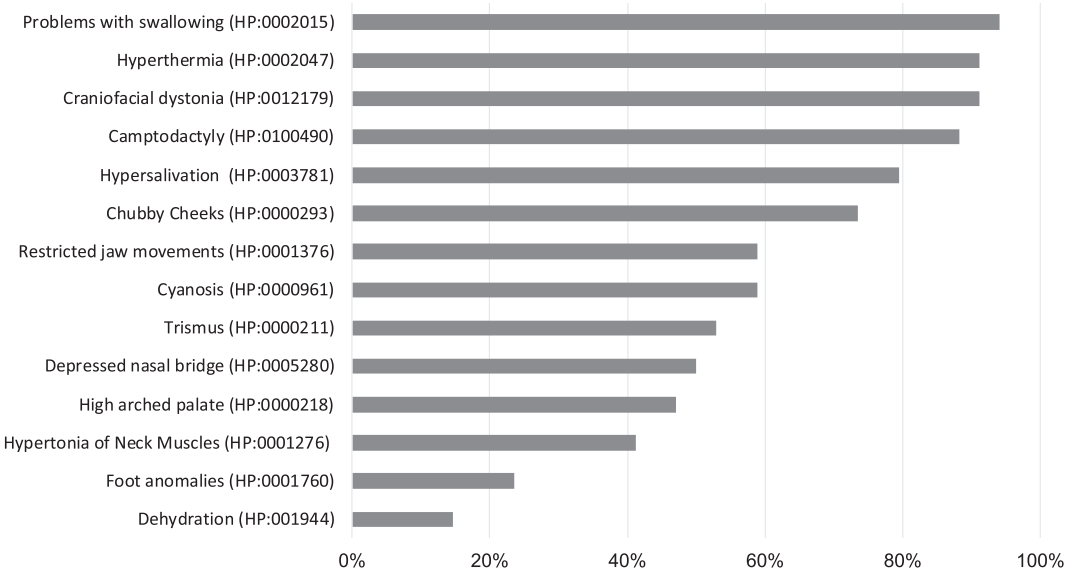

FIGURE 2 Frequency of the typical neonatal CS/CISS1 symptoms. Thirty-four CS/CISS individuals from our cohort with a completed clinical questionnaire were included in the calculation. The most common neonatal CS/CISS features are feeding and swallowing difficulties, hyperthermia, facial muscle contractions/craniofacial dystonia as well as camptodactyly

variants in *CRLF1*. We did not detect variants in *CLCF1*. The remaining 40% without variants in *CRLF1* or *CLCF1* are considered to have a CS/CISS-like phenotype.

Up to now, 37 disease causing *CRLF1* variants in 73 patients from 53 families have been reported in the medical literature.[4,7-10,12,17-30] In total, 88 CS/CISS1 individuals were identified, although 15 Sardinian CS/CISS1 individuals were not genetically analyzed because they died before *CRLF1* had been found to be associated with the disease.[1] As shown in Table 1, we report here three novel variants in 3 of 10 unreported patients (2 from Italy and 1 from India): a homozygous 23 bp duplication [c.23-45dup;p.(Leu19Asnfs*32)], a homozygous small deletion [c.120delA;p.(Ala41Leufs*2)], a missense in compound heterozygosity with an already disease-associated missense c.[226T>C];[226T>G]; p.[(Trp76Arg);p.(Trp76Gly)]. All variants were predicted to be pathogenic by the currently used algorithms (SIFT, Polyphen2 and MutationTaster). A genotype-phenotype correlation based on the type/localization of *CRLF1* variants is not possible, but can be made according to the biochemical characteristics of the mutated CRLF1 protein, in particular with its altered kinetics of secretion.[5] The Münster University Hospital Ethical Committee in Germany permitted the study protocol and all subjects gave informed written consent.

4 | PREVALENCE AND GEOGRAPHICAL DISTRIBUTION FOR CS/CISS

Different types of *CRLF1* variants associated with CS/CISS1 distributed all over the gene have been identified (Figure 3A,B, Table 1). So far, 96 CS/CISS1 individuals have been identified (of these 81 tested for variants in *CRLF1*). Most CS/CISS1 individuals originate from Europe, especially from the Mediterranean region [Italy mainland (4) and Sardinia (12 + 15 not tested for variants in *CRLF1*), Turkey (23), Spain (8), Lybia (3) and France (2)]. Others are from the Saudi Arabia (13), India, Pakistan, Japan, Australia, North or Central America.[4,7-10,12,17-30] Although most of the disease-associated *CRLF1* variants are private and found only in single families, some variants occur frequently in distinct CS/CISS1 individuals from a specific geographical region (eg, c.226T>G and c.676_677dupA in Sardinia, c.708_709delinsT in Turkey, c.983dupG in Saudi Arabia and c.713dupC in Spain, Turkey, Roma population). Piras et al[17] assumed that the occurrence of identical variants might originate from a founder effect and not from a mutational hotspot.[17] In Sardinia, where CS/CISS1 is more common than in the rest of world, Piras et al.[17]calculated the allele frequency of the two most common alleles (c.226 T > G and c.676_677dupA) and predicted an allele frequency of 1% and 0.4%, respectively, and calculated a joint carrier frequency of 1.4% with an expected incidence of about one case per 20 700 newborns. These results are in line with the epidemiological data collected in the last 45 years, during which 27 Sardinian CS/CISS1 individuals were identified. Of these, only 11 are still alive, with age ranging from one and half year to 40 years. Only two Hungarian siblings and one Australian individual with variants in the *CLCF1* gene have been identified so far. Therefore, only three CS/CISS2 individuals are known with a clinical phenotype indistinguishable from CS/CISS1, indicating locus heterogeneity for CS/CISS.[7,12,13]

5 | DIAGNOSTIC APPROACH/GENETIC COUNSELING

The clinical diagnosis of CS/CISS is quite difficult considering the relatively new phenotype, its rarity, complexity and change during development. The evidence of locus heterogeneity within the CS/CISS

TABLE 1 Summary of the known disease-associated *CRLF1* variants in CS/CISS1 patients

Origin/ethnicity	DNA variant	Exon/intron	Amino acid change	rs dbSNP	References
India	c.(?_-1)_(115 + 1_116-1)del	Exon 1	p.0?	–	19
Italy	c.23-45dup	Exon 1	p.[Leu19Asnfs*32]	–	This report
Japan/USA/Israel	c.31_53del	Exon 1	p.[Gln11Valfs*68]	rs137853929	7, 21
Spain	c.115 + 1 G > A	Intron 1	p.0?	–	17
India	c.120delA	Exon 2	p.[Ala41Leufs*2]	–	This report
Sardinia	c.221 T > C	Exon 2	p.[Leu74Pro]	–	17
Spain	c.223 T > G	Exon 2	p.[Tyr75Asp]	rs756560447	10
Italy	c.226 T > C	Exon 2	p.[Trp76Arg]	–	This report
Sardinia	c.226 T > G	Exon 2	p.[Trp76Gly]	rs137853143	4, 9
Israel	c.242G > A	Exon 2	p.[Arg81His]	rs104894670	8
USA	c.303delC	Exon 2	p.[Asn102Thrfs*47]	rs137853931	7
Saudi Arabia	c.322C > T	Exon 2	p.[Gln108*]	–	30
Italy	c.[338 A > T; c.341 T > C][a]	Exon 2	p.[Asn113Ile;	–	10
			Leu114Pro]	rs774359694	
Unknown	c.397 + 1G > A	Intron 2	p.0?	rs137853932	11
Turkey	c.413 C>T	Exon 3	p.[Pro138Leu]	rs137853930	29
Pakistan	c.433 T>C	Exon 3	p.[Ser145Pro]	–	17
Turkey	c.475delG	Exon 3	p.[Ala159Profs*75]	–	23
Yemen	c.527+5G>A	Intron 3	p.0?	–	9
Spain	c.527+5G>T	Intron 3	p.0?	–	17
Turkey	c.(398-456_697+747)del	Exon 3–4	p.0?	–	17
Canada	c.538C>T	Exon 4	p.[Gln180*]	rs137853926	12
Libya	c.539dupA	Exon 4	p.[Asp181Glyfs*5]	–	10
Saudi Arabia	c.605delC	Exon 4	p.[Ala202Valfs*32]	–	27
British/Pakistan	c.646 C > T	Exon 4	p.[Arg216Cys]	–	17
Sardinia	c.676_677dupA	Exon 4	p.[Thr226Asnfs*104]	–	4, 9
Turkey	c.(697 + 1_?)del	Exon 5–9	p.0?	–	25
Turkey	c.708_709delinsT	Exon 5	p.[Pro238Argfs*6]	–	4, 22, 28
Roma/Spain/Turkey	c.713dupC	Exon 5	p.[Pro239Alafs*91]	–	9, 10, 17, 24
Australia	c.721_737dup	Exon 5	p.[Gly247Cysfs*3]	–	17
Turkey	c.776 C>A	Exon 5	p. [Ser259*]	–	17
Spain	c.[803T>C; c.1018 C>T][a]	Exon 5;7	p.[Phe268Ser;Arg340Cys]	rs761982168	17
				rs771459625	
Turkey	c.829 C>T	Exon 5	p.[Arg277*]	rs137853145	18, 26
Norway	c.844_845delGT	Exon 5	p.[Val282Glyfs*47]	rs137853928	7, 8
Canada	c.852G>T	Exon 5	p.[Trp284Cys]	rs137853927	12
Italy	c.(856-1_?)del	Exon 6–9	p.0?	–	20
Italy	c.935G>A	Exon 6	p.[Arg312His]	rs137853933	20
Australia	c.935G>C	Exon 6	p.[Arg312Pro]	–	17
Saudi Arabia	c.983dupG	Exon 6	p.[Ser328Argfs*2]	rs1064793354	17, 27
Turkey	c.1102 A>T	Exon 7	p.[Lys368*]	rs137853144	4
Israel	c.1121T>G	Exon 7	p.[Leu374Arg]	rs104894668	8

[a]These mutations are in *cis*, so we cannot unambiguously ascertain which is the causative one, although functional prediction from multiple algorithms suggests as pathogenic c.341C>T and c.803C>T.

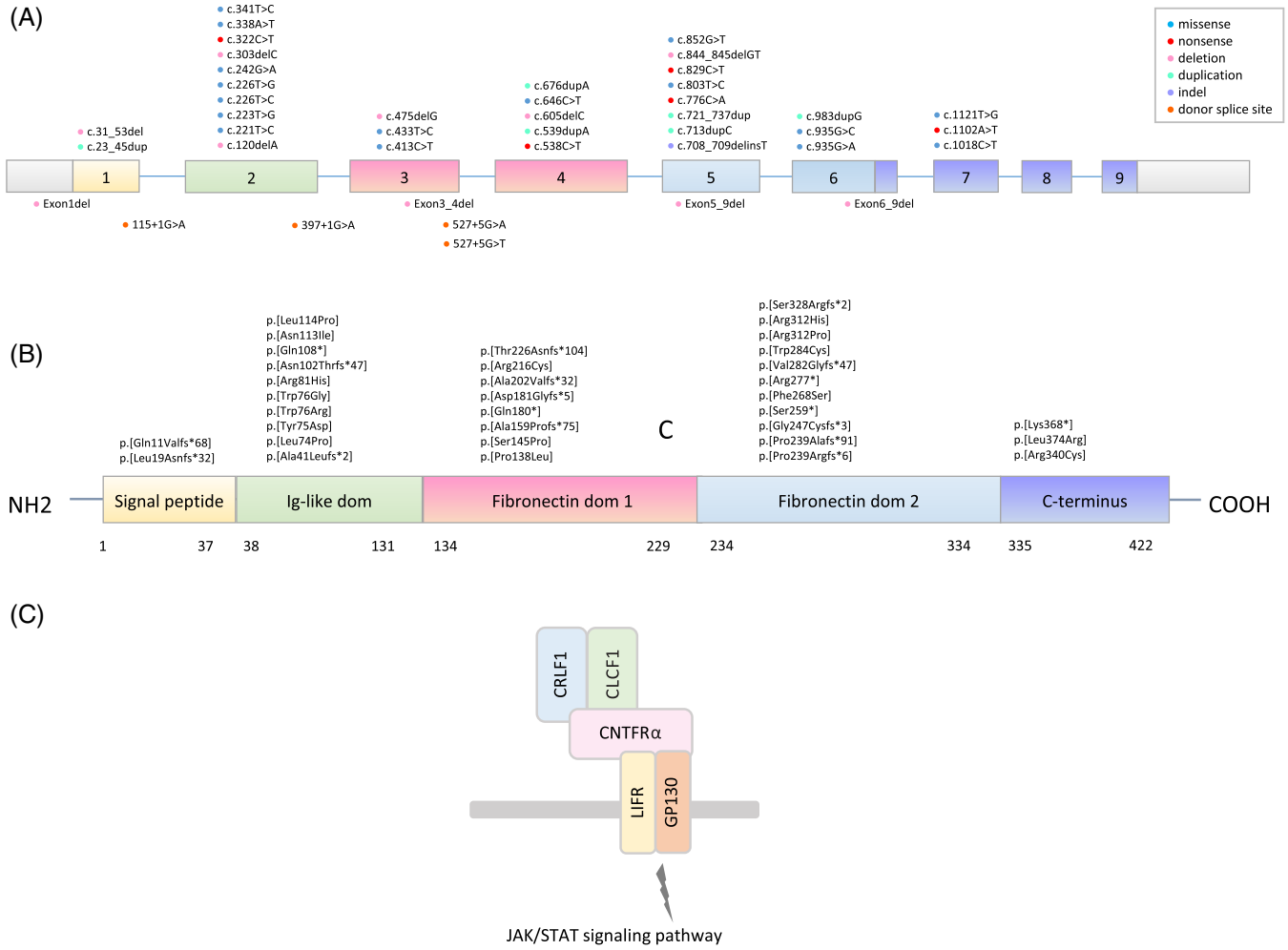

FIGURE 3 Disease-associated *CRLF1* variants and CNTFR pathway. Variants at the gene level (A) and at the protein level (B). Binding of the CRLF1/CLCF1 complex to CNTFRα initiates the dimerization of gp130 and LIFR and finally results in stimulation of the JAK/STAT signaling cascade. CNTFR pathway is important for embryonic development of facial motor neurons and for cholinergic differentiation of sympathetic neurons that innervate sweat glands (C)

phenotype range and the clinical similarities with several disorders, mostly in the neonatal period, demands careful differential diagnoses. CS/CISS would be expected in neonates and infants with one or more of the principal clinical features such as: recurrent periods of hyperthermia, orofacial/laryngeal muscular involvement with paroxysmal muscle contractions resulting in feeding or respiratory difficulties and camptodactyly. Out of the 73 reported CS/CISS cases with identified variants in *CRLF1*, 62% show the all principal CS/CISS clinical features in infancy such as hyperthermia, orofacial/laryngeal muscular involvement and camptodactyly. Eleven percentage show hyperthermia and orofacial/laryngeal muscular involvement but no camptodactyly. Five percentage had no hyperthermia but orofacial/laryngeal muscular involvement and camptodactyly, while 5% had only orofacial/laryngeal muscular involvement. One percentage of the CS/CISS cases present only camptodactyly. Due to incomplete data, 16% of CS/CISS cases are phenotypically unclear. To sum up, 83% of the CS/CISS individuals reported so far show orofacial/laryngeal muscular involvement and 73% hyperthermia. Camptodactyly arised in 68% of CS/CISS individuals. A combination of at least two of the four clinical symptoms is highly likely to lead to CS/CISS diagnosis. However, confirmation of CS/CISS by molecular genetic testing is crucial for assessing the etiological diagnosis. The identification of disease-associated variants in the *CRLF1* or *CLCF1* genes gives a definite CS/CISS diagnosis. CS/CISS has an autosomal recessive pattern of inheritance therefore for each sibling of a CS/CISS individual the probability of being affected is 25%. The determination of genetic risk should be done before pregnancy, and appropriate genetic counseling should be offered to CS/CISS adults as well as to those who are carriers or are at risk of being carrier. If the variant running in the family has been identified, molecular genetic testing in at-risk couples can be done in laboratories offering the test. In populations with identified disease associated *CRLF1* founder variants and enlarged occurrence of CS/CISS, a prenatal diagnosis of the syndrome may be supposed when presence of camptodactyly "sign of the horns" is identified by fetal ultrasound examination.[33]

6 | PATHOGENESIS

CRLF1 is an orphan soluble cytokine receptor sharing high homology with the receptor subunits of the IL-6 cytokine family.[34] This family comprises IL6, LIF, CLCF1 and CT-1, and regulates cell growth and differentiation in diverse biological systems such as immunity, inflammation or the nervous system.[34] CRLF1 forms an intracellular heterodimeric complex with CLCF1. The secreted heterodimer binds to CNTFR.[35] CNTFR comprises CNTFRα, the subunit responsible for ligand-binding, and two signal transducing subunits, glycoprotein 130 (gp130) and LIFRβ. Binding of the CRLF1/CLCF1 complex to CNTFRα initiates the dimerization of gp130 and LIFR and finally results in stimulation of the JAK/STAT signaling cascade (Figure 3C).[36] CNTFR is found in the nervous system and is important for the differentiation and endurance of several types of neuronal cells during and after development.[35] Structural studies revealed that CRLF1 controls the secretion of CLCF1 but not its activity. Either CLCF1 alone or the CRLF1/CLCF1 complex induce biological activity on cells expressing CNTFR.[37] STAT3 is phosphorylated by LIF in CS/CISS1 fibroblasts.[9,10] Therefore, even if CRLF1 is not necessary to activate the CNTFR pathway, its secretion appears to be important for proper CLCF1 secretion and adequate activation of the CNTFR pathway. We found that some *CRLF1* variants may trigger disease without disturbing the cellular secretion of CLCF1, which infers that CRLF1 is other than just a helper of CLCF1 secretion and has a more complex function.[10] Mouse pups with targeted deletions of *Crlf*1,[38] *Clcf*1,[39] *Cntfr*[40] or *Lifr*[41] display an identical phenotype, with reduction of facial and lumbar motor neuron, decreased facial motility, inability to suckle and die soon after birth due to malnutrition. The phenotype of these mouse models is in accordance to the clinical phenotypes of the "CNTF receptor-related disorders", with decreased facial motility, inability to suckle and neonatal lethality, such as CS/CISS1, CS/CISS2, and STWS.[4] These observations demonstrate the significant role of the CNTFR/gp130/LIFRβ tripartite receptor and the CRLF1/CLCF1 complex for embryonic development of facial motor neurons. Furthermore, they illustrate that each subunit in the signaling tripartite complex CRLF1:CLCF1:CNTFR is crucial in vivo. Additionally, the CNTFR pathway is involved in the cholinergic differentiation of sympathetic neurons. In humans, sweat production is regulated by the sympathetic nervous system.[42] Parasympathetic neurons possess a cholinergic phenotype and use acetylcholine as neurotransmitter whereas most of the sympathetic neurons possess an adrenergic phenotype with the neurotransmitter NA. Sweat glands, periosteum and skeletal muscle vasculature are innervated by postganglionic sympathetic neurons, which prenatally display adrenergic properties.[43] After birth, these neurons switch to a cholinergic phenotype induced by a retrograde soluble signal derived from the target tissue. In case of sweat glands, this switch is mediated via gp130/LIFR.[42] Skin biopsies of CS/CISS1 individuals show that there is no conversion from adrenergic to cholinergic phenotype probably due to loss of CRLF1 function.[20] These findings led to the hypothesis that CLCF1/CRLF1, mediate the shift from adrenergic to cholinergic properties of sympathetic neurons innervating sweat glands. Furthermore, defective conversion from adrenergic to cholinergic phenotype might explain the bone deformities and muscle symptoms, and the high variability in the clinical presentation of CS/CISS in different stages of life, because cholinergic sympathetic neurons also innervate periosteum and vasculature of the skeletal muscles. However, precise function of CRLF1 in the tripartite complex with CNTFR and CLCF1 is poorly investigated, and recent findings even indicate that CRLF1 might have distinct functions and different interaction partners such as IL 28, SorLA or IL12.[44-50] Thus, CRLF1 might have other functions and may target so far unidentified receptors.

7 | DIFFERENTIAL DIAGNOSTIC

7.1 | CS/CISS-like phenotype

In 2016 we identified in five CS/CISS-like individuals without disease causing variants in *CRLF1* or *CLCF1*, biallelic disease causing variants in *KLHL7*.[51] All affected individuals showed typical CS/CISS symptoms in infancy such as orofacial/laryngeal muscular involvement, camptodactyly, but only some presented periods of hyperthermia. As part of E3 ubiquitin ligase complex consisting of KLHL7, Cullin3 and ROCK1, KLHL7 recruits proteins for poly-ubiquitination and finally for proteasome-mediated degradation.[51] The identified variants in *KLHL7* probably lead to a loss of KLHL7 function due to affected substrate binding properties. Previously, variants in *KLHL7* with an autosomal dominant inheritance were found to be associated with late onset retinitis pigmentosa (adRP, MIM#612943), especially disturbing rod photoreceptors.[52,53] In accordance with this, two of our CS/CISS-like individuals also show RP. Autosomal recessive *KLHL7* variants were also found to be associated with Bohring-Opitz syndrome-like (BOS MIM#605039) characterized by intrauterine growth retardation (IUGR), failure to thrive, facial dysmorphism, camptodactyly, foot malformations and severe developmental delay.[54] Recently, individuals with an overlapping phenotype of CS/CISS, BOS and/or RP caused by *KLHL7* variants were identified. Hence, physicians have to be aware of the range of variability in presentation of individuals with *KLHL7* variants.[51,54-57]

7.2 | Stüve-Wiedemann syndrome/Schwartz-Jampel type 2 syndrome (STWS)

STWS (MIM#601559) is an autosomal recessive disorder characterized by bowed long bones, joint restrictions and dysautonomia.[58] Further typical symptoms are hyperthermic episodes, respiratory distress, feeding and swallowing difficulties.[14] Similar to CS/CISS individuals, most people with STWS die within the first months of life.[59] Those who survive the first year of life show intermitted thermoregulatory crises and unusual sweating.[60] Cold-induced sweating was reported in two unrelated individuals and another personally seen individual (Hahn, unpublished).[61] During development, survivors may present dental deterioration and progressive kyphoscoliosis.[59] Clinically, STWS and CS/CISS can be distinguished by congenital bowing of the

long bones in early childhood. Variants in *LIFR* were identified to cause STWS.[14] As part of CNTFR, LIFR dimerizes with gp130 and activates the JAK/STAT signaling pathway and therefore a clinical overlap of CS/CISS and STWS may be expected.

7.3 | Neonatal tetanus

Today, neonatal tetanus is a very rare disorder in the industrial nations. However, it remains an important cause of neonatal death especially in developing countries.[62] Tetanus is characterized by striking autonomic instability, and essentially affects the sympathetic nervous system.[63] Tetanus neurotoxin (TeNT) is a metalloprotease that cleaves proteins of the neuroexocytosis apparatus such as synaptobrevin at the presynaptic membrane resulting in inhibition of neurotransmitter release. TeNT in particular inhibits the release of glycine and gamma-aminobutyric acid (GABA) and therefore influences the function of inhibitory neurons. Disinhibition of the autonomic nervous system results in failure of autonomic control, combined with sympathetic over activity and excessive plasma catecholamine levels.[64] Affected individuals show an increased muscle tone and episodic spasms, called "tetanic spasms", which affect both agonist and antagonist muscle groups. The tetanic spasms are triggered spontaneously or by sensory stimulation. Spasms may be almost continual, leading to respiratory failure. Furthermore, intense muscular rigidity and spasms result in facial contractions similar to the convulsions of CS/CISS individuals. Initially, CS/CISS1 was defined as a new disorder consisting of tetanus-like spasms with typical dysmorphic features such as round chubby cheeks, broad nose with anteverted nostrils, long philtrum, and camptodactyly.[1] The combination of typical CS/CISS features and the genetic analysis of *CRLF1* or *CLCF1* helps in the clinical differentiation between the two diseases.[19]

7.4 | Congenital contractures of the limbs and face, hypotonia, and developmental delay syndrome (CLIFAHDD)

CLIFAHDD (MIM#616266) is an autosomal dominant disorder with strong clinical overlap to distal arthrogryposis type 2A (DA2A, MIM#193700) and is caused by variants in *NALCN*.[65] Affected individuals show the following clinical symptoms: congenital contractures of the limbs and face resulting in distinctive facial features, neonatal respiratory distress, hypotonia and variable grades of developmental delay. CLIFAHDD individuals also show limb deformities including camptodactyly, foot abnormalities ranging from various defects to clubfoot. In 2019, Angius et al identified two persons with CS/CISS-like phenotype harboring variants in *NALCN*.[16] The affected individuals had no thermoregulatory problems but show typical dysmorphic features of CS/CISS including chubby cheeks and depressed nasal bridge. Furthermore, both individuals had foot deformities as well as camptodactyly and contractions of the oropharyngeal muscles. The spasmodic facial muscle contraction and puckering of the lips of the CS/CISS-like individuals may bear some resemblance to CLIFAHDD, although this feature is not present in relaxed and sleeping CS/CISS children. Furthermore, microstomia is not present in CS/CISS individuals, whereas thermoregulatory dysfunctions are not reported in individuals with CLIFAHDD. Based on the clinical similarities of both syndromes, it is not surprising that CS/CISS was included in the differential diagnosis of CLIFAHDD syndrome.[65] As mentioned above CLIFAHDD shows a clinical overlap to DA2A in particular for CS/CISS-like features such as spasmodic facial muscle contraction or camptodactyly, but the clinical course is completely different.[11]

7.5 | Chitayat-Hall syndrome (CHS)/Schaaf-Yang syndrome (SHFYNG)

CHS (MIM#208080) also known as SHFYNG (MIM#615547) syndrome is an inherited autosomal dominant multisystem disease with a variety of symptoms including intellectual disability, delayed psychomotoric development and neonatal hypotonia with poor suckling, feeding problems in infancy and behavioral anomalies.[66,67] CHS/SHFYNG is caused by variants on the paternal *MAGEL2* allele. *MAGEL2* is an imprinted, maternally silenced, gene localized at 15q11-13, in the Prader-Willi syndrome (PWS, MIM#176270) region.[66,67] Recently, Angius et al[16] identified variants in *MAGEL2* in two CS/CISS-like individuals, showing camptodactyly, swallowing and feeding difficulties as well as dysmorphic features such as chubby cheeks. One of them had episodes of hyperthermia and profuse sweating. These observations let assume that variants in *MAGEL2* lead to an overlapping phenotype of CS/CISS and CHS/SHFYNG. MAGEL2 is strongly expressed in the hypothalamus. Together with E3 ubiquitin ligase TRIM27 and USP7 deubiquitinating enzyme, MAGEL2 forms a multi-subunit protein complex. In *MAGEL2* knockout mice, impaired suckling activity followed by altered feeding resulting in 50% mortality is observed within the first days of life. These findings suggest that MAGEL2 is implicated in suckling deficit observed in CHS/SHFYNG neonates.[68]

7.6 | Early infantile epileptic encephalopathy-11 syndrome (EIEE11)

Infantile/childhood onset epileptic encephalopathies or early infantile epileptic encephalopathies (EIEE) include different severe seizure conditions. Particularly, EIEE11 (MIM#613721) is an inherited autosomal dominant disease with early onset of severe seizures and subsequent developmental delay. In some cases, EIEE11 occurs with autistic type symptoms.[69] Variants in *SCN2A* are linked to a broad spectrum of clinical syndromes (ie, Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, infantile spasms). However, the underling pathomechanisms remain unclear.[70] Nevertheless, it is known that *SCN2A* encodes the voltage-gated sodium channel Nav1.2, an important neuronal sodium channel that is involved in initiation and conduction of action potentials in nerve and muscle. Mutated SCN2A was also described in a CS/CISS-like individual, presenting dysmorphic features such as depressed nasal bridge, thermoregulatory instability, camptodactyly and contractions of the muscles.[16] However, we

cannot rule out that in this case the *SCN2A* mutation co-occurs with a still unrecognized genetic defect.

In Table 2 is reported the comparison of the clinical symptoms between CS/CISS and disorders with a similar neonatal phenotype.

7.7 | Recommendations for clinical practice: management and therapy

CS/CISS is a paradigm of disability in which the interrelationship with the environment hinder the full participation of CS/CISS individuals in society. Currently, there is no therapy available for CS/CISS. Management is mostly symptomatic and has to be tailored for each individual to prolong survival, to increase quality of life, to relieve fatigue and discomfort, to promote growth and normal development and therefore to minimize the impact of the disease on the family life. The management is based on the typical progression of the disease in patients (Table 3). Long-standing follow-up is needed, and this requires a multidisciplinary approach. Parents must be involved in the daily care of the patients and should receive psychological support if necessary. It is of particular importance to train them from the beginning on the management and care of the affected child. Based on our 45 years' experience, neonatal assistance is very critical. Correct management can reduce mortality even in hospitals with limited resources. The newborns affected by CS/CISS need a dedicated environment, a dark quiet room, reduced manipulations that should be carried out as gently as possible (during the cleaning and change of clothes), limitations in blood sample taking (following the guidelines for analgesia in minor procedures) and all potential stressful situations. Intensive nursing care by personnel trained on the management and treatment of newborn emergencies is necessary. Stimulation must be minimized because the neonates are exquisitely sensitive to light, touch, and sound. Room temperature as well as temperatures of incubators

TABLE 2 Comparison of the clinical symptoms between CS/CISS and disorders with a similar neonatal phenotype

Symptoms	CS/CISS	CS/CISS-like phenotype	STWS	Neonatal tetanus	CLIFAHDD syndrome	SHFYNG syndrome	EIEE11 syndrome
Disease causing gene(s)	*CRLF1* *CLCF1*	*KLHL7*	*LIFR*		*NALCN*	*MAGEL2*	*SCN2A*
Hyperthermia	+	+	+	–	–	–	–
Febrile seizures	+	+	+	–	–	–	+
Camptodactyly	+	+	+	–	+	+	–
Feeding difficulties	+	+	+	+	–	+	–
Muscle contractions	+	+	+	+	+	–	+
Chubby cheeks	+	+	–	–	+	–	–
Difficulty in swallowing	+	+	+	+	–	–	–
Depressed nasal bridge	+	+	–	–	+	–	–
High arched palate	+	+	–	–	–	–	–
Joint contractures	+	–	+	–	+	–	–
Cyanosis	+	–	+	+	–	–	–
Foot anomalies	+	+	–	–	+	–	–
Psychomotor retardation	+	–	–	–	+	+	+
Hypersalivation	+	–	–	+	–	–	–
Dehydration	+	–	–	+	–	–	–
Cold-induced sweating	+	–	+	–	–	–	–
Scoliosis	+	–	+	–	+	+	–
Retinal photoreceptor dysfunction	–	+	–	–	–	–	–
Retinitis pigmentosa	–	+	–	–	–	–	–
Bowed long bones	–	–	+	–	–	–	–
Tetanic spasms	–	–	–	+	–	–	–
Microstomia	–	–	–	–	+	–	–
Neonatal hypotonia	+	–		–	+	+	–
Obstructive and/or central sleep apnea	–	–	–	–	–	+	–
Autism spectrum disorder	–	–	–	–	–	+	+
EEG abnormalities	–	–	–	–	–	–	+

TABLE 3 Recommended evaluations and treatment following a diagnosis of CS/CISS

Specialist evaluation or assessment/instrumental examination	Frequency or frame rate
Pediatric evaluation with measurement of growth parameters	At diagnosis; 6-monthly in the first 3 years then annual
Child neuropsychiatric evaluation	At diagnosis; every 6 months in the first 2 years, every year up to 6 years, then depending on the evolution
Ophthalmic evaluation	At diagnosis, then annually up to 6 years with a time frame determined by the evolution
Orthopedic/physiatric evaluation	At diagnosis, every 6 months up to 6 years thereafter with a time schedule determined by the problems present
Dental evaluation	At diagnosis, subsequently annual or with a timing determined by the problems present
Gastroenterological evaluation	At diagnosis, every 6 months in the first 2 years thereafter on clinical indication
Nutritional/dietetic evaluation	At diagnosis, every 6 months in the first 2 years thereafter on clinical indication
Endocrinological evaluation	At puberty, on clinical indication
Nutritional haematochemical tests	On clinical indication
RX spine	On clinical indication
RMN skull-spinal cord	On clinical indication
Acute complication	Age group
Hyperthermic crisis, epileptic crises	Neonatal age and early childhood
Respiratory distress with cianosis	Neonatal age and early childhood
Pneumonia ab ingestis	Neonatal age
Dehydration	All ages
Paradoxical sweating	Second childhood, adolescence, adulthood
Behavioral problems, agitation, expression of pain, esophagitis from gastroesophageal reflux	Neonatal age and early childhood

should not exceed 20°C (summer and winter). The thermoregulatory dysfunctions do not respond to antipyretic drugs and can only be partially controlled by physical mean (cold water). The newborns need continuous monitoring of cardiorespiratory parameters, oxygen saturation and body temperature. Feeding problems frequently require the use of nasogastric tubes or PEG with feed pump. The gastroesophageal reflux is treated pharmacologically, with positional therapy and diet. Ergotherapy, bracing or plastic surgery may be needed to ameliorate camptodactyly. Surgical intervention or continued bracing may be necessary to fix up a progressive kyphoscoliosis. Keratopathy is frequently present in CS/CISS individuals and to counteract the beginning of surface erosion or, more severe corneal injury, it is recommended to use artificial tears or lubricating gel since birth. The individuals affected by CS/CISS must not only deal with progressive scoliosis, camptodactyly, feeding difficulties but also with the environmental changes in temperature and humidity. CS/CISS, individuals must limit time or prolonged physical activity in hot environment. The hyperthermic crises constrain the young CS/CISS individuals to live constantly in temperature-controlled environment. Everyday life for the child and the family is marked by the inability to move outdoors or to public places without the indispensable presence of air conditioning. Moreover, when they try a social life such as going to kindergarten, to school, to perform sports, fever with peaks at 42°C will be inevitable increasing the risk of not surviving. When the hyperthermia crises fade away (around 6 years of age), the paradoxical sweating starts, and occurs several times daily, accompanied by physical discomfort and severe psychological distress. This condition limits the possibility of independent life and relationship, with considerable difficulties in integrating at school and work. Conceiving is possible and no complications during pregnancy are mentioned. Although complications with the anesthetic care of CS/CISS individuals have not been reported, potential difficulties should be anticipated. Perioperative implications and recommendations for anesthetic use are reported in Rafiq et al[71]

7.8 | Pharmacological treatment of cold-induced sweating

There are currently no treatment options available for the neonatal symptoms of CS/CISS. Only cold-induced sweating can be successfully treated with clonidine/amitriptyline or moxonidine.[5,7,12] Clonidine belongs to the active substance group of imidazolines and is an α_2-adrenergic agonist. Clonidine reduces synaptic NA release by feedback inhibition via a G-protein mediated signaling pathway leading to reduction of the sympathetic tonus. In order to ensure good tolerability of clonidine, possible contraindications should be clarified before ingestion such as potential cross reactions with already prescribed medications. If there are no contraindications, the drug is applied at the lowest dose required for acceptable symptom control. Usually, oral doses of 0.05 mg to 0.1 mg of clonidine twice a day successfully decrease cold-induced sweating and are well tolerated in these concentrations. Because of habituation, the positive effects of clonidine may be depleted within a few weeks. Slight enhancement of the daily dose to maximum doses of 0.1 mg four times a day may be accompanied by side effects such as dry mouth or fatigue. If clonidine has to be recessed, the medication should be reduced step by step over 4 to 6 days to avoid side effects such as hypertension. If the positive effects of clonidine are depleted or the symptoms are not effectively controlled, amitriptyline, 10 mg orally at bedtime, can be added to the prescription of clonidine. The maximum dose of 25 mg four times daily (taken together with clonidine) should not be exceeded. Similar

to clonidine, moxonidine is an agonist on imidazoline type 1 receptors. Through reduction of synaptic NA release, moxonidine causes reduction of sympathetic nerve activity. Due to its higher affinity to I1-imidazoline sites, moxonidine has a higher specificity and is associated with less side effects and therefore well tolerated in short term studies. The maximum dose of 6 μg/kg/d was shown to provide effective symptom relief in two teenage siblings with CISS.[5] During pregnancy, the administration of moxonidine should be interrupted in order not to interfere with the development of the fetus.

8 | CONCLUSION AND FUTURE PERSPECTIVE

Given the significant phenotypic similarity between CS/CISS and other disorders reported here, the clinical geneticist should use the existing medical diagnostic standard for CS/CISS with caution, particularly in the neonatal period. Correct counseling should be carried out only when the clinical suspect has been proven by molecular genetic analysis. In newborns suspected to have CS/CISS, without disease-associated variants in *CRLF1* or *CLCF1*, sequencing analysis of *LIFR*, *KLHL7*, *NALCN*, *MAGEL2* or *SCN2A* should be performed, since an accelerated and precise diagnosis can ameliorate patient care and is critical to achieve a specific clinical follow up. Upcoming research will focus on better understanding the molecular mechanisms underlying the clinical phenotype including identification of new genes, genotype-phenotype correlations and modifiers of the phenotype, through NGS techniques, recombinant systems, proteomics approaches and mouse models. Unfortunately, *Crlf1* null mice die on postnatal day 1, a conditional model using the Cre-loxP system might be successful in exploring the organ-specific consequences of CRLF1 deficiency. A better dissection of the pathophysiological mechanisms underlying CS/CISS and similar disorders under consideration for differential diagnosis could lead to a better understanding of their involvement in possible collaborative network(s), and promote the development of innovative therapeutic options based on molecular knowledge of the disease.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Leiden Open (source) Variation Database (LOVD) system at https://databases.lovd.nl/shared/genes/CRLF1.[72] All listed variants are named according to the guidelines of the Human Variation Society (HGVS) and are tested by the Mutalyzer database.[31,32]

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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