With the body in mind

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SELFINJURIOUSBEHAVIOR

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CORNELIADELANGESYNDROME

Sylvia Huisman

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With the body in mind

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Contents

1

General introduction

CoDeLaGe (acronym for 'Cornelia de Lange Gedragsonderzoek')

A translational study on self-injurious behavior in people with Cornelia de Lange Syndrome

INCENTIVE

Dennis and I were the same age, I had just started my first job as a physician in 1998 and he was one of my first patients. He had Cornelia de Lange Syndrome. I was called because Dennis would not stop hitting and banging his head. At his house I found Dennis surrounded by support workers and the psychologist. They alternately held his hands and arms. As soon as they let go, the sound of dumb blows against his skull filled the room. Both his hands and feet were restrained, his face was bruised and scarred even though he wore a helmet, his lips and ears were deformed. The people around him were desperate and in fear and Dennis looked desperate and in fear too.

CORNELIA DE LANGE SYNDROME

Cornelia de Lange Syndrome (CdLS) is a multisystem malformation syndrome, characterized by short stature, facial dysmorphism, major malformations and intellectual disability. Behavioral characteristics include autism spectrum disorder and a predisposition to engage in challenging behavior, especially self-injurious behavior (SIB). Genetically, this rare disorder is heterogeneous and all six known causative genes share a cohesin complex function.

PROBLEM

Self-Injurious Behavior (SIB) is by far the most serious behavioral problem (prevalence ~60%) in CdLS. Injuries vary from bruises to facial fractures, blindness and deafness. SIB is a major causative factor for failed care and impaired quality of life. Etiology and pathogenesis are mainly unknown and there is no cure or prevention possible at present. SIB is complex: both somatic (genetic, physical, medical) and (psycho)behavioral factors are involved. Former studies focused mainly on behavioral factors and therefore very limited SIB research has been performed in medical sciences.

The Dutch CdLS support group prioritized the topic via an online questionnaire and supported this research.

AIMS

Initially we described our primary aim as:

Effective treatment regimes and preventive tools of SIB in CdLS by studying phenomenology, etiology and pathogenesis. The secondary aims were creating a flow chart for SIB indicating the various diagnostic tests and subsequent best management strategies for CdLS patients, and to set up the total in such a way it could serve as a model for studying behavior in other rare human disorders.

However, we soon realized there was a lack of basic data so we decided to adapt and focus on SIB characteristics within and across syndromes to delineate somatic substrates of the behavior. In addition we realized there were significant questions that needed detailed behavioral assessments and the input of a behavioral scientist. Therefore collaboration was established with Paul Mulder, MSc, special needs education.

RESEARCH QUESTIONS

1. How is phenomenology of SIB in CdLS?
2. What is etiology of SIB in CdLS?
3. What is pathogenesis of SIB in CdLS?
4. How can etiology and/or pathogenesis be influenced in order to develop tailored treatment regimens for CdLS patients with SIB?

HYPOTHESES SCHEME

In this PhD trajectory we started off with a scheme of initial hypotheses on SIB in CdLS (Figure 1.1).

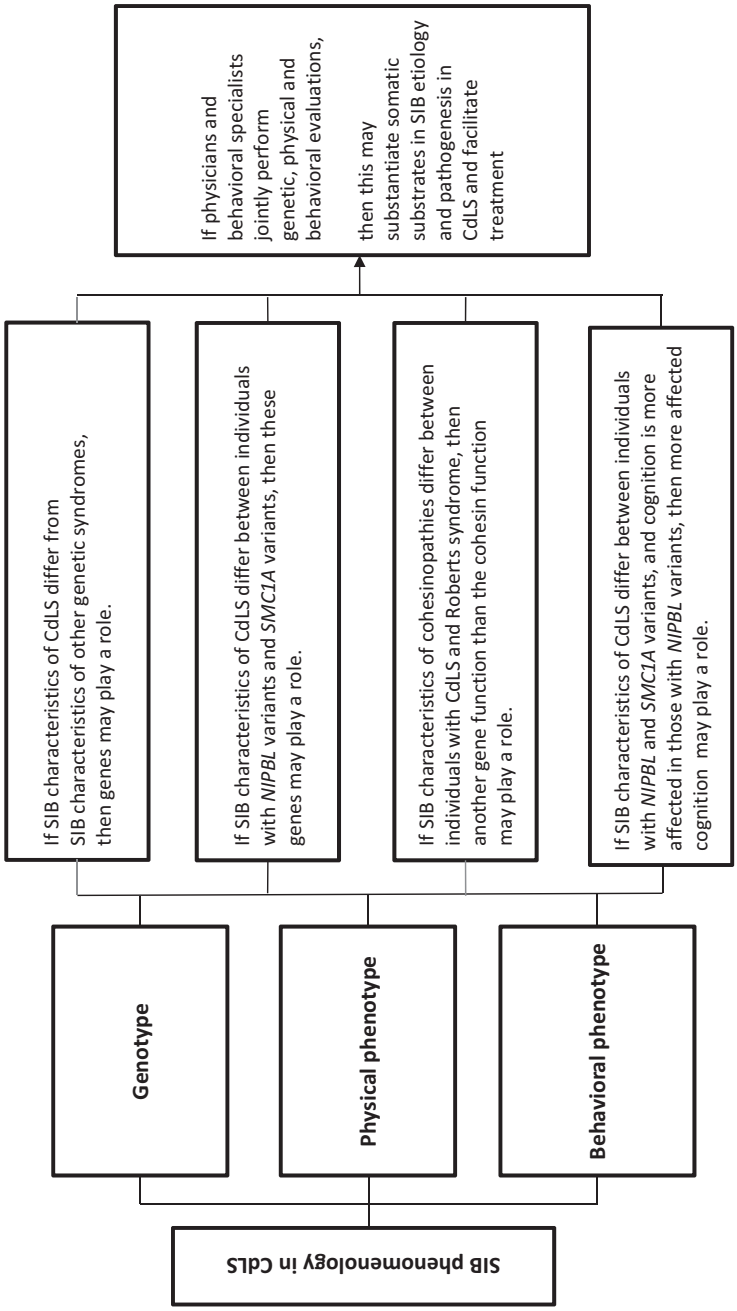

Figure 1.1 Initial hypotheses scheme SIB in CdLS.

METHODS

1. Comprehensive literature study
2. Wiki based information and parents' generated data collection
3. Studying group of CdLS individuals:
   a. genotyping: molecular investigations
   b. phenotyping:
      - clinical evaluation (medical history, physical examination including detailed description of morphology, anthropometrIcs, 2 and 3D photography)
      - behavioral evaluation (questionnaires, direct assessments)
      - additional (physical and neurological) investigations
4. Studying individuals with other cohesinopathies
5. Developing flow chart for diagnostic and management strategies

THESIS OUTLINE

Chapter 1 is the General introduction.

Chapter 2 provides a literature overview on definitions, prevalence and phenomenology of SIB in people with intellectual disabilities of unknown origin, CdLS and in eleven other genetic syndromes.

Chapter 3 describes the high rate of somatic mosaicism in CdLS and the increase of genetic confirmation by adding buccal swabs to diagnostics.

Chapter 4 highlights the importance of collaboration with parents as they are the most important sources of information, and the possibilities to share information via an online platform.

Chapter 5 shows that understanding of behavioral characteristics in CdLS requires uniform assessments for behavioral phenotyping and presents a 'criterion standard' of instruments.

Chapter 6 reflects on comparisons of phenotypes in people with *SMC1A* and with *NIPBL* variants, and on implications for genetic and physical factors in SIB.

Chapter 7 presents case illustrations and lessons from practice.

Chapter 8 forwards a cri du coeur to a broad medical audience to pay attention to SIB, and offers tools for an effective approach.

Chapter 9 contains the Summary and General discussion, followed by a Summary in Dutch.

2

Self-injurious behavior

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ABSTRACT

Self-injurious behavior (SIB) is a relatively common behavior in individuals with intellectual disabilities (ID). Severe SIB can be devastating and potentially life-threatening.

There is increasing attention for somatic substrates of behavior in genetic syndromes, and growing evidence of an association between pain and discomfort with SIB in people with ID and genetic syndromes.

In this review on SIB phenomenology in people with ID in general and in twelve genetic syndromes, we summarize different SIB characteristics across these etiologically distinct entities and identify influencing factors. We demonstrate that the prevalence of SIB in several well-known genetic intellectual disability syndromes is noticeably higher than in individuals with ID in general, and that characteristics such as age of onset and topographies differ widely across syndromes. Each syndrome is caused by a mutation in a different gene, and this allows detection of several pathways that lead to SIB. Studying these with the behavioral consequences as specific aim will be an important step toward targeted early interventions and prevention.

INTRODUCTION

Self-injurious behavior (SIB) is a relatively common behavior in individuals with intellectual disabilities (ID). Severe SIB can be devastating and potentially life-threatening (Figure 2.1), and is associated with compromised mental health in parents and caregivers, high service needs and excessive health care costs.[1-4]

While there is abundant scientific interest in SIB in behavioral sciences, only limited attention is paid to SIB in medical sciences, despite increasing attention for somatic substrates of other behavior and evidence of an association between pain and discomfort with SIB.[5-13] Studying specific genetic syndromes, with different molecular or metabolic etiologies, may show different characteristics of SIB depending on etiology, allowing various pathways leading to SIB to be discovered.

In this review we highlight twelve genetic syndromes in which sufficient phenomenological data are available: Angelman Syndrome (AS), Cornelia de Lange Syndrome (CdLS), Cri du Chat Syndrome (CdCS), Down Syndrome (DS), fragile X Syndrome (fraX), Lesch-Nyhan Syndrome (LNS), Lowe syndrome (LS), Prader-Willi Syndrome (PWS), Rett Syndrome (Rett), Smith-Magenis Syndrome (SMS), Tuberous Sclerosis Syndrome (TSC), and Williams-Beuren Syndrome (WBS).

The paper is based on a review of the literature concerning SIB studies with detailed analysis of phenomenology. Information regarding review methods and individual studies can be found in the Supplemental Materials.

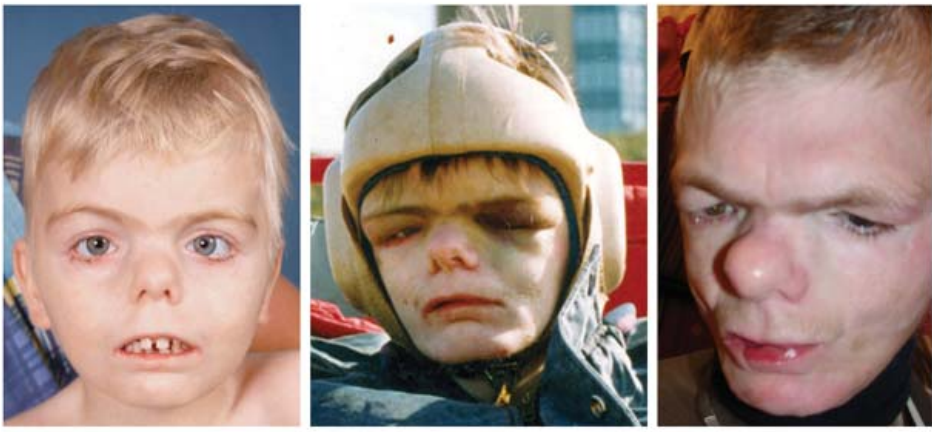

Figure 2.1 Individual with Cornelia de Lange Syndrome at 7, 21 and 38 years of age.
Self-injurious behavior started before 7 years of age and deteriorated during puberty and adolescence. Hitting and head banging resulted in permanent sensory loss due to bilateral blindness, bilateral ear deformations and hearing impairments.

CONCEPTUALIZATION AND DEFINITION

The term SIB was introduced by Tate and Baroff in 1966, to replace earlier labels such as masochism, auto-aggression, self-aggression and self-destructive behavior. Tate and Baroff stated that the term SIB did not imply an attempt to destroy, nor did it suggest aggression. It simply meant behavior that produces physical injury to the individual's own body.[14]

Subsequently, numerous authors have used variations of this definition (Table 2.1). The main elements in definitions were: self-initiated; directed towards the body; involves specific forms and body parts; contains repetition; can be chronometrically or chronographically quantified (frequency, duration, intensity); and its effects or extent of tissue damage can be classified. Disqualifiers are intent of suicide or sexual arousal. Hence, we propose to define SIB as non-accidental behavior resulting in demonstrable, self-inflicted physical injury, without intent of suicide or sexual arousal. Typically the behavior is repetitive and persistent.

SIB PREVALENCE

In this review twelve genetic syndromes are highlighted in which sufficient data were available: Angelman Syndrome (AS), Cornelia de Lange Syndrome (CdLS), Cri du Chat Syndrome (CdCS), Down Syndrome (DS), fragile X Syndrome (fraX), Lesch-Nyhan Syndrome (LNS), Lowe syndrome (LS), Prader-Willi Syndrome (PWS), Rett Syndrome (Rett), Smith-Magenis Syndrome (SMS), Tuberous Sclerosis Syndrome (TSC), and Williams-Beuren Syndrome (WBS).

The paper is based on a review of the literature concerning SIB studies with detailed analysis of phenomenology. Detailed information regarding review methods and individual studies can be found in the Supplemental Materials.

SIB prevalence rates within and across genetic syndromes heavily depend on the methodology employed, i.e. definition, recruitment, sample characteristics and etiological diagnoses of ID. In populations of people with ID of unknown etiology, not stratified for age of levels of functioning, the prevalence of SIB in a non-residential care setting is ~30%, irrespective of age and level of cognitive functioning versus 41% in a residential care setting.[15-20] If autism spectrum disorders (ASD) are present the prevalence rises markedly, varying from 42% to 70%.[21,22] In a number of specific syndromes prevalence figures can differ strikingly from prevalence rates in individuals with ID in general, and can be very high (Figure 2.2a). Highest prevalence rates have been reported in LNS, SMS, PWS, CdCS and CdLS.

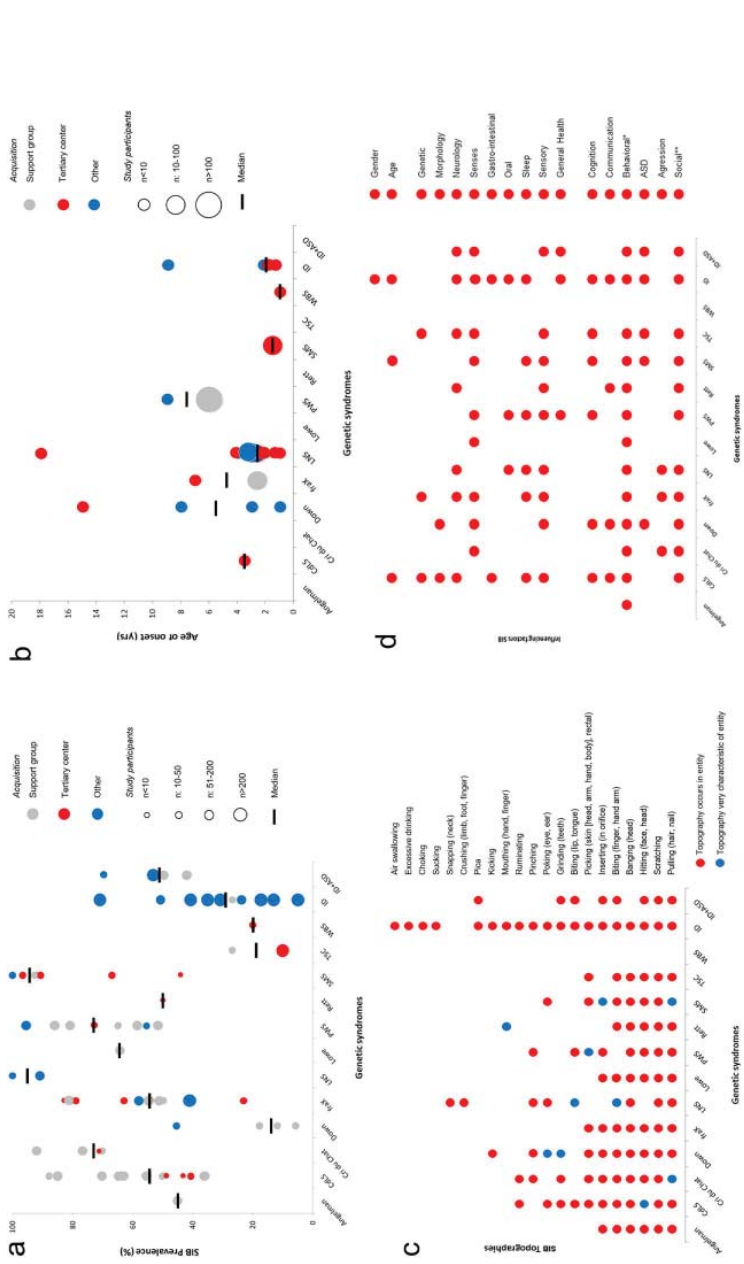

Figure 2.2 Phenomenology of SIB in selected genetic syndromes, in ID of unknown origin and those with ID of unknown origin and ASD.
(a) Prevalence. (b) Age of onset. (c) Topographies. Some topographies have been indicated as being very characteristic for syndromes: this is based on the literature review and personal experiences but could not be determined statistically due to small numbers. (d) Influencing factors.
Subscripts for Figure 2.2d: *Behavioral: i.e. stereotypy, repetitive, compulsive, impulsive behavior, hyperactivity, distractibility, anxiety, prolonged distress, nervousness, mood, affect, tantrums, disturbing interpersonal behaviors. ** Social: social contact, adult attention, ignoring, demand avoidance, automatic reinforcement, thwarting, boredom, solitude, being teased, frustration, change of routine, changes environment, length of institutionalization.

Table 2.1 Main definitions of self-injurious behavior used in literature

Author		Body object[1]	Individual subject[2]	Reocurrence[3]	Topography[4]	Chronometrics[5]	Effects severity[6]	Exclusion[7]
Tate & Baroff, 1966[14]	Behavior which produces physical injury to the individual's own body, i.e. relatively repetitive self-hitting; series of responses that are repetitive and sometimes rhythmical	X	X	X	X			
Bachman, 1972[43]	Behavior of individuals who inflict physical damage and, perhaps, pain upon themselves	X	X				X	
Carr, 1977[44]	Behavior that involves any of a number of behaviors by which the individual produces physical damage to his or her own body. Some individuals engage scratching, biting, or head banging to the point at which bleeding occurs and sutures are required. Others may engage in self-inflicted punching, face slapping, or pinching, thereby producing swellings and bruises over large areas of their bodies	X	X		X		X	
Solinick et al., 1977[45]	Any repetitive making and breaking of contact between one part of the body and another. Some of these contacts quite forceful, producing bruises and scars	X		X			X	
Mizuno et al., 1979[46]	Aggressiveness toward oneself		X					
Pace et al., 1986[26]	Behavior that results in physical injury to the individual's own body; in general, it is chronic and repetitious, occurring at frequencies ranging from several times per week to hundreds of times per hour over a sustained period of time	X	X	X		X		
Oliver, 1988[47]	Non-accidental behavior initiated by an individual which directly results in physical harm; it can lead to sensory impairments, brain damage and other disability	X	X				X	X
Winchel & Stanley, 1991[48]	The commission of deliberate harm to one's own body. The injury is done to oneself, without the aid of another person, and the injury is severe enough for tissue damage (such as scarring) to result. Acts that are committed with conscious suicidal intent or are associated with sexual arousal are excluded	X	X				X	X

Baumeister et al., 1993[49]	Acts that result in physical injury to a person's own body. In particular, SIB usually refers to acts that are repetitive, sometimes rhythmic, as acts which would likely produce immediate pain in the absence of some sensory impairment, and acts which occur in certain clinical populations with diminished intelligence	X	X	X			X	
Saloviita, 2000[20]	A large group of differing behaviors which are usually highly repetitive, and which result in direct physical harm or tissue damage to the person himself, e.g. head-banging, or slapping, scratching, or biting of oneself	X	X	X	X		X	
Schroeder et al., 2001[50]	Acts directed toward one's self that result in tissue damage	X	X				X	
Ross Collins & Cornish, 2002[51]	Behavior that causes demonstrable damage to one's own body, including hitting the head with a hand or other body part; self-biting; hitting the head with or against objects; and hair pulling	X	X		X		X	
Wisely et al., 2002[52]	Any behavior, initiated by the individual, which directly results in physical harm to that individual, including bruising, lacerations, bleeding, bone fractures and breakages, and other tissue damage	X	X				X	
Kahng et al., 2002[53]	A response that produces physical injury to the individual's own body	X	X				X	
Baghdadli et al., 2003[54]	Aggressive behaviors directed towards one's self but they can have varying onset, duration, topographies	X	X		X	X		
Moss et al., 2005[55]/ Hall et al., 2008[56]	Non-accidental behaviors which produce temporary marks or reddening of the skin or cause bruising, bleeding or other temporary or permanent tissue damage (self-biting, head banging, head punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing)	X			X		X	X
Oliver et al., 2006[57]	Non-accidental body-to- body contact behaviors that may have resulted in tissue damage, such as hand-biting, face-hitting, and body-picking	X			X		X	X
Staley et al., 2008[58]	Behavior that results in physical injury to one's own body	X	X				X	
Danquah et al., 2008[59]	Any behavior, initiated by the individual, which directly results in physical harm to that individual, including bruising, lacerations, bleeding, bone fractures and breakages, and other tissue damage	X	X				X	

Table 2.1 continues on next page

Table 2.1 ***Continued***

Author		Body object[1]	Individual subject[2]	Reocurrence[3]	Topography[4]	Chronometrics[5]	Effects severity [6]	Exclusion[7]
Richman, 2008[60]	An act directed towards oneself that results in tissue damage	X	X				X	
Langthorne & McGill, 2008[61]	Behaviors, such as head-hitting or scratching, that people direct towards themselves and that results in tissue damage	X	X		X		X	
Cooper et al., 2009[33]	A. The general diagnostic criteria for problem behavior are met. B. Self-injury sufficient to cause tissue damage, such as bruising, scarring, tissue loss and dysfunction, must have occurred during most weeks of the preceding six month period, e.g. ranging from skin-picking/ scratching, hair-pulling, face slapping, to biting hands, lips, and other body parts, rectal/ genital poking, eye-poking, and head-banging. C. The self-injurious behavior is not a deliberate suicide attempt.	X	X	X	X	X	X	X
Buono et al., 2010[22]	Represents behavioral characteristics that can damage body tissue. Behavior that produces immediate or cumulative physical damages to one's own body; self-biting, head banging, self scratching; disturbance caused by stereotyped movements, ie voluntary, repetitive, stereotyped, non-functional	X	X	X	X		X	
Wachtel & Dhossche, 2010[62]	Any self directed action resulting in bodily harm; can include multiple topographies, like head banging, self-hitting, etc directed at any body surface. Frequency and intensity varies widely, but may reach extreme levels of complications	X	X		X	X	X	
Taylor et al., 2011[19]	Repeated, self-inflicted, non- accidental injury producing bruising, bleeding, or other temporary or permanent tissue damage, and repetitive behaviors that had the potential to do so if preventive measures were not taken	X	X	X			X	X

Limeres et al., 2013[63]	Behavioral disturbance consisting of deliberate destruction of or damage to body tissues, not associated with a conscious intent to commit suicide. Characteristics: socially unacceptable, direct, repetitive, mild or moderate damage. Most common forms: cuts, burns, scratches, blunt injury, bites, and interference with wound healing. Most frequently affected regions are head, hands, and neck	X	X	X	X		X	X
Medeiros et al., 2013[64]	Self-directed behavior that causes or has the potential to cause physical damage, occurs repeatedly in idiosyncratic form, including banging head or body with other body parts or objects, self-biting, self-scratching, self-pinching, gouging body cavities with fingers, and self-hair pulling	X	X	X	X		X	
Tureck et al., 2013[65]	Behavior or set of behaviors that can result in injury to the person's body and that occurs repetitively	X		X			X	
Wolff et al., 2013[66]	Particularly troubling form of repetitive motor behavior that involves purposeful and repeated patterns of self-inflicted bodily injury without intent of suicide	X	X	X			X	X
Proposed definition	Non-accidental behavior resulting in demonstrable, self-inflicted physical injury, without intent of suicide or sexual arousal. Typically the behavior is repetitive and persistent.	X	X	X	X	X	X	X

[1] Body object: the behavior is directed towards the body; physical target.
[2] Individual subject: actor exhibits the behavior to oneself; self-directed.
[3] Reoccurrence: reiteration, repetition.
[4] Topography: compromised body site/location of action, i.e. head to body, body to body, head to object, body to object; e.g. head-banging.
[5] Chronometrics (frequency, duration, temporal distribution, intensity): acts per time unit/rate, per unit area/impact force.
[6] Effects severity: severity of the effects/extent of tissue damage (description/classification).
[7] Exclusion: conditions disqualified, i.e. without intent of suicide.

SIB has also been reported in a number of other genetic syndromes such as chromosome imbalances and non-genetically determined entities including teratogenic entities such as rubella encephalopathy and Fetal Alcohol Syndrome.[23-28] The divergent prevalence figures for the twelve selected genetic syndromes and other entities advocate to organize early intervention, assessment and treatment strategies that are syndrome sensitive.

SIB PHENOMENOLOGY

Age of onset

Generally SIB starts in early childhood: 50% of individuals showed SIB before 3 years of age, 70% before 7 years of age up to 90% before 10 years of age; percentage rates in larger genetic syndrome studies vary from 12% <1 year, 63% <4 and 93% <11 years of age in fraX, versus 72% <7 years of age in DS, and 73–91% < 7 years of age in PWS.[22,29-31] Wide variation exists as in individual cases age of onset may occur in the first year of life, or SIB may first become manifest in adulthood. Case series in individuals with ID of unknown origin and in individuals with ASD demonstrated similar rates, but in the different syndromes median ages of onset vary widely (Figure 2.2b). Rates may be prone to selection bias and can be overestimations, especially in small case series. Conversely, age of onset, may be underestimated when outcomes like physical damage is a criterion, and identifying SIB in childhood is difficult as behavior like self-hitting and even head banging may sometimes be judged as age appropriate behavior and is seen in typical development.

Course of SIB

Figures about the course of SIB are sparse. SIB has been reported as persistent in 62% over 2 years, in 71% over 7 years and in 84% over 18 years.[19,32-34] Long-term persistence of SIB is more likely with early onset and head directed self-injury.[32] SIB present at 20 years of age or older has an 84% chance to be chronic.[19] The relative risk of SIB increases until 30–40 years of age and starts to decrease after the age of 50.[35]

Severity

Severity of SIB is determined by a combination of characteristics: chronography (frequency, duration), topography (form, localization, number), and physical damage. Both in research and patient care quantifying severity comprehensively is informative for comparisons of studies.

1. Chronography

Chronographic parameters (frequency, duration, intensity) can objectively quantify clinical severity and the effectiveness of interventions. These are parameters typically more accurately presented in case reports but less so in studies of larger cohorts. Therefore only limited data are available.

In general ID population studies SIB occurs occasionally in 27% and frequently in 14%;[20] and every 30 min in 18%, hourly in 11%, daily in 43%, weekly in 19%, monthly in 8% and yearly in 1%, respectively.[20,36] In various syndromes this can be markedly different: for instance in LNS SIB is typically almost continuously present and may even occur during sleep, without changing over time.

2. Topography

There are many forms of SIB involving divergent body sites, which are referred to as topographies. The most common forms are pulling (hair or nails), scratching, hitting, banging and biting. When hitting oneself a part of the body is typically used as the 'instrument' to hit, but objects can be used as well. Other common forms are inserting in orifice, picking, grinding, poking (eyes or ears), pinching and ruminating. Less common forms are mouthing, pica, crushing, snapping (neck), excessive drinking and air swallowing, sucking and choking (Figure 2.2c). These less common forms can also occur without the other characteristics of SIB and this behavior should not always be considered SIB. The most commonly involved body parts are the head, the hands and fingers. SIB remains confined to a single body part in 28–46% of individuals, but involvement of several body parts frequently occurs, particularly in CdLS and SMS.[19,37,38]

3. Physical damage

Physical damage as result of SIB is one of the main reasons for serious concerns of the caregivers, and for medical consultation. The physician needs not only to qualify but also to objectively quantify clinical severity, both to indicate immediate medical interventions and to judge the effectiveness of interventions. Although medical evaluation of physical damage is obligatory, very limited data have been reported on specific physical damage due to SIB. In seven of the twelve selected genetic syndromes in this review no data on severity of physical damage are provided. Detailed information on physical consequences in the remaining five syndromes has been best described in case reports. The Challenging Behavior Interview provides a four point Likert scale item on physical injury and the Self-Injury Trauma scale scores physical consequences in a subjective and time-consuming way, but otherwise there is no instrument available to the physician for scoring physical

damage.[39,40] Hence, we have designed a relatively simple scoring system for the physician defining the degree of severity based on the physical consequences of SIB and providing guidance on the need for further medical measures:

1. (relatively) mild: indicating non-permanent, minor tissue damage such as scratches, abrasion, bruises, temporary reddening of the skin, teeth marks;
2. moderate: indicating non-permanent, marked tissue damage or function loss, such as deep fissures, fractures, large scars and ulcerations;
3. severe: indicating permanent tissue loss, loss of sensory function (deafness; blindness), loss of neurological function (brain damage) and life-threatening consequences.

Since there are only small series that report information on tissue damage and function loss, it proved not to be possible to present results across genetic syndromes in a figure. We can only state reliably based on available literature and personal extensive experiences that severe tissue damage is commonly prominent in LNS and CdLS. The frequent use of constraints in both syndromes is an indirect indication of the SIB severity.

Factors influencing SIB

A main issue in managing SIB is to assess and define factors predisposing, evoking and maintaining SIB as they indicate potential intervention strategies. These factors may be personal (gender; age), somatic (including genetic, neurobiological and medical conditions) and behavioral (including operant learning) in nature. Physicians in charge of SIB patients have a role that is complementary to that of the behavioral specialist, to evaluate health and functioning, paying specific attention to (painful) physical conditions which may lead to SIB. Behavioral specialists have a key role in assessing cognitive, adaptive and communicative abilities of SIB patients, in evaluating psychopathology that might be related to SIB and in performing a functional behavioral assessment.

1. Somatic

Somatic influencing factors of SIB in genetic syndromes (Figure 2.2d) are subdivided in: genetic mutation, morphology, neurology, senses, gastro-intestinal, oral/dental, sleep, sensory and general health.

Larger numbers of different somatic influencing factors are reported in studies in individuals with ID of unknown origin, and also in CdLS and fraX. Senses (visual and hearing impairments) and other sensory (pain and tactile sense) problems are reported most across the various entities. However, most publications on SIB fail to report on even basic

physical examinations by physicians who might evaluate potential physical causes of SIB, such as constipation, gastro-esophageal reflux disease (GERD)/esophagitis, intestinal obstruction, dental problems, urinary tract infection, otitis media, sinusitis, presence of a foreign body, or fracture. Information on visual and hearing abilities is needed due to their high prevalence in individuals with ID, and their influence on adaptive and communicative abilities.

Furthermore, SIB is known to occur very frequently in several specific genetic syndromes and to occur in most of these genetic entities more frequently than in a population with ID of unknown origin (Figure 2.2a). In the present analyses of studies on SIB the number of individuals in whom no or only partly genetic and metabolic diagnostic studies have been performed was remarkably high, which hampers optimal use of the knowledge of behavior in such entities, including the somatic substrates of behavior (Table 2.2).

2. Behavioral

Behavioral factors influencing SIB are presented in Figure 2.2d and for the overview divided in 2 categories: developmental (i.e. cognitive, communicative and adaptive abilities) and behavioral (intrapersonal and interpersonal). Intrapersonal characteristics include: stereotypy, repetitive, compulsive, impulsive behaviors, hyperactivity, distractibility, anxiety, and mood. Interpersonal behavioral characteristics encompass social contact and environmental dimensions such as adult attention, ignoring, demand avoidance, solitude, change of routine, changes to environment, institutionalization. ASD and aggression are presented separately. However, ASD as a distinctive etiology is problematic because ASD can be difficult to classify in these entities and symptoms of adaptive impairments and repetitive and stereotyped behaviors are also clustered within developmental and behavioral factors. These characteristics influence behavior dysregulation and operant learning, and hence possible leads for behavioral interventions.

DISCUSSION

SIB can be a devastating problem. It is devastating for the individuals who harm themselves, and who may experience a significant physical and psychological distress due to their SIB. It is devastating for the parents who see progressive damage to the one they love and who feel they cannot offer the protection they want to offer as a parent. It is devastating to caregivers who may feel ineffective and can experience this as a failure of their care.

Table 2.2 Summary of a literature review of SIB in genetic syndromes

Syndrome	Study characteristics											Somatic aspects				Self-injurious behavior		
	Design[1]					Acquisition					Participants	Confirmed diagnosis[2]		Physical examination[3]		Prevalence (%)	Age of onset (yr)	Characteristic topography
	n	case-control	cohort	cross sectional	case series	support group	specialized centers	combination	other	not mentioned	M/F	molec/ metabolic	clinical	full	limited	median	median	
Angelman	1	-	-	1	-	1	-	-	-	-	58/46	-	-		1	45.1	-	
CdLS	17	4	-	8	5	10	3	4	-	-	353/445*	1	4	4	7	55.3	3.5	hitting
Cri du Chat	4	-	-	3	1	3	-	-	-	1	65/83	2		1	2	73.9	-	pulling
Down	21	5	1	1	14	3	5	-	7	6	156/139	4		2	6	15.0	5.5	grinding poking
fraX	13	6	-	4	3	4	4	4	1	-	2949/1199*	11		1	6	54.8	4.8	
LNS	30	1	-	2	27	-	22	1	6	1	166/3	20		9	9	95.5	2.6	biting
Lowe	1	-	-	1	-	1	-	-	-	-	56/0	-	-		1	64.3	-	
PWS	24	4	-	11	9	10	8	2	4	-	532/556*	15	1	3	9	73.0	7.5	picking

Rett	6	2	-	1	3	1	4	-	-	1	0/119		2		3	50.0	-	mouthing
SMS	10	2	-	5	3	2	3	4	-	1	105/128	9		3	2	94.8	1.5	pulling inserting
TSC	5	2	-	-	3	1	3	-	1	-	20/20*	1	1		4	18.5	-	
WBS	1	-	-	-	1	-	1	-	-	-	7-mrt	1				20.0	1	
ID	46	5	5	13	23	1	11	9	21	4	8710/6498*			2	16	28.9	1.9	
ID+ASD	4	3	-	1	-	2	-	-	2	-	505/103				2	51.5	-	

* Total n is larger than M+F due to missing gender data. When no data are available, sections are empty.

[1] Study design: Case-control study: observational, analytical, sampling based on outcome; Cross sectional study: observational, analytical, cross sectional; Cohort study: observational, analytical, sampling based on exposure; Case report/series: observational, descriptive, no comparison group, no hypothesis testing.

[2] Confirmation by either metabolic, cytogenetic or molecular studies; clinical confirmation scored positive if performed by expert.

[3] Physical exams: Full: personal examination by physician, includes laboratory or imaging investigations; Limited: no full examination, e.g. health questionnaire.

Patients with SIB visit their general practitioners, pediatricians, child psychiatrists and pediatric neurologists, and later in life their internists, psychiatrists and even surgeons. Managing SIB can be a huge challenge for physicians.

SIB is common in individuals with intellectual disabilities, often starts in early childhood and can aggravate into a destructive and persistent problem if interdisciplinary assessment and interventions are not applied. Accurate and detailed information on SIB characteristics such as chronography, topography and resulting physical damage may offer clues for the physician to the causes of pain or distress, either in the past or present, which may play a crucial role in the development and maintenance of SIB.

There is need for careful interdisciplinary evaluation of every patient who shows SIB. SIB should not be seen as a diagnosis, but as a symptom of an underlying problem. The physician must be alert to symptoms of underlying pain and discomfort as medical conditions causing or prolonging SIB may go unrecognized, undiagnosed and untreated, specifically due to the impaired communications skills in patients with ID. A comprehensive medical evaluation is particularly valuable as frequent medical conditions like constipation, GERD, otitis media, dental problems, presence of a foreign body, or fracture, have excellent treatment options.

Until now several theoretical models for SIB have been proposed, varying from neurobiological (including genetic and neurochemical), medical (pain and discomfort) and behavioral or operant learning models. There is growing evidence for an integrated biological and behavioral model in which genotypic-phenotypic characteristics and operant learning principles are complementary and lead to effective interventions.[34,41] Understanding the interactions between all these influencing factors needs longitudinal studies in which phenotyping the SIB characteristics and personal (developmental and behavioral) characteristics, the physical signs and symptoms of patients demonstrating SIB, and genotyping the same individuals, will be essential.

This review demonstrates that the prevalence of SIB in several well-known genetic ID syndromes is noticeably higher than in individuals with ID in general and that characteristics such as age of onset and topographies differ widely across syndromes, each caused by a different gene with a different action when mutated. Pathogenetic mechanisms behind these differences remain to be elucidated. It may be many different pathways can cause SIB. One may also hypothesize that these genes may have more than one action, one causing the syndrome and another causing SIB. Studying these multifunctional, 'moonlighting' proteins may show a common pathway to SIB.[42] Comprehensive

phenotype – genotype studies and functional analyses will be an important step towards targeted early interventions and effective prevention.

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SUPPLEMENTAL MATERIALS

See https://doi.org/10.1016/j.neubiorev.2017.02.027 or CD-ROM for the Supplemental Materials:

Appendix I Methods

- Search strategies
- Structured data extraction form

Appendix II Results

- Figure S1 Study flow diagram
- Table S1 Summary data of all included studies

3

High rate of mosaicism in individuals with Cornelia de Lange Syndrome

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ABSTRACT

Background

Cornelia de Lange syndrome (CdLS) is a well known malformation syndrome for which five causative genes are known, accounting for ~55–65% of cases. In this study, we hypothesized that mosaicism might explain some of the ~35–45% of cases without detectable mutation in DNA derived from lymphocytes; we investigated the frequency of *NIPBL* mutations in buccal cells in individuals negative for mutations in any of the five genes in lymphocytes; and evaluated the efficiency of obtaining DNA from buccal swabs and best strategy for optimal mutation detection in CdLS.

Methods

We obtained buccal swabs from eight mutation positive and 13 mutation negative individuals with clinically diagnosed CdLS, following informed consent. We then forwarded instructions and a single mouth swab to the families; if subsequently insufficient DNA was obtained, we re-sent two mouth swabs. Buccal cells were screened for *NIPBL* mutations using Sanger sequencing techniques.

Results

Sufficient DNA for analysis was obtained in 21/22 individuals. In all six tested individuals with a known *NIPBL* mutation and in two with a known *SMC1A* mutation, the mutation was confirmed in buccal cells. In 10 of the 13 tested individuals without detectable mutation in lymphocytes a *NIPBL* mutation could be detected in buccal cells. Clinically there were no significant differences between patients with a germline and mosaic *NIPBL* mutation.

Conclusion

Somatic mosaicism for a *NIPBL* mutation is frequent (10/44; 23%) clinically in reliably diagnosed CdLS individuals. Obtaining buccal swabs at the time a blood sample is obtained will facilitate adequate molecular analysis of clinically diagnosed CdLS patients.

INTRODUCTION

Cornelia de Lange syndrome (CdLS or Brachmann-de Lange syndrome; OMIM 122470, 300590 and 610759) is a well known malformation syndrome characterized by a distinctive face, prenatal and postnatal growth retardation, limb malformations, and intellectual disability. To date five causative genes have been identified: *NIPBL*, *SMC1A*, *SMC3*, *RAD21*, and *HDAC8*.[1-6] Each of these genes have a function in the sister chromatid cohesion process and CdLS is therefore termed as a cohesinopathy.[7] Mutations in *NIPBL* are found in ~50–60% of cases; the other genes account together for about 5% of clinically confirmed diagnoses, indicating that up till now CdLS can only be molecularly confirmed in ~55–65% of patients [*Table 3.1*].[1 8-23] Studies by us and others using whole exome sequencing techniques failed to show pathogenic variants in CdLS individuals in whom mutations in the five known pathogenic CdLS genes had already been excluded (unpublished data). We hypothesized that this was caused by mosaicism and that searching for mutations using other tissues might yield additional mutations in genes known to cause CdLS.

We describe here the results of *NIPBL* mutation analysis in buccal cells in CdLS individuals without a detectable mutation in one of the five known genes in lymphocytes. Furthermore, we report on the efficiency of molecular analysis of buccal swabs, genotype-phenotype correlations in patients with and without mosaicisms, and discuss strategies for optimal mutation detection in CdLS.

METHODS

Recruitment

In our earlier study[9] we studied 39 CdLS individuals, to which we added five other CdLS individuals who were negative for *NIPBL* mutation analysis in lymphocytes. We asked eight mutation positive CdLS individuals described in the earlier study[9] to participate by obtaining a buccal swab, to test for the reliability of molecular analysis of buccal swabs. All agreed. We then asked 17 individuals in whom no mutation was found in the five known genes to participate. Fourteen of them responded with consent.

We forwarded a single mouth swab to all families, asking parents to perform a buccal swab of their child. If insufficient DNA was obtained, we re-sent two mouth swabs to the families and asked them to repeat the procedure. No particular modifications were applied to increase the isolation of DNA from the swabs.

Severity scores

The severity score[9] in the earlier described CdLS individuals was updated and the same severity score was added in the five patients that were not in the earlier study.

Molecular investigations

Genomic DNA was isolated from buccal swabs by using the Maxwell Buccal Swab LEV DNA Purification kit (Promega). Primers used for amplification of the 46 *NIPBL* coding exons (exons 2–47, NM_133433.3), and the corresponding exon-intron boundaries were designed using the Primer3 software (http://frodo.wi.mit.edu/primer3/). PCR fragments were sequenced using the Big Dye Terminator cycle sequencing kit v2 (Applied Biosystems), and analyzed on a 3130 Genetic Analyzer sequencing machine (Applied Biosystems). Sanger sequencing is not yielding reliable quantitative results. The ratio between the variant and wild-type of a locus was evaluated by eyeballing only.

Ethics

The present study is part of a wider study in individuals with CdLS ('CoDeLaGe') and has been approved by the medical ethics committee of the Academic Medical Center in Amsterdam, and by the board of the Dutch CdLS support group.

Statistics

For analysis of correlations between ordinal categorical variables, the Chi-Square Test for trend was used. Analysis was performed using SPSS V.20. The significance threshold was set at $p < 0.05$.

RESULTS

We obtained buccal swabs from a total of 22 individuals with CdLS and eventually sufficient DNA for mutation analysis could be harvested in 21/22. In five individuals we needed an extra pair of buccal swabs as the amount of DNA from the first swab was insufficient. In one patient in whom we had found no mutation in lymphocytes sufficient DNA could not be harvested from buccal cells despite collection of an extra set of buccal swabs.

In the total group of 44 individuals with CdLS we found 25 mutations in *NIPBL*, 2 in *SMC1A*, and none in the three other genes *SMC3*, *RAD21* and *HDAC8* (Table 3.1).

Table 3.1 Overview of studies describing results of mutation analysis in four or more individuals with clinically diagnosed CdLS*

Author	Number of patients	Methods	Mutations							
			NIPBL N (%)	*SMC1A* N (%)	*SMC3* N (%)	*RAD21* N (%)	*HDAC8* N (%)	Mosaicism N (%)	Any mutation N (%)	No detectable mutations N (%)
Gillis (2004)	120	Sequencing / FISH	56 (47%)						56 (47%)	64 (53%)
Deardorff (2007)	115 *NIPBL*-	Sequencing		10 (9%)	1[5] (1%)				11 (10%)	104 (90%)
Chatfield (2012)	319[1]		130 (41%)	15 (4.7%)	1 (0.3%)				146 (46%)	173 (54%)
Borck (2004, 2006, 2007)	30	Sequencing / aCGH / sequencing 5'ÚTR	13 (43%)	2 (7%)	0				15 (50%)	15 (50%)
Miyake (2005)	15	Sequencing / FISH	4 (27%)						4 (27%)	11 (73%)
Yan (2006)	28	Sequencing	13 (46%)						13 (46%)	15 (54%)
Ratajska (2010)	11 *NIPBL*- / *SMC1A*-	MLPA, aCGH	1[2] (9%)	0					1 (9%)	10 (91%)
Selicorni (2007), Gervasani (2008), Russo (2012)	200	Sequencing / FISH aCGH / MLPA	75 (38%)	0	0				75 (38%)	125 (62%)
Schoumans (2007)	a: 11 b: 4	a: Sequencing b: MPLA / 5'UTR / aCGH	a: 7 (64%) b: 1[3](25%)	0					a: 7 (64%) b: 1 (25%)	a: 4 (34%) b: 3 (75%)
Pie (2010)	30	Sequencing	11 (37%)	3 (10%)	0				14 (47%)	16 (53%)
Zhong (2012)	4	Sequencing	2 (50%)	0	0				2 (50%)	2 (50%)
Bhuiyan (2006,2007, present study)	44	Sequencing / MLPA / sequencing buccal	25 (57%)[4]	2 (5%)	0	0	0	10[6] (23%)	37 (84%)	7 (16%)

[1] Individuals with congenital heart disease. [2] Deletions detected by MLPA. [3] 9p duplication. [4] One with deletion detected by MLPA. [5] 1/96 studied. [6] Until now in 4/17 without detectable mutation in lymphocytes nu buccal swabs could be obtained. * If a gene was not sequenced in the study the square is left blank.

We were able to confirm in DNA derived from buccal cells the mutation found in *NIPBL* in all six individuals in whom such mutation was earlier detected in DNA derived from lymphocytes (Table 3.2) and also the *SMC1A* mutation was retrieved in DNA isolated

Table 3.2 Mutation detection rate in buccal swabs in relation to findings in lymphocytes

	NIPBL mutation in buccal cells detected	*NIPBL* mutation in buccal cells not detected	Total
NIPBL mutation in lymphocytes **detected**	6	0	6
NIPBL mutation in lymphocytes **not detected**	10	3	13
Total	16	3	19

Table 3.3 Mosaic *NIPBL* mutations detected in present CdLS cohort

	Lymphocytes	Buccal cells	Comment
1.	Wild type	c.358+3G>T	1, 2
2.	Wild type	c.4543G>T, p.Glu1515*	
3.	Wild type	c.1345C>T, p.Gln449*	
4.	Wild type	c.2389C>T, p.Arg797*	1
5.	Wild type	c.7263+5G>A	2
6.	Wild type	c.742_745dup, p.His 249Profs*9	
7.	Wild type	c.7168G>A, p.Ala2390Thr	1
8.	Wild type	c.790del, p.Met264*	
9.	Wild type	c.3327del, p.Asp1110Metfs*63	
10.	Wild type	c.459-9G>A	2
11.	Wild type	Wild type	
12.	Wild type	Wild type	
13.	Wild type	Wild type	
14.	c.2479_2480del, p.Arg827Glyfs*2	c.2479_2480del, p.Arg827Glyfs*2	1
15.	c.2771del, p.Asn924Thrfs*5	c.2771del, p.Asn924Thrfs*5	
16.	c.6156G>C, p.Glu2052Asp	c.6156G>C, p.Glu2052Asp	
17.	c.2324A>G, p.Lys775Arg	c.2324A>G, p.Lys775Arg	
18.	c.7062+1G>A	c.7062+1G>A	2
19.	c.6892C>T, p.Arg2298Cys	c.6892C>T, p.Arg2298Cys	1

1: Detected in other CdLS patients as well (LOVD database).
2: In silico splicing predictions show disrupted splice sites (Alamut prediction).
CdLS, Cornelia de Lange syndrome.

from buccal cells in the two tested CdLS individuals. Of 13 individuals with CdLS in whom no mutation was detectable earlier on in lymphocytes, a mutation in *NIPBL* was found in buccal swabs in 10 of them (Tables 3.2–3.3).

The ratio between the pathogenic variant and wild-type was estimated to be about equal. As this mosaicism was unexpectedly high and might in theory point to an increase for *NIPBL* mutations in buccal cells irrespective of the presence of CdLS, we obtained a mouth swab from three healthy controls and excluded *NIPBL* mutations in them. Also the two CdLS individuals with a *SMC1A* mutation in lymphocytes were checked for a *NIPBL* mutation in buccal cells and were found to be negative.

We checked in DNA isolated from lymphocytes in each CdLS individual whether the variant detected in their buccal cells was present in the lymphocytes as well, by re-sequencing (Sanger sequencing) for that particular mutation, but none was retrieved (Figure 3.1). In three CdLS individuals from the original group previously reported,[9] no mutation was detected in either lymphocytes or buccal swabs.

The clinical characteristics of the CdLS individuals with a mutation detectable in lymphocytes, those with a *NIPBL* mutation detectable only in buccal swabs, and those without

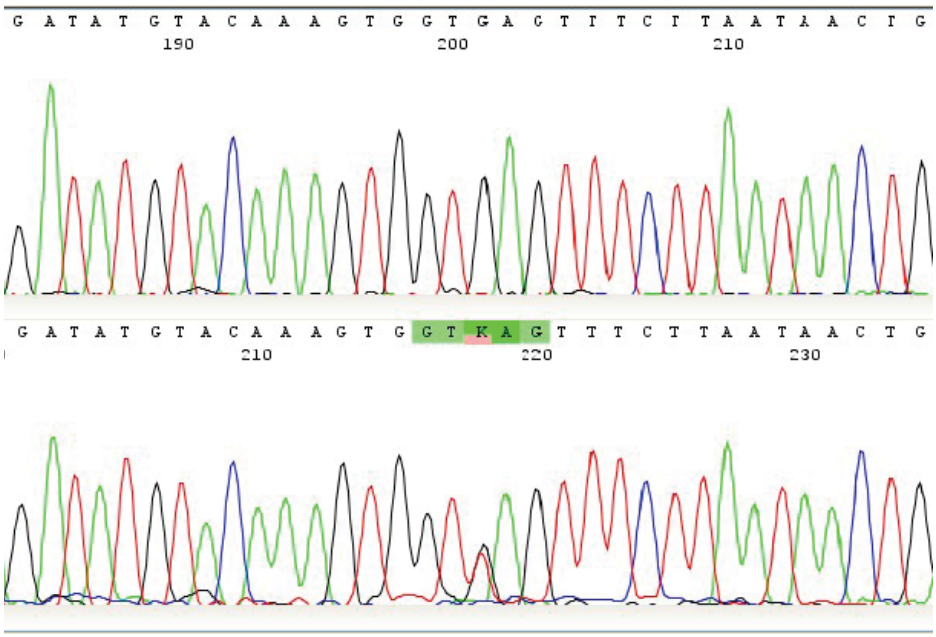

Figure 3.1 Chromatogram showing the mutation c.358+3G>T in intron 4 identified in buccal DNA (lower lane) which is not present in lymphocyte DNA (upper lane).

Table 3.4 Severity score features related to molecular findings

	Molecular findings		
	NIPBL mutation + in lymphocytes	*NIPBL* mutation + mosaic	*NIPBL* mutation – in lymphocytes and buccal cells
Number of patients	25	10	2
Gender (M/F)	14/11	3/7	0/2
Age median (min–max) (yr)	23.5 (10.5–54.2)	15.2 (3.8–33)	22.1 (13.5–31)
Birth weight mean (SD) / median (g)	2227 (703) / 2110	2325 (506) / 2375	3395 (1266) / 3395
Postnatal growth**			
>P75	4 (17)	3 (30)	2 (100)
P25–P75	15 (62)	7 (70)	
<P25	5 (21)		
Skull growth**			
>-2SD	3 (14)	2 (20)	1 (50)
<-2SD and >-4SD	11 (50)	4 (40)	1 (50)
<-4SD	8 (36)	4 (40)	
Limbs**			
No reduction defect	19 (79)	10 (100)	2 (100)
Partial reduct defect	1 (4)		
Severe reduct defect	4 (17)		
Face			
Classic type	20 (80)	7 (70)	
Mild type	5 (20)	2 (20)	
Possible CdLS*		1 (10)	2 (100)
IQ score			
0–20	8 (32)	2 (20)	
21–35	8 (32)	4 (40)	1 (50)
36–50	5 (20)	3 (30)	
51–70	4 (16)	1 (10)	
71–85			1 (50)

Total Severity Score**	Nonsense mutation	Missense mutation	Nonsense mutation	Missense mutation	
Classic type	12 (86)	3 (50)	5 (56)		0
Mild type	1 (7)	1 (17)	4 (44)	1 (100)	1
Possible CdLS*	1 (7)	2 (33)			1

Data are displayed as N (%) unless stated otherwise; * CdLS, Cornelia de Lange Syndrome; ** Reliable data on some patients missing.

detectable mutation were compared using the severity score (Table 3.4). The comparison is limited to the 37 CdLS individuals for whom we had sufficient data. Statistical analysis failed to show any significant difference between the group of individuals with a germline *NIPBL* mutation and mosaicism for a *NIPBL* mutation, and between the group

of individuals with a germline *NIPBL* nonsense and a mosaicism for a *NIPBL* nonsense mutation (p = 0.704 and p = 0.335, respectively). However, numbers were small and minor differences may have gone unrecognized.

DISCUSSION

Molecular confirmation of the clinical diagnosis of CdLS is of the utmost importance for adequate genetic counselling of families, and is critical in exploring genotype-phenotype correlations and for understanding pathogenesis of the various manifestations of CdLS. We report here an unexpected and unusually high frequency of somatic mosaicism in CdLS individuals.

Mosaicism in CdLS has been reported before only infrequently: a chromosomal mosaicism was reported in 1965,[24] and in 2010 mosaicism for a c.2827delA mutation in *NIPBL* was published.[25] The cohort of individuals with CdLS investigated in this study has been previously reported in an earlier genotype-phenotype study[9] and a selection bias seems unlikely.

A similarly high frequency of mosaicism in a malformation syndrome with or without intellectual disability is unknown to us, except for entities that already show clear signs fitting mosaicism such as asymmetries or pigmentation abnormalities.[26-28] In the present series of people with CdLS a single individual showed a difference in color between the left and right eye (Figure 3.2), but otherwise none showed a significant clue for

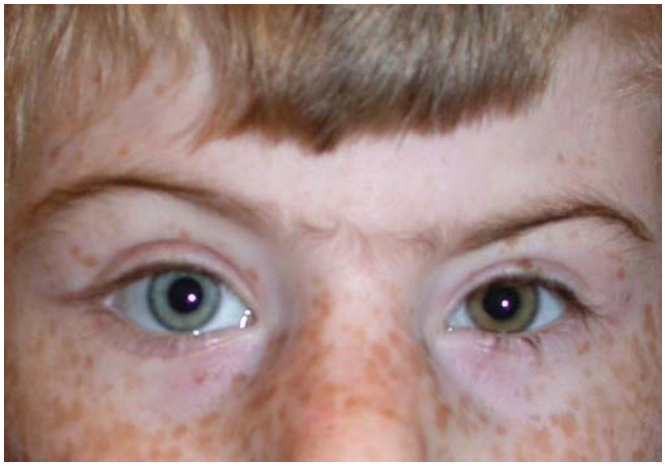

Figure 3.2 Individual with Cornelia de Lange syndrome and a mosaic NIPBL mutation showing differently colored irides.

mosaicism. Heterochromia of the iris occurs in non-mosaic Mendelian conditions such as Waardenburg syndrome, but is not a recognized sign in CdLS and must be very unusual as many individuals with CdLS have been published. Heterochromia of the iris can occur in disorders caused by mosaic mutations such as Proteus syndrome, and therefore it seems possible that the heterochromia found in an individual mosaic for a *NIPBL* mutation is associated with the mosaicism. We cannot exclude, however, that its presence is coincidental.

There are several other malformation syndromes with intellectual disability, such as Rubinstein-Taybi syndrome and Kabuki syndrome, in which molecular confirmation of the clinical diagnosis is possible in only a limited percentage of cases, and we suggest performing similar studies in these entities. We have used only buccal swabs as second tissue to evaluate, but it has to be determined in each entity whether this is the right tissue to use. It might be that other easily available tissues such as bladder epithelial cells and hair bulbs are more suitable in other disorders. We do not exclude that further mosaicism can be detected in CdLS if other tissues are studied as well. Screening for mosaicism is especially important before initiating next generation sequencing studies (NGS) to detect additional pathogenic genes. If settings in evaluating whole exome sequencing studies are adequately set, one may be able to detect very low levels of mosaicism in NGS, but it would be an expensive approach.

The high rate of mosaicism for *NIPBL* mutations detected in the present study is remarkable and remains as yet unexplained. Theoretically the main mechanisms underlying this include somatic mutations (shortly) after fertilization, loss of mutations in lymphocytes due to reversion, and selection against mutant cells specifically in lymphocytes.[29] The absence of a difference in phenotype between CdLS individuals with a mosaic and germline *NIPBL* mutation argues against a somatic mutation after fertilization. Reversion is a rarely detected phenomenon and mainly known with skin disorders, and would be unusually frequent for the various *NIPBL* mutations detected in the present study. We favor the hypothesis that there is a selection against lymphocytes with the mutation. This selection should take place specifically in lymphocytes and not in other easily available tissues. One may speculate an external influence such as acetylation of the cohesin complex to be of significance here.

Buccal swabs were shown to be an adequate way to obtain DNA from a second tissue in the present study. Swabs are cheap, can be performed at home by parents or other caregivers, and success rates in obtaining sufficient DNA after one (14/20) or a repeat swab (5/6) or both (19/20; 95%) were high, despite the fact *NIPBL* is a relatively large

gene. The families did not consider taking one or two buccal swabs to be a significant burden.

The detection of a somatic mutation in a significant number of individuals (10/44; 23%) allowed us to detect a causative mutation in 37/44 individuals (84%), which is high compared to earlier reported studies (Table 3.1). Possibly in these studies a significant number of cases will have somatic mosaicisms as well. There is no significant difference in the classical CdLS signs and symptoms between individuals with a causative mutation detectable in lymphocytes and those with a mutation detectable in buccal cells (Table 3.4), and it seems impossible to discern in advance those with and without somatic mosaicism. We restricted the present molecular analysis in buccal cells to sequencing of only *NIPBL* as it is by far the most frequently mutated gene in CdLS. We plan to perform further analysis in DNA derived from buccal cells for the other four genes known to cause CdLS as well. The first results of Sanger sequencing of *SMC1A* of DNA isolated from buccal cells of two CdLS individuals who were negative for the five known genes in lymphocytes and for *NIPBL* in buccal cells indicated no mutation was present. Further analysis is in progress.

An efficient and effective screening strategy to detect mutations in individuals with clinically diagnosed CdLS is important in daily patient care. We have adapted our diagnostic strategy and take a pair of buccal swabs in each CdLS patient together with the initial blood sampling. We sequence the buccal sample first for a *NIPBL* mutation; if negative we continue by sequencing the other four CdLS candidate genes in lymphocytes. If an *NIPBL* mutation is identified on buccal swab DNA, we then sequence *NIPBL* in DNA isolated from lymphocytes, because finding the mutation in both tissues will have consequences for the recurrence risk. We anticipate that with time NGS techniques will be used in diagnostics, using a targeted analysis of the results for variants in the five genes known to cause CdLS. Despite the high sensitivity of this technique to detect mosaicisms we have sincere doubts as to whether it will allow detection of mosaic *NIPBL* mutations in CdLS individuals. NGS of DNA isolated from buccal cells is in principle possible but technically demanding and unlikely to be available for patient care in the near future. Individuals who will be negative for both lymphocyte and buccal cell studies will be candidates for NGS using samples of both parents as well (trio strategy).

CONCLUSION

We conclude there is a significant number of CdLS individuals who have somatic mosaicism for a *NIPBL* mutation. DNA derived from buccal cells using a buccal swab is a reliable

way to investigate whether a patient may have a somatic mosaicism if lymphocyte analysis has failed to show a mutation. Obtaining a buccal swab at the time the initial blood sample is obtained will facilitate adequate molecular analysis of clinically diagnosed CdLS individuals.

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4

Building treasures for rare disorders

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ABSTRACT

The internet pre-eminently marks an era with unprecedented chances for patient care. Especially individuals with rare disorders and their families can benefit. Their handicap of low numbers vanishes and can become a strength, as small, motivated and well-organized international support groups allow easily fruitful collaborations with physicians and researchers. Jointly setting research agendas and building wikipedias has eventually led to building of multi-lingual databases of longitudinal data on physical and behavioral characteristics of individuals with several rare disorders which we call waihonapedias (waihona meaning treasure in Hawaiian). There are bumps to take, like online security and reliability of diagnoses, but sharing experiences and true collaborations will allow better research and patient care for fewer costs to patients with rare disorders.

INTRODUCTION

One of the authors recently visited his 93-year-old father and found him sitting in the garden skyping using his iPad with a son in Italy. Indeed, 97% of all Dutch households has access to the internet.[1] The internet use is expanding worldwide, from 670 million people in 2002 to 2.45 billion in 2011, so nowadays 39 of every 100 world citizens are using the internet.[2,3] Similarly, our individual world is expanding: we can now access and share information with more people than ever and with people we would have never encountered otherwise.

A group that should benefit significantly from the gains of internet are individuals with rare disorders.[4] In the European Union a disorder is considered rare if it affects less than 1 in 2000 individuals, in the USA if less than 1 in 1500.[5,6] Patients and their families are in great demand for validated comprehensive information. Reliable information means information on large groups of patients. For rare disorders numbers are by definition small but should still be as large as possible. This means all patients from a single country, and for ultra-rare disorders one needs to think global.[7]

(Patient) support groups are extremely helpful in contacting such groups of individuals with rare disorders. They are often organized internationally and can easily reach out to their members around the world. They have their own website, Facebook page, or Google group, and communicate with their members by e-mail. They have a digital infrastructure in place, and the trust of their members. Patients and their families are also the most important source of information: no-where the number of bits of knowledge and experience on physical complaints, development, behavior, or reactions on treatments is as large as with groups of patients with the disorder involved. The sum of this knowledge is what affected individuals like to know and constitutes a treasure of information. Here we describe the gains of collaborations between support groups and their physicians-researchers to obtain and distribute such treasures of information.

RESEARCH AGENDA

Physicians/researchers and support groups can assess knowledge gaps together: both prefer research topics where needs and wishes of affected individuals are met. Cornelia de Lange syndrome (CdLs) is a rare disorder characterized by intellectual disability, behavioral problems and many major and minor malformations, and most of these characteristics were in need of further evaluation. A digital survey was posted in the

CdLs website asking families to indicate which research topic would be most important to them. The families prioritized self-injurious behavior, so such research project was started. Participation of the CdLs families was extremely high and allowed a fast and very effective study flow.

Researchers may fear support groups will only ask for studies that can be implemented in practice right immediately. Marshal-Smith syndrome (MSS) is an ultra-rare entity with fewer than 100 patients described in literature to date. Main clinical features are intellectual disability, unusual behavior, kyphoscoliosis and characteristic face.[8] The MSS support group was asked during a support group meeting which topic of research they found the most important. The families realized the progressive osteoporosis was the main health issue and should be studied in detail before it could be treated. So they asked for basic research, i.e. to build a mouse model to study the influences on bone of the gene causing MSS. The model has been build and studies are at present in progress.

WIKIPEDIAS

A Wiki(pedia) is an interactive website with information which allows users to add, modify, or delete content in collaboration with each other.[9] In wikis for rare disorders the number of potential contributors is small. We have built such wiki for MSS. The basis was data in existing scientific literature. Blocks of information were written in lay terms on demarcated topics like vision, teeth, or heart and put on the MSS site. We had knowledge of affected MSS individuals living in 10 countries using 8 languages and arranged translation of the information in each language. The support group offered families private access to the information on the site, and all families added information. The medical advisors of the support group updated the information from time to time and families reacted to remarks of one another. The self-regulating capacity of the wiki was remarkable. The end result was detailed, cross-sectional information in lay terms on an ultra-rare entity that outclasses information on many common disorders. The information was also used to write an overview for a peer reviewed medical journal.[8] Access to information empowers patients.[4]

WAIHONAPEDIA

A wiki provides cross-sectional information but longitudinal information would be even more valuable. Some families use Facebook for this: they maintain a profile, often with

personal information and pictures, and keep this updated. The use of Facebook by many support groups show how important this is in communicating with one another. The disadvantage is that information is usually unstructured and not usable for research, and there are significant privacy problems.

We build on a joint database with longitudinal information for Pitt-Hopkins syndrome (PTHS). PTHS is an entity characterized by intellectual disability, major and minor malformations and unusual respiration patterns. We have built an extremely comprehensive general questionnaire which asks questions about family, early history, physical problems, and cognition. To this we added a series of validated behavioral questionnaires. All have been translated in 7 languages. The questionnaire was announced on various PTHS support group sites, and a key has been forwarded to the families allowing them to put in data. Data have been entered by 100 families within a few months.

This extensive series of questionnaires was a one-off. The families receive now automatically a yearly request to provide an update using a short questionnaire, on somatic findings and especially on behavioral aspects. The information gathered systematically over a long period of time will become an increasingly valuable treasure for everyone involved in care or research for this disorder. We are now using the same systematics for individuals with CdLs.

Wikipedia is derived from the words ‘encyclopedia’ and the word ‘wiki’ which means ‘rapid’ in Hawaiian. In analogy we have called our longitudinal database ‘waihonapedia’ from the Hawaiian word ‘waihona’ meaning ‘treasure’. The waihonapedias will provide unprecedented information for everyone studying the disorder and everyone who plans interventions and would like to compare results to the natural history.

CONDITIONS

A wikipedia or waihonapedia requires a reliable diagnosis in participating affected individuals. Confirmation by biochemical, metabolic or molecular tests will be required if possible, and otherwise diagnoses should be assessed by medical advisors of support groups with outstanding experience in the disorder. Our way of assuring reliably diagnosed participants only has been instrumental in detecting the gene causative for MSS as it allowed fast testing of a large group of MSS individuals through the support group (indeed all have been found to carry a mutation[10]). Our search for mosaicisms in CdLs depended heavily on a large group carefully clinically diagnosed patients without a

mutation, and the finding of mosaicism in 76% of until then molecularly unproven CdLs individuals is of considerable significance for patient care.[11]

Security and privacy are main challenges of all forms of eHealth. In (ultra)rare disorders, there is a specific additional privacy concern next to safe data transmission: data can be present in only a limited number of individuals and may allow recognition of individuals if combined to other data such as age and country. We use the help of skilled computer professionals to ensure privacy.

CONCLUSION

Everyone wants to be special, but nobody wants to have a rare disorder. Individuals with rare disorders, their families and caregivers are in great demand of reliable knowledge about their disorder, but information is scarce and difficult to understand. Affected individuals are usually extremely motivated to overcome obstacles as they experience their disorder 24/7. They constitute the major source of information, and are well contactable through support groups. The use of existing infrastructure of support groups can act as stepping stone to intensive collaboration between all involved, in many aspects of research, and particularly in gathering extremely valuable longitudinal data. Digital tools empower this to a great extent. There are key concerns to solve, and awareness to increase. Still, collaboration between support groups and researchers, facilitated by modern media, can lead to better healthcare and quality of life for all with rare disorders.

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5

Behavior in Cornelia de Lange syndrome: a systematic review

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ABSTRACT

Aim

Careful study and accurate description of behavior are important to understand developmental challenges for individuals with Cornelia de Lange syndrome (CdLS). Here we present a systematic review of current understanding of behavior in CdLS.

Method

A systematic search was performed for articles published between January 1946 and December 2015 evaluating autism, self-injury, and/or cognition in CdLS. After study-selection, 43 papers were included. The Cochrane quality criteria were adjusted to assign quality scores to the included studies.

Results

Participants were mostly categorized in the severe/profound developmental level. Methodology and quality were very heterogeneous, as well as reporting occurrence of autism. Self-injurious behavior was reported in 15 papers. Physical conditions were reported in 21 studies, mostly related to hearing and vision. Only nine studies mentioned details about medication.

Interpretation

Comparison of presented results was hindered by heterogeneous assessment methods. Improving our understanding of behavioral characteristics in CdLS requires more uniform methodology. We propose a 'criterion standard' of instruments that can ideally be used in assessment of behavior and development. This will improve understanding of behavior in the context of developmental level and daily functioning.

INTRODUCTION

Cornelia de Lange Syndrome (CdLS) is a genetic disorder characterized by distinctive facial features, limb abnormalities, and intellectual disability. The syndrome is mainly caused by mutations in the genes *NIPBL*, *SMC3*, and *SMC1A*.[1-3] Reported levels of intellectual functioning range from normal/borderline to profoundly disabled.[4,5] The behavior seen in CdLS includes autism characteristics, self-injurious behavior (SIB), aggression and expressive-receptive language discrepancy.[6-8] Anxiety (particularly social anxiety), aggression, and SIB are examples of behavior that disrupt daily functioning.[9]

In the past decades, several studies have been performed to identify the behavioral phenotype in CdLS.[7,10-13] However, no systematic review of published studies on behavior in CdLS has previously been undertaken. Careful study and accurate description of behavior is important to understand developmental challenges for individuals with CdLS. Collating this information will improve future research and will eventually inform treatment. Here we present a systematic review of current understanding of behavior in CdLS. We highlight five areas of interest, namely developmental level, autism spectrum disorder (ASD), SIB, physical conditions, and medication use. Methodology and quality of publications will be systematically evaluated to enable insight in strengths and weaknesses of previous behavioral research in CdLS, so as to improve future research on behavioral phenotypes in CdLS and other rare genetic disorders.

The main aim of this study is to identify what we already know about the behavioral phenotype in CdLS and which questions still remain.

METHODS

Literature search

A systematic search for articles published between January 1946 and December 2015 evaluating autism, self-injury, and/or cognition in CdLS was performed in two steps. First, index terms and free text words were identified from an initial set of papers retrieved by random search (Table 5.1). These terms were used to systematically search the online literature databases PsychINFO, EMBASE, and Ovid MEDLINE for relevant papers. Searches were performed by combining terms for phenotype AND/OR behavior AND/OR autism AND/OR cognition AND/OR self-injurious behavior with search terms for CdLS (including Brachmann - de Lange Syndrome). Titles and abstracts were checked

Table 5.1 Search strategy

1	(phenotype* or behavior* or autis* or self-injurious* or SIB* or pervasive developmental* or pdd* or social skill* or intellectual development* or cognit* abilit*).ab,ti.
2	(de Lange syndrome* or de Lange or Cornelia de Lange or CdLS).ab,ti.
3	1 and 2

SIB = Self injurious behavior; pdd = Pervasive Developmental Disorder; CdLS = Cornelia de Lange Syndrome; autis = autism, autism spectrum disorder(s), autistic; cognit = cognition, cognitive, cognitively; abilit = ability, abilities.

for eligibility. In the second step references of the included papers were checked for additional relevant papers (snowballing).

Study selection and data extraction were performed by two reviewers (PAM and SP), who scored all identified papers independently from each other. Consensus was sought in case of discrepancies by consulting a third reviewer (IDCvB). Papers published in English, German, French, Spanish, or Dutch were eligible for review if they presented original research; if participants had a confirmed diagnosis of CdLS (molecularly confirmed or clinically validated by an experienced clinician); if series of at least three participants were described; and if behavior was described. When validation of diagnosis was not defined and authors could not be reached for a definitive answer, papers were excluded. Three studies that reported confirmed diagnosis based on parent reports were included.[14-16] Risk of bias was reduced by removing duplicates. We checked all studies for method of recruitment (Table 5.2 and Appendix 5.1).

Data extraction

Two reviewers (PAM and SP) systematically extracted data through a standardized data-extraction form. Study design, population, and behavioral characteristics were extracted. The appraisal form was based on subscales from questionnaires such as the Problem Behavior Inventory-01[17] and Social Communication Questionnaire,[18] direct assessment subscales from the Autism Diagnostic Observation Schedule[19] and an adapted version of the Cochrane data collection checklist.[20] The following variables were extracted: country, study population, acquisition, genotype, assessment method, study design, number of participants, age, outcome measure, quality assessment, used instruments, physical condition, medication, developmental level, ASD, SIB, and other behavior.

The Cochrane quality criteria were adjusted to suit the included studies and their methodology. We adapted the Cochrane data collection checklist using the following criteria: baseline measurement included, assessment/intervention is independent of

Table 5.2 Summary of key study characteristics

Key study characteristics	Number of studies (n=43)
Country	
USA	7 (16%)
EU	13 (30%)
It	6 (14%)
NL	2 (5%)
Be	1 (2%)
Spa	1 (2%)
Ger	3 (7%)
UK	23 (54%)
Recruitment[a]	
Foundation (parent associations/support groups)	32 (74%)
Hospital	6 (14%)
Previous studies	10 (23%)
Other (e.g. research center, advertisements)	11 (26%)
Study design	
Case control	19 (44%)
Cohort	4 (9%)
Cross sectional	12 (28%)
Case report/series	8 (19%)
Genetic analyses[b]	6 (14%)
NIPBL	6 (14%)
SMC1A	4 (9%)
SMC3	2 (5%)
Other (*SMC*)	1 (2%)
Report on medication	9 (21%)
Studies including comparison group(s)	20 (47%)
Behavior and developmental outcome measure[c]	
Developmental level	31 (72%)
Autism Spectrum Disorder	19 (44%)
Self-injurious behavior	15 (35%)
Other (e.g. challenging behavior, repetitive behavior & communication problems)	36 (84%)
Quality assessment	
≥ 4/7	14 (33%)
≤ 3/7	11 (26%)
≥ 3/6	12 (28%)
≤ 2/6	6 (14%)
Assessment method[d]	
Physical examination	19 (44%)
Questionnaire(s)	36 (84%)
Interview(s)	15 (35%)
Observation(s)	5 (12%)
Direct assessment(s)	14 (33%)
Other (e.g. medical reports)	3 (7%)

[a] Studies could have used more than one form of recruitment. [b] Studies could have analyzed more than one mutation. [c] Studies could have used more than one behavioral outcome measure. [d] Studies could have used more than one assessment method. USA = United States of America; EU = European Union; It = Italy; NL = the Netherlands; Be = Belgium; Spa = Spain; Ger = Germany; UK = United Kingdom.

other changes, data were obtained through validated and standardized instruments, data collection was unlikely to have been affected by assessment/intervention, blinded assessment of primary outcome(s), completeness of dataset and reliable primary outcome measure(s). Criteria were scored as follows: done, not clear, not done, and not applicable.

These criteria were applied to the behavioral outcome measures, even when these were not the main outcome measures of the study. Other outcome measures were not scored in accordance with the aim of this review. Papers could receive a maximum score of seven out of seven only when study design included a baseline measurement. When study design did not allow a baseline measurement, studies could receive a maximum score from six out of six (Appendix 5.1).

RESULTS

We identified 551 papers and selected 43 eligible papers to include in the review (Figure 5.1).

Table 5.2 presents a summary of key study characteristics (more detailed information in Appendix 5.1). Notably, most participants were recruited through National Foundations of Parent Support (74%). Eight papers (19%) used only questionnaires for data collection, 34 papers (79%) used two or more methods (e.g. questionnaire, interview, and/or observation) of data collection, and 14 papers used a direct assessment tool (33%). Twenty studies used one or more comparison group(s) (47%). Mutation analyses were performed in six studies (14%). Nine papers mentioned medication use by participants (21%).[8,11,12,21-26] Limited specifics were provided regarding medication use, information ranged from 'numerous medications' and 'antipsychotic medication' to medication used for 'hyperactivity, sleep problems, or aggressiveness'. Data on effectiveness of medication were presented in three studies only, ranging from 'without success' and 'minimal to variably positive' to '33% useful'.[11,21,24]

Appendix 5.2 contains information on key outcomes on behavior and development. Studies that did not use standardized assessments (n=7) were excluded from further behavioral analysis. Thirty-six papers were included. Thirty-one of these studies reported on developmental level (86%), 19 studies reported on ASD (53%), 15 presented information about SIB (42%), 21 studies show details on physical conditions (58%), and nine studies presented data on use of medication (25%). From Appendix 5.2 it becomes clear that assessment tools for studying behavioral characteristics vary widely depending

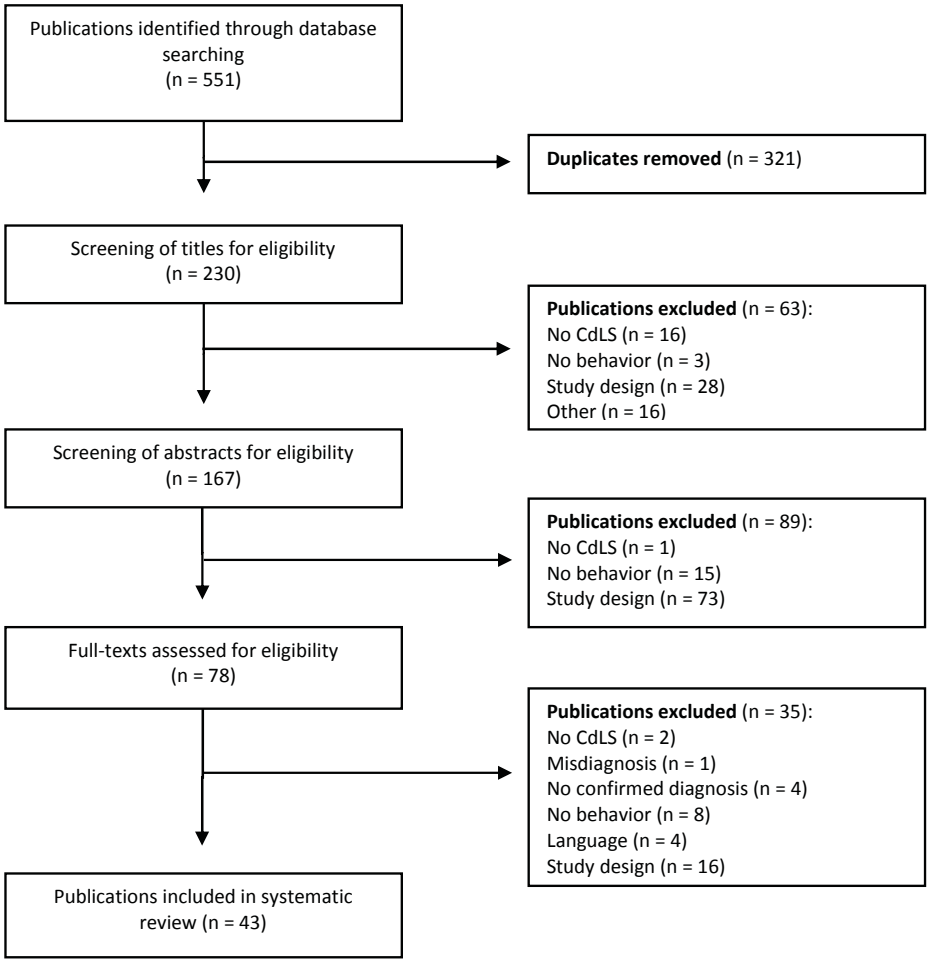

Figure 5.1 Flowchart study selection.
CdLS, Cornelia de Lange Syndrome.

on the focus of the study. For example, methodology of describing ASD phenomenology differs strongly. Some studies give only mean scores and/or cut-off scores from used assessment tools,[3,27] other studies describe the observed behavior in more detail.[13,28]

Six studies reported the presence of mutations in one or more genes.[3,5,29-32] Four of these studies stratified data by genetic cause for development and behavior. Nakanishi et al. reported Autism Diagnostic Interview-Revised (ADI-R) and Vineland Adaptive Behavior Scales (VABS) results for patients with a *NIPBL* mutation (n=22) and ADI-R results for patients with a *SMC1A* mutation (n=3).[3] The authors did not find significant differences

in ADI-R scores between the two genotypes. Patients with a *NIPBL* mutation had a VABS Adaptive Behavior Composite (VABS ABC) score of 57. Pié et al. reported mild (<2y, n=3), moderate (>2y, n=3), and severe (n=1) developmental delay in patients with a *NIPBL* mutation. One patient with a *SMC1A* mutation had a moderate delay.[31] The study by Kline et al. reported results on intellectual disability in patients with a *NIPBL* mutation (n=13) and one patient with a *SMC1A* mutation. Eight patients with a *NIPBL* mutation had a severe intellectual disability and five had a mild intellectual disability. One patient with a *SMC1A* mutation also had a mild intellectual disability.[32] Bhuiyan et al. described adaptive functioning of patients with a *NIPBL* mutation (n=22) using the VABS. Mildly/moderately impaired adaptive functioning was found in six patients and severely/profoundly impaired adaptive functioning in 16 patients. Autism was found in 15 patients according to the Diagnostic Interview for Social and Communication Disorders (no autism: n=7) and in 12 patients according to the Developmental Behavior Checklist (no autism: n=10).[29]

Five areas of interest

To highlight results on the five areas of interest in this systematic review, we selected studies that scored four out of six or five out of seven quality criteria and present these in Appendix 5.3. We report the most noteworthy results from these studies.

With regard to developmental level, as expected, most participants (33–74%) were categorized as profoundly/severely disabled. Three studies report developmental level in age equivalent scores according to the VABS.[8,14,33]

In this selection of 14 studies, seven articles studied the presence of ASD. Presence of ASD was reported in different categories according to the specific assessment method used. For example, Oliver et al. report presence of ASD based on videotaped observations measured with the Childhood Autism Rating Scale and present results in categories ‘no autism’, ‘mild to moderate autism’, and ‘severe autism’, where Berney et al. report the presence of ASD as ‘pronounced’, ‘indeterminate’, and ‘absent’ according to the judgement of an experienced clinician based on the results from postal questionnaires.[8,11] Results in these studies showed that ASD is scored in 27% to 82% of the participants.[8]

Eight out of 14 studies reported results regarding SIB. SIB is present in 25% to 62% of studied participants. One study used SIB as an inclusion criterion, so SIB was present in all participants.[14] Five studies reported specific forms of SIB,[11,14,23,29,34] two reported only on the presence of SIB,[4,25] and one reported frequency of occurrence.[5] Most reported specific forms of SIB are (self-)biting (5 out of 5 studies), head banging (3 out of 5 studies), and (skin)picking (2 out of 5 studies).

Physical conditions were reported in eight articles, with the most reported physical conditions being vision problems, hearing problems, and limb reduction. Hearing problems were reported in 7% to 80% of participants, and vision problems in 6% to 67%. Limb reduction was seen in 20% to 44% of participants. Other commonly mentioned symptoms were gastroesophageal problems, cleft palate, and limited mobility.

Medication is the last area of interest. Very few studies presented data on medication, with four studies reporting drug-groups used, including anti-psychotics, anti-epileptics, non-psychoactive medicines, and sleep medication. Only one study mentioned (parent/carer reported) efficacy in medication used for reducing SIB, 'Few had tried medication and, of those who had, only 33% found it useful'.[11]

DISCUSSION

In this systematic review we present data from 43 eligible studies which studied behavior in CdLS. To our knowledge this is the first systematic review on behavioral characteristics in CdLS. It highlights five areas of interest, namely developmental level, ASD, SIB, physical conditions, and use of medication. This review also considered methodological properties. No firm conclusions on developmental and behavioral phenotype in CdLS can be drawn because of the heterogeneity of used assessments, variety in reported data, and methodological differences.

Developmental level

According to Appendix 5.3, 31 studies presented data on developmental level. The results from the 14 selected studies show that, as expected, most participants (33–74%) were categorized as profoundly/severely disabled. Developmental level was mostly determined through the VABS. Direct in-person cognitive assessments were performed in only seven studies. Several instruments were used in direct in-person assessments and description of data differed from individual IQ-scores to International Classification of Diseases and related health problems (ICD-10) classifications. Description of results in specific task performances such as verbal tasks, performance tasks, memory, and processing was lacking in all studies. This would have been of interest, because for example Ajmone et al. found that short, non-verbal tests such as the Leiter scale may be preferable (in their study population) to the Wechsler scales because the Leiter scale demands less of language, attention, and motor skills.[30]

The VABS, an indirect assessment, was widely used. Assessments like the VABS offer an indirect indication of a person's abilities in daily functioning. They provide insufficient information on individual limitations, possibilities to tackle these, and what implications this may have for social and learning environments.

Autism spectrum disorder

Assessment of ASD was undertaken in 19 studies, and was mostly based on parent/carer informed questionnaires or interviews. Results were reported in cut-off scores and sometimes highlighted some specific characteristics (e.g. repetitive behavior, social withdrawal, and play). ASD was found in 27% to 82% of participants. Two studies performed direct in-person assessments with the Autism Diagnostic Observation Schedule, both offered more specific information on ASD-behavior seen in CdLS (e.g. significantly greater anxiety in CdLS group than the ASD group).[13] When studying behavior such as ASD in CdLS and other rare genetic syndromes, an important issue is the difficulty in differentiating between behavior as part of ASD or as part of (severe) intellectual disability. As Bhuiyan et al. pointed out, the number of ASD characteristics seen in CdLS increases when the level of adaptive behavior decreases.[29] It is important to evaluate ASD symptoms in individuals with intellectual disability carefully and accurately, as a diagnosis of ASD is based on behaviorally defined criteria. An individual with a(n) (severe) intellectual disability may meet the diagnostic criteria for ASD, even though his abilities match his developmental age.

Self-injurious behavior

Data on SIB were presented in 15 papers, which is relatively few because SIB is regularly seen in CdLS.[12,34] Most described forms of SIB were biting, (head-)banging, and (skin) picking. All studies mentioned also other forms of SIB. SIB entails tremendous distress to the individual, parents, and caregivers. Studying this behavior is important to inform guidelines for interventions to reduce SIB. In general, in these studies' data were gathered through parent/carer informed questionnaires or interviews, with only four studies including observational data. As pointed out before, combining indirect with direct assessments is necessary to precisely map this behavior within certain environments. Aspects influencing SIB are social context and social interaction, biological factors, somatic issues, level of intellectual disability, and communicative abilities.[14,15,35] Efficacy of reinforcement-based treatment of SIB may be improved by use of a functional assessment.[36] Executing a functional assessment has the advantage of studying SIB in the context of an individual's daily life.

Physical conditions

When presenting data on level of development, ASD, SIB, or other behavioral characteristics, it is important to report possible physical constraints as they may interfere with a person's abilities. Data on physical conditions were reported in 21 studies only, mostly by means of the Wessex scale.[37] Eight out of 14 selected papers presented data on vision and hearing impairments and limb reduction. Visual and hearing impairments were observed in 6% to 67% and 7% to 80% of individuals, respectively, and limb reduction in 20% to 44% of participants. It is well known that, in addition to intellectual disability, sensory impairments may cause limitations in communication which can lead to challenging behavior.[38-40] Physical discomfort (most reported were gastroesophageal problems and dental/mouth problems) is also a risk marker for challenging behavior.[41] Considering possible concurrent physical issues when assessing individuals remains of utmost importance to understand the implication of certain behaviors.

Medication

Remarkably, medication use was reported in nine studies only. Elucidation was mainly limited to type and indication (e.g. anti-epileptic, anti-psychotic, hyperactivity, and sleep problems). Little was mentioned on effect (e.g. 'no improvements' or 'useful'). No data on doses were provided, and hardly any additional information was provided on indication and efficacy. This lack of published data (group level) on pharmacological effects may hinder prescription of effective medication by healthcare professionals.

It is striking that sensory processing[42] has hardly been studied in CdLS. Information is available on hearing and visual problems, but the impact of aberrant sensory processing in daily life in CdLS is unclear. Following the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), sensory processing is an important domain to be looked for when ASD is being studied.[43] Impaired sensory processing can, next to hearing and visual problems, influence the way stimuli are processed and interpreted. Understanding the individual's sensory processing style may also be useful for adapting communication strategies in daily functioning.

An additional noteworthy finding is that only a few studies performed a genetic analysis. This is partly because 11 studies were conducted before specific causal gene mutations were identified in CdLS in 2004.[1,2] Six studies found one or more gene mutations, of which four reported developmental and/or behavioral data stratified to genetic cause.[3,29,31,32] Such limited data preclude definite conclusions. Future studies should not only perform genetic analysis, but also stratify physical and behavioral data by genetic cause(s).

Different genotypes may entail different observable behavioral patterns and mapping these molecular subgroups carefully could support identification of concurrent patterns in clinical behavior.

Methodological characteristics

Behavioral outcome measures were as diverse as assessment methods, in part because of several conceptual and practical considerations. Thirty-six papers used questionnaires (sometimes combined with other assessment methods) to gather data. Using a survey approach may improve feasibility of a study[9] as it increases the accessibility of a population. However, the phenotype in CdLS is diverse; to cover the whole population, researchers should not restrict participation to national patient foundations and/or parent support groups, as this carries the risk of selection bias. Recruitment should also take place through professionals and healthcare institutions.

Because no suitable quality assessment method for behavioral studies was found fitting the goal of this review, we adapted relevant items of the data collection checklist from the Cochrane Effective Practice and Organization of Care Review Group.[20] None of the included papers achieved a maximum score. Criteria most often unmet were inclusion of baseline measurement, blinded assessment of primary outcome(s), and reliable primary outcome measure(s). This is related to behavior not being an objective outcome (such as laboratory test values, length or height), inter-rater reliability was often lower than 0.80 (kappa), and only a few studies used matched controls.[8,28,44] Therefore, lower scores do not necessarily reflect the potential value of a study; rather, they may be considered an indication of the diverse nature of assessed studies and the broad inclusion criteria.

There is a clear need for more uniform assessment of behavior in individuals with CdLS using appropriate, validated instruments. Direct in-person individual assessments as well as assessment of the developmental phase and cognition should become a routine part of studying behavior in rare syndromes. Table 5.3 contains a proposal for more uniform assessment of behavior in (rare) genetic syndromes using high-quality instruments.

Strengths and weaknesses

A strength of this study is that the extensive search method minimized selection bias and data were systematically extracted by two independent researchers by means of a standardized appraisal form. We not only systematically evaluated behavior that was reported, but also evaluated the method and quality of the studies. This increases the usefulness of this review for future behavioral studies in other (rare) syndromes.

Table 5.3 Recommended assessment methods in (rare) syndromes

Outcome measure	Assessment/characteristics
Cognition	Bayley-III,[45] Wechsler Nonverbal Scale of Ability[46]
Adaptive functioning	Vineland Adaptive Behavior Scales[47]
Autism spectrum disorder (characteristics)	Autism Diagnostic Observation Schedule,[19] Autism Diagnostic Interview-Revised,[48] Social Communication Questionnaire[18]
Sensory processing	Sensory Profile[42]
Self-injurious behavior	Behavior Problems Inventory – 01,[17] direct assessment and/or observation, Challenging Behavior Interview[49]
Physical characteristics	Vision, hearing, mobility (e.g. Wessex scale[37]), physical evaluation
Medication	Label, indication, doses, effect
Context of daily life	Environment (e.g. developmental history, residence), support (e.g. speech therapy, pediatrician)

A possible weakness is that there was no suitable method available to evaluate the studies on their methodological quality. This was because of the heterogeneity of study designs and outcome measures. However, to provide insight into the quality of the papers, the commonly used Cochrane quality criteria were adapted to evaluate the quality of the articles in the most objective way.

We aimed to reduce the risk of bias by removing duplicates. In addition, our aim was to identify current knowledge regarding behavior and development of persons with CdLS rather than comparing and summarizing effectiveness of interventions, causing bias to be less of an issue. Three studies described different selections of outcome measures for the same participant population.[8,25,34] Moreover, few researchers study behavior and development of individuals with a rare syndrome. Inevitably, certain authors are cited often and study populations described repeatedly.

This systematic review aimed to present an overview of current developmental and behavioral manifestations in CdLS. We presented five areas of interest, namely developmental level, ASD, SIB, physical conditions, and medication use. The results show that assessment methods were heterogeneous, making comparison of presented results difficult. Improving our understanding of behavioral characteristics in CdLS requires more

uniform methodology. We propose a 'criterion standard' of instruments that can ideally be used in assessment of cognition, adaptive functioning, ASD, sensory processing, SIB, physical characteristics, medication use, and evaluating the context of individuals with a (rare) syndrome (Table 5.3). This will improve understanding of behavior in the context of developmental level and daily functioning. Combining a survey approach with direct in-person assessments is necessary to improve our in-depth understanding of behavior in CdLS[30] and other (rare) syndromes.[3] It may eventually lead to tailored, effective interventions to improve quality of life in individuals with rare syndromes.

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Appendix 5.1 Key criteria included studies

Reference	Objective of the study	Country[a]	Study population[b]	Acquisiton/ recruitment[c]	Genotype(s)	Assessment Methods[d]	Study design[e]	N (CdLS patiënts)	Age (Mean / SD)	Outcome measure[f]	Quality assessment[g]
Welham et al., 2015[1]	Food-related behavior problems	UK	CdLS, AS, PWS, FXS, 1p36DS	Fnd	N.D.	Q	CC	32	10.2y (4.0)	Impaired satiety, preoccupation with food & comp. negative behavior	4/7
Crawford et al., 2015[2]	Face scanning and spontaneous emotion preference	UK	CdLS, RTS	RC Fnd	N.D.	Q/I/ DA	CC	15	18.4y	FS, SEP, ASD & AF	5/7
Cochran et al., 2015[3]	Age related changes in ASD	UK	CdLS, FXS, CDCS	Fnd PrSt	N.D.	Q	CS	67	20.8y /9.25y	ASD	3/7
Srivastava et al., 2014[4]	ASD traits in children & adolescents with CdLS	USA	CdLS	Fnd, Adv.	N.D.	Q / I	CS	41	11.4y	ASD, AF, AbB	4/6
Nelson et al., 2014[5]	Affect in children and adults with CdLS	UK	CdLS, CdCS, FXS	PrSt. Fnd	N.D.	Q	CC	67	T1:17.3y (9) T2:20.0y (9)	MIP, insistence on sameness, ASD	4/7
Ajmone et al., 2014[6]	Communication, cognitive and behavioral impairments in CdLS	It	CdLS	FndHsp	10 NIPBL 1 SMC	Q / DA	C	17	8.2y	Comm., Cogn. & Behavior	2/6
Moss et al., 2013[7]	Autism spectrum disorder characteristics in CdLS & FXS	UK	CdLS, FXS, tASD	PrSt, Fnd	N.D.	Q	CC	103	17.19y	ASD	4/7
Moss et al., 2013[8]	Social behavior and characteristics of autism spectrum disorder in CdLS, AS, CDCS	UK	CdLS, AS, CDCS	PrSt, Fnd	N.D.	Q / I / DA	CC	15	12.4y	ASD, SI skills, social motivation, social enjoyment	3/7
Nakanishi et al., 2012[9]	Autistic features in individuals with mild to moderate CdLS	USA	CdLS	Hsp, Fnd	22 NIPBL 3 SMC1A 1 SMC3	Q / I / PhE	CS	49	15.2y	ASD	3/6

Moss et al., 2012[10]	Characteristics of autism spectrum disorder in CdLS	UK	CdLS, tASD	PrSt	N.D.	Q/I/DA	CC	20	11.34y	ASD	3/7
Oliver et al., 2011[11]	ASD, hyperactivity and affect in CdLS	UK	CdLS, AS, CDCS, PWS, FXS, SMS, LS, IDma	Fnd	N.D.	Q	CC	101	17.5y	ASD, hyperactivity, impulsivity, affect	4/7
Arron et al., 2011[12]	SIB and aggressive behaviors	UK	CdLS, AS, CDCS, FXS, LS, PWS, SMS	Fnd PrSt	N.D.	Q	CC	101	17.49y/17.49y	SIB, AB, ASD, Mood & level of ability	4/7
Pié et al., 2010[13]	Genotype-phenotype correlations in CdLS	Spa	CdLS	Fnd	11 NIPBL, 3 SMC1A	PhE, PsE	CS	30	N.D.	Mutations & variants in NIPBL, SMC1A & SMC3	1/6
Wulffaert et al., 2009[14]	Behavioral and physical characteristics & parenting stress in CdLS	NL	CdLS	Fnd	20 NIPBL, 2 SMC1A, 0 SMC3	Q / I / PhE	CS	37	18.1y (13)	Behavioral characteristics, parenting stress, ASD, AF	4/6
Sloneem et al., 2009[15]	Presence and degree of association between SIB & environmental events	UK	CdLS, IDma	Fnd	N.D.	Q / I / Obs	CC	27	14.4y (7.3)	SIB	3/7
Richards et al., 2009[16]	Social anxiety in CdLS	UK	CdLS, CDCS	PrSt	N.D.	I / Obs	CC	12	11y (5.2)	Eye contact, hand movements, participant-comm., examiner-comm., social anxiety	5/7
Oliver et al., 2009[17]	Prevalence, phenomenology of SIB in CdLS	UK	CdLS, IDma	Fnd, Prof	N.D.	Q / I / DA / PhE	CC	54	13.9y (8.9)	SIB, SB, ComB, AbB, AF	5/7
Olioso et al., 2009[18]	Clinical problems and everyday abilities in CdLS	It	CdLS	Fnd	N.D.	Q / PhE	CS	45	22.5y	Pheno, behavioral problems, personal autonomies, school & work	3/7

Appendix 5.1 continues on next page

Appendix 5.1 ***Continued***

Reference	Objective of the study	Country[a]	Study population[b]	Acquisiton/ recruitment[c]	Genotype(s)	Assessment Methods[d]	Study design[e]	N (CdLS patiënts)	Age (Mean / SD)	Outcome measure[f]	Quality assessment[g]
Moss et al., 2009[19]	Repetitive behavior in genetic syndromes	UK	CdLS, AS, CDCS, FXS, PWS, LS, SMS, IDma	Fnd	N.D.	Q	CC	101	17.49y	RB, ASD	4/7
Oliver et al., 2008[20]	Behavioral phenotype in CdLS, specifically ASD	UK	CdLS, IDma	Fnd	N.D.	Q / I / PhE	CC	54	13.9y (8.6)	ASD, ComB, AF, AbB	5/7
Moss et al., 2008[21]	Autism spectrum phenomenology in CdCS, CdLS	UK	CdLS, CDCS	PrStFnd	N.D.	Q / I / DA	CC	34	12.39y / 3.8y	ASD	3/7
Marchisio et al., 2008[22]	Otitis media with effusion and hearing loss in CdLS	It	CdLS	RC, Fnd	N.D.	DA / Q / PhE	CS	50	N.D.	N.D.	4/6
Hall et al., 2008[23]	SIB, health and sleep problems in CdLS	UK	CdLS, IDma	Fnd	N.D.	Q / PhE	CC	54	13.88y / 5.88y	CB, sleep problems&HP	5/7
Collis et al., 2008[24]	Facial expression of affect in CdLS	UK	CdLS, CDCS, IDma	PrSt	N.D.	Q/I/DA	CC	14	6y	Affect	5/7
Sarimski 2007[25]	Infant attentional behaviors in CdLS	Ger	CdLS	N.D.	N.D.	Q / Obs	CR/S	7	T1: 8.8m T2: 33.3m	Social relatedness	3/7
Lorusso et al., 2007[26]	Theory of Mind in narrative production	It & NL	CdLS, DS, WS, TDC	RC	N.D.	DA / MRc	CC	6	14.87y	Language, Cogn., ToM	4/7
Kline et al., 2007[27]	History of aging in CdLS	USA	CdLS	Fnd	13 NIPBL 1 SMC1A	MRc/ Q / PhE	CS	49	17.9y	Physical and behavioral changes with aging	0/6
Berg et al., 2007[28]	Contemporary health problems & associations with affect	UK	AS, CdLS, CDCS	PrStFnd	N.D.	Q/ PhE	CC	108	16.6y	HP & affect	5/7

Basile et al., 2007[29]	Examining the behavioral phenotype in CdLS	It	CdLS	FndHsp	N.D.	Q/I/DA	C	56	10y;7m	Pheno, behavior& Cogn.	3/6
Arron et al., 2006[30]	Effects of social context on social interaction and SIB in CdLS	UK	CdLS	Fnd	N.D.	Q / I / DA	CR/S	16	7.6y (3.7)	Social initiation and avoidance & SIB	3/6
Bhuiyan et al., 2006[31]	Genotype-phenotype correlations in CdLS	NL	CdLS	Fnd	22 NIPBL	Q/I/ PhE	C	39	N.D.	GT, Pheno, BP, AF & ASD	4/6
Moss et al., 2005[32]	Environmental events and SIB in CdLS	UK	CdLS	Fnd	N.D.	DA / Q / I	CR/S	8	9.10y	SIB	4/6
Sarimski 2002[33]	Preverbal competencies in CdLS	Ger	CdLS, CDCS, DS	Prof	N.D.	Q / Obs / PhE	CC	13	5y	Comm. behaviors	3/7
Hyman et al., 2002[34]	SIB, Self-restraint and compulsive behaviors	UK	CdLS	Fnd	N.D.	Q	CS	88	12.89y / 8.02y	SIB, self-restraint, CB	3/6
Berney et al., 1999[35]	Behavioral phenotype	UK	CdLS	Prof Fnd	N.D.	Q/ PhE	C	49	10.2y / 7.8y	Cogn., ASD, SIB	4/6
Sarimski 1997[36]	Communication, social-emotional development and parenting stress in CdLS	Ger	CdLS	FndHsp	N.D.	Q / PhE	CS	27	7.1y (4.9)	Social comm., SIB, parenting stress	4/6
Selicorni et al., 1993[37]	Heterogeneity of phenotype in classiscal vs. mild CdLS	It	CdLS	Hsp	N.D.	Q / PhE	CR/S	30	61m	Physical Pheno	2/7
Moeschler et al., 1993[38]	Phenotypic and developmental characteristics in mild CdLS	USA	CdLS	Prof	N.D.	PhE / DA	CR/S	3	N.D.	Pheno &develop. outcomes	3/7
Kline et al., 1993[39]	Prognosis, psychomotor achievements & level of ID in CdLS	USA	CdLS	HspFnd	N.D.	Q/E/DA	CS	122	N.D.	Psychomotor development and ID	2/6
Hawley et al., 1985[40]	Natural course, problems requiring medical attention, heterogeneity, inheritance 7 recurrence risks	USA	CdLS	Fnd	N.D.	Q / PhE	CS	64	7y	Course, Pheno, risks	3/6

Appendix 5.1 continues on next page

Appendix 5.1 ***Continued***

Reference	Objective of the study	Country[a]	Study population[b]	Acquisiton/ recruitment[c]	Genotype(s)	Assessment Methods[d]	Study design[e]	N (CdLS patients)	Age (Mean / SD)	Outcome measure[f]	Quality assessment[g]
Fraser et al., 1978[41]	Voice, speech and language in CdLS	UK	CdLS	Prof	N.D.	DA / PhE	CR/S	6	N.D.	Voice, speech, language	3/7
Evens et al., 1977[42]	Ocular symptoms in CdLS	Be	CdLS	N.D.	N.D.	PhE	CR/S	3	14y	Ocular symptoms	0/6
Bryson et al., 1971[43]	Self-mutilation in CdLS	USA	CdLS	Hsp	N.D.	Obs/ PhE	CR/S	4	16.25y	SIB	1/6

[a] Be, Belgium; Ger, Germany; It, Italy; NL, Netherlands; Spa, Spain; UK, United Kingdom; USA, United States of America.

[b] AS, Angelman Syndrome; CDCS, Cri du Chat Syndrome; CdLS, Cornelia de Lange Syndrome; DS, Down Syndrome; FXS, Fragile X Syndrome; IDma, Intellectual Disability of mixed aetiology; LS, Lowe Syndrome; PWS, Prader-Willi Syndrome; RTS, Rubinstein-Taybi Syndrome; SMS, Smith-Magenis Syndrome; tASD, typical Autism Spectrum Disorder; TDC, Typically developing children; 1p36DS, 1p36 Deletion Syndrome.

[c] Adv, advertisements; Fnd, CdLS foundation/support group; Hsp, Hospital; Prof, through professionals; PrSt, previous studies; RC, Research Centre.

[d] Q, Questionnaire(s); I, Interview; Obs, Observation; DA, Direct individual Assessment; MRc, Medical Records; PhE, Physical Examination; PsE, Psychological Evaluation.

[e] CC, Case Control; C, Cohort; CR/S, Case Report/Series; CS, Cross-Sectional.

[f] AB, Aggressive Behavior; AbB, Aberrant Behavior; AF, Adaptive functioning; ASD, Autism spectrum disorder; Beh.Pheno, Behavioral Phenotype; CB, Challenging Behavior; Cogn., Cognition; Comm., Communication; ComB, Compulsive behavior; FS, Face Scanning; GT, Genotype; HP, Health Problems; ID, Intellectual Disability; MIP, Mood, Interest & Pleasure; Pheno, Phenotype; RB, Repetitive Behavior; SB, Stereotypic Behavior; SEP, Spontaneous Emotion Preference; SIB, Self-injurious behavior; SI skills, Social Interaction skills; ToM, Theory of Mind.

[g] Quality assessment; Baseline measurement; Assessment/Intervention is independent of other changes; Data were obtained through validated and standardised instruments; Is the assessment/ intervention unlikely to affect the data collection?; Blinded assessment of primary outcome(s); Completeness of dataset; Reliable primary outcome measure(s) → Scored: Done / Not clear / Not done.

N.D., Not Described; y, years; m, months.

Appendix 5.2 Key outcomes on behavior (studies without standardised measurements are excluded)

Reference	Outcome measure(s)	Assessment(s)[a]	Physical conditions	Developmental level [b](N)	ASD[c]	SIB[d] (N)	Other Behavior (n)
Welham et al., 2015[1]	Impaired satiety, preoccupation with food and composite negative behaviors (food-related problems)	DemoQ, Wessex, FRPQ	Mobility: 72% mobile	Speech: 36% verbal	N.D.	N.D.	Food related problems (e.g. preoccupation with food, impaired satiety, composite negative behavior)
Crawford et al., 2015[2]	Eye tracking, ASD characteristics and adaptive behavior	DemoQ, SCQ, VABS, eye tracking tasks	N.D.	VABS ABC-score: M= 59.87 (SD 24.99), score range 20-121 VABS Communication score: M= 53.47 (SD 25.89), score range 21-104	Meeting cut off for ASD (4)	N.D.	Eye tracking behavior
Cochran et al., 2015[3]	ASD phenomenology	DemoQ, SCQ, Wessex	Mobile 87% Able/partly able 37%	54% verbal	T1 – Autism cut-off: 46% T1 – ASD cut-off: 80% T2 – Autism cut-off: 43% T2 – ASD cut-off: 74%	N.D.	Restricted, repetitive and stereotyped behaviors
Srivastava et al., 2014[4]	ASD features, adaptive functioning & aberrant behavior	CARS, ABC[1], VABS	N.D.	VABS Total group scores 38.3 (SD 23.1) 49.8 (SD 25.5) 40.6 (SD 25.2) 34.1 (SD 25.3)	No autism (7) 17% Mild autism (17) 41% Autism (17) 41%	N.D.	Overactivity& impulsivity, Irritability

Appendix 5.2 continues on next page

Appendix 5.2 ***Continued***

Reference	Outcome measure(s)	Assessment(s)[a]	Physical conditions	Developmental level [b](N)	ASD[c]	SIB[d] (N)	Other Behavior (n)
Nelson et al., 2014[5]	Affect, insistence on sameness, ASD, health problems	DemoQ, Wessex, MIPQ-S, HQ, RBQ, ASQ	T_1: Fully mobile 67% Vision: 67% normal Hearing: 61% normal T_2: Fully mobile: 71% Vision: 65% normal Hearing: 64% normal	T_1: Self-help: 50 % partly able/ able Speech: Partly verbal/verbal 59 % T_2: Self-help: 50 % partly able/ able Speech: Partly verbal/verbal 59 %	ASQ: T_1 : M = 20.1 (SD 6.4) [cut-off ASD ≥ 15; autism ≥ 22] ASQ: T_2 : M = 20.5 (SD 6.5) [cut-off ASD ≥ 15; autism ≥ 22]	N.D.	Mood Interest and Pleasure; insistence on sameness
Ajmone et al., 2014[6]	Communication, cognition, behavior	Cognitive tests (LIPS, GS), VABS, language tests (McACDI, PPVT, TVL, TCGB), CBCL, CARS	N.D.	According ICD-10: Normal IQ (3) Borderline IQ (2) Mild ID (1) Moderate ID (4) Profound ID (2) VABS mean AE: Motor 43 months Mental 37 months Socialization 39 months Communication 40 months Everyday skills 30 months	CARS: Non-autistic to borderline (7) Mild autistic features (4) Severe autistic features (6)	N.D.	Inter- (8) and externalizing (4) behavior
Moss et al., 2013[7]	ASD symptomatology & adaptive behavior	DemoQ, Wessex, SCQ, ASQ	Vision: 65% normal Hearing: 59% normal	Fully mobile 57% Self-help 5.63 (SD 19.4)	78% > ASD cut-off 45% > Autism cut-off	N.D.	All percentages of SCQ items scored as 'impaired' are given

Moss et al., 2013[8]	ASD, social interaction skills, social motivation and enjoyment, contact with familiar vs. unfamiliar persons	SCQ, VABS, DOSI and CSRS (developed for DOSI)	N.D.	Communication [M; range]: Expressive 1.17; 0.70–3.50 Receptive 1.20; 0.10–4.70 Written 2.41; 1.10–6.90 Daily Living Skills [M, range]: Personal 1.39; 0.10–3.11 Domestic 1.61; 0.10–5.60 Community 1.71; 0.10–7.00 Socialization [M, range]: Interpersonal 0.96; 0.10–3.20 Play and leisure 1.34; 0.10–3.11 Coping skills 1.43; 0.10–4.80	46% cut-off for Autism 100% cut-off for ASD	N.D.	Social enjoyment, social interaction skills, social motivation
Nakanishi et al., 2012[9]	Autistic features in mild-moderate CdLS	VABS, SCQ, ADI-R	N.D.	VABS-ABC mean = 60 (20-101) Disability level: ≥71 (10) 51–70 (28) 36–50 (5) 21–35 (0) ≤20 (6)	Scoring > ASD cut-off: SCQ Total score (24) ADI-R Autism (21)	N.D.	N.D.
Moss et al., 2012[10]	ASD symptomatology	ADI-R, VABS, BPVS, ADOS	N.D.	VABS group AE: Mental 34 months Socialization 37 months Communication 31 months Everyday skills 34 months	Above ASD cutt off: Communication (18) = 90% Social interaction (18) = 90% Total social-communication (17) = 85% Above Autism cutt off: Communication (12) = 60% Social interaction (13) = 65% Total social-communication (13) = 65 %	N.D.	Anxiety more present

Appendix 5.2 continues on next page

Appendix 5.2 ***Continued***

Reference	Outcome measure(s)	Assessment(s)[a]	Physical conditions	Developmental level [b](N)	ASD[c]	SIB[d] (N)	Other Behavior (n)
Oliver et al., 2011[11]	ASD symptomatology, affect & hyperactivity	DemoQ, Wessex, ASQ, TAQ, MIPQ	Vision: 67% normal Hearing: 66% normal	Self Help: 53 % partly able/ able Mobility: 59 % mobile	>ASD cut-off (67) 79% > Autism cut-off(39) 46%	N.D.	<18 yr: 8% hyperactivity, 3% negative affect, 2% low interest & pleasure, 3% positive affect, 5% high interest & pleasure, 10% impulsivity >18yr: 5% hyperactivity, 13% negative affect, 0% low interest & pleasure, 0% positive affect, 0% high interest & pleasure, 25% impulsivity
Arron et al., 2011[12]	Prevalence & phenomenology of SIB and aggression, ASD, mood and level of ability	Wessex, ASQ, TAQ, MIPQ, DemoQ, CBQ	Vision: 67 % normal Hearing: 66 % normal	Mobility: 59% mobile Self-help: 53% able/partly able	More present in those showing SIB, specifically on Repetitive Behavior & Social Interaction	70% showed SIB: Hits self against object, self-biting, body-hitting, self-scratching, stuffing objects, nail pulling	Physical aggression 40%

Wulffaert et al., 2009[14]	Behavioral characteristics, parenting stress, ASD and AF	DBC-P (DBC-ASA), VABS, DISCO-10, NPSI-S	Physical severity scores were calculated for use of CdLS severity	According VABS: Profound (19) Severe (6) Moderate (6) Mild (5) Borderline (1)	Combin. DBC-ASA & DISCO Autistic disorder (20) - 15 profoundly AF - 2 severely AF - 3 moderately AF Possible autistic disorder (6) No autistic disorder (11)	Frequently: 22% Occasionally: 38% Absent: 41%	Severe problem behavior 47% Most problems: Self-absorbed, social relating Least problems: communication disturbances In between: disruptive/antisocial behavior and anxiety.
Sloneem et al., 2009[15]	SIB	VABS, CBI, obs. data (videotaped)	Wheelchair use: Never (14) Occasionally (11) Always (2)	VABS Daily Living Skills domain Mean standard score: 27.48 (SD 14.74)	N.D.	Locations of SIB: Body (9), face (10), sensory (6), head (19), hand (1), mouth (4) Forms of SIB: Picking (19), Poking (3), biting (14), Striking (5), body to object (4) Environmental association: Most in demand or attention	N.D.
Richards et al., 2009[16]	Eye-contact, hand movements, communication, social anxiety	VABS, BPVS, video structured social interactions	N.D.	Mild (3) Moderate (5) Severe (4)	N.D.	N.D.	Communication, hand movements, eye-contact, social anxiety

Appendix 5.2 continues on next page

Appendix 5.2 ***Continued***

Reference	Outcome measure(s)	Assessment(s)[a]	Physical conditions	Developmental level [b](N)	ASD[c]	SIB[d] (N)	Other Behavior (n)
Oliver et al., 2009[17]	SIB, stereotyped, compulsive and aberrant behavior, level of ability	CBI, DemoQ, ISQ, GARS, ABC[1], CBC, VABS, StP, Obs. data	N.D.	VABS: Profound: (27) Severe: (13) Moderate: (8) Mild: (6) Wessex - wheelchair use: - Never: (30) - Sometimes: (18) - Always: (6)	Mean score: 92.24 Cut off: 'probably autistic' ≥90	Total (30); self-biting (57%), Body hitting (28%), Poking (21%), Skin picking (76%) SIB Targets: Body 64%, Face 68%, Head 31%, Hand 76% Mouth 11%	Stereotypic & compulsive behaviors, inappropriate vocalisations (19), destruction of property (22), hyperactivity, pain and sleep problems
Moss et al., 2009[19]	Repetitive behavior, ASD	DemoQ, ASQ, Wessex, RBQ	Hearing: 66% normal Vision: 67% normal	Self-help: 53% partly able/ able Mobility: 59% mobile Speech: 45% verbal	ASQ: M = 17.5 (SD 12.2), range 4–40 [cut-off ASD ≥15; autism ≥22]	N.D.	Repetitive behavior (e.g. tidying, lining up objects etc.) stereotypic behavior
Oliver et al., 2008[20]	ASD, compulsive behavior, adaptive behavior and aberrant behavior	VABS, Wessex, ABC, CBC, CARS	Mobility: Not able 46%; Partly Able 41%; Able 13%	Profound ID: 50% Severe ID: 24 % Moderate ID: 15 % Mild ID: 11 % Borderline/Normal: 0% VABS mental sc.: M = 27 months	CARS: 52% non-autistic 15% mild-moderate autism 32% severe autism	N.D.	Hyperactivity, stereotypy, compulsive behaviors

Moss et al., 2008[21]	ASD phenomenology	DemoQ, VABS, BPVS, ADOS, SCQ	N.D.	Based on VABS score: Profound (9) Severe (16) Moderate (6) Mild (3) Borderline (0) VABS group AE: ABC-score: 42.66 months Receptive language AE: BPVS: 51 months	Scoring > autism cut-off: ADOS - Communication (21) 62% - Social Interaction (24) 71% - Total Score (21) 62% SCQ - Total score (8) 24% Scoring > ASD cut-off: ADOS - Communication (28) 82% - Social interaction (26) - Total Score (25) 74% SCQ - Total Score (14) 41%	N.D.	Extremely shy (2), speech (64.7% verbal)
Marchisio et al., 2008[22]	SIB, cognition	Observational data, WS, L-R	Sensorineural Hearing loss 20%, impaired hearing in 80%, acute otitis media in 14%, Gastroesophageal reflux 46%, cleft palate in 18%	Developmental impairment (language & cognitive imp.): 40% severe 48% severe-mild /moderate 12% mild-moderate	N.D.	Total 52%	N.D.

Appendix 5.2 continues on next page

Appendix 5.2 ***Continued***

Reference	Outcome measure(s)	Assessment(s)[a]	Physical conditions	Developmental level [b](N)	ASD[c]	SIB[d] (N)	Other Behavior (n)
Hall et al., 2008[23]	Self-injury, health & sleep problems	DemoQ, Wessex, CBI, HQ, ISQ	Epilepsy 33%, Limb abnormalities 44%, eye 67%, ear 73%,dental 75%, cleft palate 18%, GI-tract 71%, heart 38%,lung 33%, liver 6%,diabetes 2%, genitalia 29%, bowel 27%, skin 53%, hernia 25%, Wheelchair use: - Always 11% - Occasionally 33% - Not 56%	Self Help: - Not able 46% - Partly able 41% - Able 13%	N.D.	% CdLS pts with specific health problems showing SIB: Present 25–62% Absent 52–69%	Mild – severe sleep problems in 52%
Collis et al., 2008[24]	Affect (facial expression)	Wessex, VABS, videotaped data	N.D.	VABS Receptive AE: mean 25.7 months (AF) VABS Expressive AE: mean 16.9 months (AF)	N.D.	N.D.	Facial expression: Positive affect: median 2.59%; mean 3.55% Negative affect: median 0%; mean 1.02%
Sarimski 2007[25]	Social relatedness	IPDS, video observations	Moderate-severe hearing loss: 3 Severe upper limb malformations: 1	T_1: developmental stage III (7) T_2: developmental stage IV (5) developmental stage VI (2)	N.D.	N.D.	Visual attention, involvement with object, object related acts, socially related acts

Lorusso et al., 2007[26]	Language, cognitive development and ToM	WS, TVL, picture story telling (videotape recorded)	N.D.	FIQ 54 FIQ 47 FIQ 56 FIQ 95 FIQ 54 FIQ 75	N.D.	N.D.	Expressive language, ToM
Berg et al., 2007[28]	Health problems and affect	DemoQ, Wessex, MIPQ-S, HQ	56% fully mobile 13% able Vision problems 6% Hearing problems 7%	27% verbal	N.D.	N.D.	Mental and behavioral problems in 6%
Basile et al., 2007[29]	Clinical, behavioral and cognitive characteristics	WS, L-R, SBIS, GS, VABS, DBC-P, ABC[2], CARS	N.D.	According DSM-IV-R: Profound MR (12) Severe MR (15) Moderate MR (15) Mild MR (5) Borderline (7) Normal IQ (2) VABS AE: <18 months (19) 18-132 months (37)	CARS: Mild-moderate autism (12) Severe autism (3) ABC: Indicative of autism (9) Associated autism (6) 28/56 participants showed a combination of impaired sociability, communication deficits and restricted repetitive behaviors	Total n=20; self-biting, head-hitting, self-scratching, skin picking, sleep disorder (7)	Anxiety (36), Aggression (11), Compulsive (26), no speech (23), hyperactivity (33), emotional instability (28), high pain threshold (36), oppositional (48), attention disorder (47)
Arron et al., 2006[30]	Social initiation and avoidance, SIB	VABS, CBI, experimental setting and obs. data	N.D.	MA composite score: 0.58–1.67 yrs. Mean AE total VABS: 11.63 months (SD4,86) Socialization AE in months: 11.06 (SD 4.33) Communication AE in months: 9.50 (SD 4,21) Mean AE in months: 12.31 (SD 5.62)	N.D.	Total (9); head/face hitting (3), Body hitting (2), Skin picking (6)	Destructive behavior (10), social initiation (13), social avoidance (14), inappropriate vocalisations (10), aggression (7)

Appendix 5.2 continues on next page

Appendix 5.2 ***Continued***

Reference	Outcome measure(s)	Assessment(s)[a]	Physical conditions	Developmental level [b](N)	ASD[c]	SIB[d] (N)	Other Behavior (n)
Bhuiyan et al., 2006[31]	Genotype-fenotype, BP, AF, ASD	DBC, DISCO, VABS	N.D.	Normal/borderline AF (0) Mild/moderate AF (11) Severe/profound AF (25)	DISCO: 24 ASD / 12 no ASD DBC: 22 ASD / 14 no ASD	Self-biting, Pica, Head banging	Aggression, mood changes, self-absorbed behavior, disruptive behavior
Moss et al., 2005[32]	SIB	Wessex, VABS, videotaping school environmental events and settings	Poor vision (3) Poor hearing (2) Normal vision (5) Normal hearing (4) Little or no hearing (2)	VABS age equivalence score: P1: 2;5 yrs (ambulant) P2: 3;11 yrs (ambulant) P3: 1;2 yrs (ambulant) P4: 3;9 yrs (ambulant) P5: 1;9 yrs (Partially-ambulant) P6: 2;8 yrs (Partially-ambulant) P7: 0;8 yrs (ambulant) P8: 0;6 yrs (non-ambulant)	N.D.	Total (8); self-biting (4), Head/face hitting (4), Ear poking (1), Hair pulling (1), Picking of: face (2), neck (1), body (1), arm (1), hand/finger (5)	N.D.
Sarimski 2002[33]	Communicative behaviors	IBSE, PVCS, taped low-structured play sessions	Severe upper limb malformations (4), severe hearing impairments (3), feeding & GI-tract (7)	Developmental model Dunst & McWilliam: Stage II: (3), Stage III: (2) Stage IV: (6), Stage V: (2)	N.D.	N.D.	Communicative acts
Hyman et al., 2002[34]	SIB, self-restraint and compulsive behaviors	Wessex, CBQ, SRC, CBC	Hearing (19) Vision (6) Both (13)	Ambulant (52) Partly mobile (12) Non-ambulant (16) Literate (6) Able and verbal (7) Able only (5) Verbal only (9) Neither able, literate nor verbal (60)	N.D.	SIB (56) Self-restraint (47)	Destructive behavior (47), aggressive behavior (38), stereotypic behavior (50), compulsive behavior (77)

Berney et al., 1999[35]	Degree of MR, ASD, SIB and other behavioral disturbances	SSBP questionnaire, EAS temperament questionnaire, DOTS-R, modified ABC[2]	Seizures (14), severe limb reduction (10), GI-symptoms 67%	Borderline 10% Mild 8% Moderate 18% Severe 20% Profound 43%	Based on modified ABC and clinician: Autism (18), indeterminate (8), absent (23)	Self-restrictive behaviors 30%, 55% SIB: Reasons for SIB: Thwarting or frustration 34% Anxiety or fear 18% Boredom 13% Demand avoidance 5% Forms: biting, scratching, eye-poking, head banging	Daily aggression 49% Hyperactivity: 1 symptom 74%, 4 symptoms 14%, temper tantrums 25%, cyclical mood disturbance 27%, Sleep disturbance: 1 symptom 55%, ≥3 symptoms 24%
Sarimski, K. 1997[36]	Social-communication, SIB, parenting stress	PVCS, SSBP, BPI, PSI	Ocular abnormalities (9), hearing loss (3), epileptic seizures (3), severe limb reduction (6), failure of growth (6), extreme failure of growth (4), GI-reflux (6)	Moderate ID (8) Severe ID (19)	N.D.	2/14 (<6 yrs) 9/13 (>6 yrs) Self-biting (8), Self-scratching (11), Self-pinching / head banging (9), Hair pulling / rumination (8), teeth-grinding (14)	Communication problems, social interaction deficits, stereotypic behavior, aggression, anxiety, destructive behavior, hyper/hypo-activity, mood disturbances, food problems, sleep problems

Appendix 5.2 continues on next page

Appendix 5.2 ***Continued***

Reference	Outcome measure(s)	Assessment(s)[a]	Physical conditions	Developmental level [b](N)	ASD[c]	SIB[d] (N)	Other Behavior (n)
Moeschler& Graham 1993[38]	Phenotypic and developmental characteristics	Clinical assessment, BSID / SBIS / MSCA / LIPS / WS, TACL, PPVT, PEST	Subj. 1: limited supination forearms, brachyclinodactyly of the 5th fingers Subj. 2: single palmar creases, short 5th fingers, cortical thumbs Subj. 3: low muscle tone, small hands with hypothenar hypoplasia, syndactyly of digits 2–3.	Subj. 1: last IQ measure was 66 (test unknown) Subj. 2: IQ 66 (SBIS), LIPS non-verbal = 75 Subj. 3 : FSIQ 63, VIQ 66, PIQ 65 (WISC)	N.D.	Frequent vomiting (1)	Irritability (1), feeding problems (1)
Kline et al., 1993[39]	Psychomotor development, level of development	Diverse reports on abilities, developmental test (BSID; PPVT; VABS), cognitive tests (SBIS; MSCA; WS)	N.D.	Developmental tests: BSID average 47, range <10–106 PPVT average 43, range <10–71 VABS average 48, range <20–87 Cognitive tests: IQ tests average 53, range <30–85	N.D.	N.D.	Psychomotor development (e.g. Gross motor, fine motor, speech)

Fraser et al., 1978[41]	Voice, speech and language	GDS, SBIS, LIPS, and other test (unclear which), RDLS	Diverse characteristics described per case (e.g. small hands & feet, limitation in extension of elbows, upper limb malformations)	Untestable (1) GDS: locomotor 59 wks, social 59 wks, hearing & speech 33 wks, eye-hand coordination 46 wks, performance 52 wks. GDS: locomotor 25 wks, social 25 wks, hearing & speech 17 wks, performance 17 wks. LIPS: IQ<30 SBIS: TIQ 54 SBIS: TIQ 31 / LIPS TIQ 32	N.D.	Throwing one-self over banisters (1), self-abusive (1), self-induced vomiting (2)	Destructive behavior (1), aggression (4), echolalia (1), expressive-receptive language skills (3), speech (2), one word (1)

[a] ABC[1], Aberrant Behavior Checklist; ABC[2], Autism Behavior Questionnaire; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; TAQ, Activity Questionnaire; ASQ, Autism Screening Questionnaire; BPVS, British Picture Vocabulary Scale; BSID, Bayley Scales of Infant Development; CARS, Childhood Autism Rating Scale; CBC, Compulsive Behavior Checklist; CBCL, Child Behavior Checklist; CBI, Challenging Behavior Interview; CBQ, Challenging Behavior Questionnaire; CSRS, Child Sociability Rating Scale; DBC-P, Developmental Behavior Checklist - Primary Carer; DBC-ASA, Developmental Behavior Checklist – Autism algorithm; DemoQ, Demographic Questionnaire; DISCO, Diagnostic Interview for Social and Communication Disorders; DOSI, Direct Observation of Social Interaction; DOTS-R, Dimensions of Temperament questionnaire-Revised; FRPQ, Food Related Problems Questionnaire; GARS, Gilliams' Autism Rating Scale; GDS, Griffiths Developmental Scale; GS, Griffith's Scales; HQ, Health Questionnaire; IBSE, Infant Behavioral Summarized Evaluation; IPDS, Infant Psychological Developmental Scales ; ISQ, Infant Sleep Questionnaire; LIPS, Leiter International Performance Scale; L-R, Leiter-R; MSCA, McCarthy Scales of Children's Abilities; McACDI, McArthur Communicative Development Inventories; MIPQ-S, Mood, Interest and Pleasure Questionnaire-Short; NPSI-S, Nijmegen Parenting Stress Index-Short; PEST, Pattern Elicitation Syntax Test; PSI, Parenting Stress Index; PPVT, Peabody Picture Vocabulary Test; PVCS, Pre-Verbal Communication Schedule; RBQ, Repetitive Behavior Questionnaire; RDLS, Reynell Developmental Language Scale; SBIS, Stanford Binet Intelligence Scales; SCQ, Social Communication Questionnaire; SRC, The Self-Restraint Checklist; SSBP, Questionnaire of the Society for the Study of Behavioral Phenotype; TACL, Test for Auditory Comprehension of Language-Revised; TCGB, Test de Comprensione Grammaticale per Bambini; TVL, Test di Valutazione del Linguaggio; VABS, Vineland Adaptive Behavior Scales; WS, Wechsler Scales.

[b] IQ, Intelligence Quotient; AF, Adaptive Functioning; AE, Age Equivalence; MA, Mental Age; ID, Intellectual Disability; MR, Mental Retardation.

[c] Based on SCQ/ADOS subscales, cut-offs from CARS, ASQ, DISCO, ABC, DBC-P, GARS.

[d] Based on e.g. BPI-01.

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Appendix 5.3 Highlighting five areas of interest

Author(s)	Developmental level (n)	ASD (n)	SIB (n)	Physical conditions	Medication
Crawford et al., 2015[1] n=15	VABS[a] ABC-score: M=59.87 (SD 24.99), VABS Communication score: M= 53.47 (SD 25.89)	Meeting ASD cut off (4)	N.D.	N.D.	N.D.
Srivastava et al., 2014[2] n=41	Composite: 38.3 (SD 23.1) Socialization: 49.8 (SD 25.5) Communication: 40.6 (SD 25.2) Daily activities: 34.1 (SD 25.3)	No autism (7) 17 % Mild autism (17) 41% Autism (17) 41 %	N.D.	N.D.	N.D.
Wulffaert et al., 2009[3] n=37	Profound (19) Severe (6) Moderate (6) Mild (5) Borderline (1)	Autistic disorder (20) Possible autistic disorder (6) No autistic disorder (11)	Frequently: 22% Occasionally: 38% Absent: 41%	Physical severity scores were calculated for use of CdLS severity	N.D.
Richards et al., 2009[4] n=12	Mild (3) Moderate (5) Severe (4)	N.D.	N.D.	N.D.	N.D.
Oliver et al., 2009[5] n=54	Profound (27) Severe (13) Moderate (8) Mild (6)	Mean: 92.24 Cut off 'probably autistic' ≥ 90	Total (30); self-biting (57%), Body hitting (28%), Poking (21%), Skin picking (76%)	N.D.	N.D.
Oliver et al., 2008[6] n=54	Profound ID: 50 % Severe ID: 24 % Moderate ID: 15 % Mild ID: 11 % Borderline/Normal: 0% VABS Mental AE: M = 27 months	CARS[b]: 52 % non-autistic 15 % mild-moderate autism 32 % severe autism	N.D.	Mobility: Not able 46%; Partly Able 41%; Able 13%	Anti-psychotic 3.7% Anti-epileptic 11.1% Non-psychoactive 42.6%

Marchisio et al., 2008[7] n=50	Developmental impairment: 40% severe 48% severe-mild /moderate 12% mild-moderate	N.D.	Total 52%	Sensorineural Hearing loss 20% Impaired hearing in 80% Acute otitis media in 14%	N.D.
Hall et al., 2008[8] n=54	Self Help: - Not able 46% - Partly able 41% - Able 13%	N.D.	Present: 25–62 % Absent: 52–69 %	Limb abnormalities 44 % Eye problems 67%, Ear problems 73%	Anti-psychotic 3.7% Anti-epileptic 11.1% Non-psychoactive 42.6%
Collis et al., 2008[9] n=14	VABS Receptive AE: mean 25.7 months VABS Expressive AE: mean 16.9 months	N.D.	N.D.	N.D.	N.D.
Berg et al., 2007[10] n=108	27% verbal	N.D.	N.D.	Vision problems 6% Hearing problems 7%	N.D.
Bhuiyan et al., 2006[11] n=39	Normal/borderline AF (0) Mild/moderate AF (11) Severe/profound AF (25)	DISCO[c]: 24 ASD / 12 no ASD DBC[d]: 22 ASD / 14 no ASD	Self-biting, Pica, Head banging	N.D.	N.D.
Moss et al., 2005[12] n=8	VABS AE (years): P1: 2;5 P5: 1;9 P2: 3;11 P6: 2;8 P3: 1;2 P7: 0;8 P4: 3;9 P8: 0;6	N.D.	Total (8); self-biting (4), Head/face hitting (4), Ear poking (1), Hair pulling (1), Picking of: face (2), neck (1), body (1), arm (1), hand/finger (5)	Poor vision (3) Poor hearing (2) Normal vision (5) Normal hearing (4) Little or no hearing (2)	N.D.

Appendix 5.3 continues on next page

Appendix 5.3 ***Continued***

Author(s)	Developmental level (n)	ASD (n)	SIB (n)	Physical conditions	Medication
Berney et al., 1999[13] n=49	Borderline 10% Mild 8% Moderate 18% Severe 20% Profound 43%	Autism (18), Indeterminate (8), Absent (23)	Self-restrictive behavior 30 %, SIB 55 % Forms: Biting, Scratching, Eye-poking, Head banging	Severe limb reduction (10)	Anti-epileptic (8) SIB intervention: few have tried, 33% found it useful
Sarimski, K. 1997[14] n=27	Moderate ID (8) Severe ID (19)	N.D.	2/14 (< 6 yrs) 9/13 (> 6 yrs) Self-biting (8), Self-scratching (11), Self-pinching / head banging (9), Hair pulling / rumination (8), Teeth-grinding (14)	Ocular abnormalities (9) Hearing loss (3) Severe limb reduction (6)	Sleep medication (1)

[a] VABS, Vineland Adaptive Behavior Scales (AE = Age Equivalence). [b] CARS, Childhood Autism Rating Scale. [c] DISCO, Diagnostic Interview for Social and Communication Disorders. [d] DBC, Developmental Behavior Checklist.

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6

Phenotypes and genotypes in individuals with *SMC1A* variants

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ABSTRACT

SMC1A encodes one of the proteins of the cohesin complex. *SMC1A* variants are known to cause a phenotype resembling Cornelia de Lange syndrome (CdLS). Exome sequencing has allowed recognizing *SMC1A* variants in individuals with encephalopathy with epilepsy who do not resemble CdLS.

We performed an international, interdisciplinary study on 51 individuals with *SMC1A* variants for physical and behavioral characteristics, and compare results to those in 67 individuals with *NIPBL* variants. For the Netherlands all known individuals with *SMC1A* variants were studied, both with and without CdLS phenotype.

Individuals with *SMC1A* variants can resemble CdLS, but manifestations are less marked compared to individuals with *NIPBL* variants: growth is less disturbed, facial signs are less marked (except for periocular signs and thin upper vermillion), there are no major limb anomalies, and they have a higher level of cognitive and adaptive functioning. Self-injurious behavior is more frequent and more severe in the NIPBL group. In the Dutch group 5 of 13 individuals (all females) had a phenotype that shows a remarkable resemblance to Rett syndrome: epileptic encephalopathy, severe or profound intellectual disability, stereotypic movements, and (in some) regression. Their missense, nonsense and frameshift mutations are evenly spread over the gene.

We conclude that *SMC1A* variants can result in a phenotype resembling CdLS and a phenotype resembling Rett syndrome. Resemblances between the SMC1A group and the NIPBL group suggest that a disturbed cohesin function contributes to the phenotype, but differences between these groups may also be explained by other underlying mechanisms such as moonlighting of the cohesin genes.

INTRODUCTION

"Doctor, really wonderful that you have found that our boy has a *SMC1A* mutation! But please, what does that mean for him, and what can we expect?" In an era dominated by diagnostic tests using microarrays and exome sequencing that identify gene variants, this is in fact a major question that patients and their families like to be answered. This manuscript tries to provide some first answers to that question.

The first clinical reports on *SMC1A* described that variants in this gene cause X-linked Cornelia de Lange syndrome or a mild variant of Cornelia de Lange syndrome (CdLS).[1-3] CdLS is a multisystem disorder characterized by intrauterine growth retardation, short stature, typical face, congenital anomalies of especially the distal upper limbs, and intellectual and developmental disabilities. Behavioral characteristics include autism spectrum disorder, and a predisposition to engage with challenging behavior, especially self-injurious behavior (SIB).[4-7] CdLS is associated with variants in a series of genes; variants in *NIPBL* (~70-75%) and *SMC1A* (~5%) are the most prevalent.[8-11]

The CdLS phenotype caused by *SMC1A* variants overlaps with the phenotype in individuals with *NIPBL* variants. Individuals with *SMC1A* variants were first reported with less marked facial features, less effects on growth and without limb reduction defects.[1-3] Subsequent publications have reported on a more variable phenotype.[12-25] Through the use of panel screening aimed at identifying variants in genes linked to intellectual disability, and the use of untargeted trio exome analysis, *SMC1A* variants are increasingly detected in individuals in whom CdLS was not clinically suspected. In some of these patients the main manifestation is an epileptic encephalopathy.[26-35]

This urged us to initiate an interdisciplinary study in a relatively large series of individuals with a confirmed *SMC1A* mutation. We aimed to gather data on their physical and behavioral phenotype, and to compare the data to a series of individuals with CdLS in whom *NIPBL* variants were found.[11,36] Here we report on the detailed results of the physical studies and on the results of the behavioral studies in general; detailed results of the behavioral studies will be published elsewhere [Mulder et al., in preparation].

METHODS

Study design

We performed a cross-sectional study in a large international series of individuals with pathological *SMC1A* variants, using in person evaluations in Dutch participants, and questionnaire results and clinical pictures in patients from other countries.

Dutch SMC1A cohort

The molecular genetic laboratory of the Academic Medical Center in Amsterdam has been the central Dutch site to perform panel analysis to detect variants in any of the genes associated with CdLS, and *SMC1A* mutation analysis by Sanger sequencing. We contacted the physicians in charge of all individuals with pathological SMC1A variants, asking them to obtain permission for us to contact the family. Subsequently, we contacted all Dutch molecular laboratories that perform exome sequencing and asked whether they had detected additional *SMC1A* variants either using panel screening for intellectual disability/epilepsy or using untargeted trio analysis. Eleven families were contacted of which ten families (13 patients) agreed to participate in the study. After written consent, two authors (S.H.; R.C.H.) performed clinical evaluations (medical history, physical and morphological examination, clinical pictures) in ten individuals and collected data from three individuals who had passed away. Two other authors (P.A.M.; A.L.) performed direct behavioral assessments (ADOS & Bayley-III-NL/WPPSI-III-NL/WAIS-IV-NL) and interviews (SSP-NL and VABS-2) in eight of the remaining individuals (one had died in the meantime; one could not be contacted for further behavioral studies). In addition, we asked parents to fill out a set of behavioral questionnaires, which included the Repetitive Behavior Questionnaire (RBQ), Challenging Behavior Questionnaire (CBQ) and Gastro-esophageal Reflux Questionnaire (GRQ).

International SMC1A cohort

We invited the members of the Scientific Advisory Committee of the CdLS World Federation from Denmark, France, Germany, Italy, Poland, Portugal, Spain, Sweden, U.K., and U.S.A. to participate, requesting to identify individuals with pathological variants in their series, and to contact their molecular genetic laboratories to check for additional *SMC1A* variants. We forwarded a comprehensive, dedicated questionnaire on somatic characteristics (morphology, malformations, neurodevelopment, physical health; see Appendix 6.1) to the physicians and requested to forward a set of behavioral questionnaires to the families.

NIPBL comparison group

We collected data from the Polish CdLS database of individuals with *NIPBL* pathological variants (n=43), some of whom were included in previous publications,[36-37] and from a previously published Dutch cohort with *NIPBL* pathological variants (n=24).[11] To both sets we added data that have become available since publications.

Severity score

A severity score can be predictive of clinical course and maturation relative to other individuals affected by the same or related entity. Since Gillis and co-workers proposed the first severity classification system based on three CdLS phenotype parameters (limb reduction, cognitive abilities and growth), the severity scoring system has been modified and refined.[11,38-39] We used the classification system as suggested by Bhuiyan and co-workers, as it includes all major CdLS parameters (facial morphology, limb anomalies, growth parameters (prenatal; postnatal; skull) and cognitive/adaptive level of abilities) in a standardized and non-interdependent manner.

Statistics

Data were stored in Excel format. Descriptive statistics and Chi square test were performed using Microsoft Excel version 2011. Behavioral data were converted from the questionnaires into a coded SPSS file and were analyzed using IBM SPSS Statistics version 23.

Ethics

The present study has been supported by the national and international CdLS Support Groups, and approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam (NL39553.018.12).

RESULTS

We collected data from 51 individuals with pathological *SMC1A* variants (36 missense, 15 other types). Participants originated from the Netherlands (13 (25%)), USA (9 (18%)), the UK (8 (16%)) and smaller numbers from Argentina, Austria, Denmark, France, Germany, India, Italy, Spain, Switzerland and Turkey. Somatic questionnaires were completed from all 51 participants. Behavioral questionnaires were obtained from 31 participants (response rate 60%). Median age was 13 years (range: 0–46 years), gender ratio was 14M

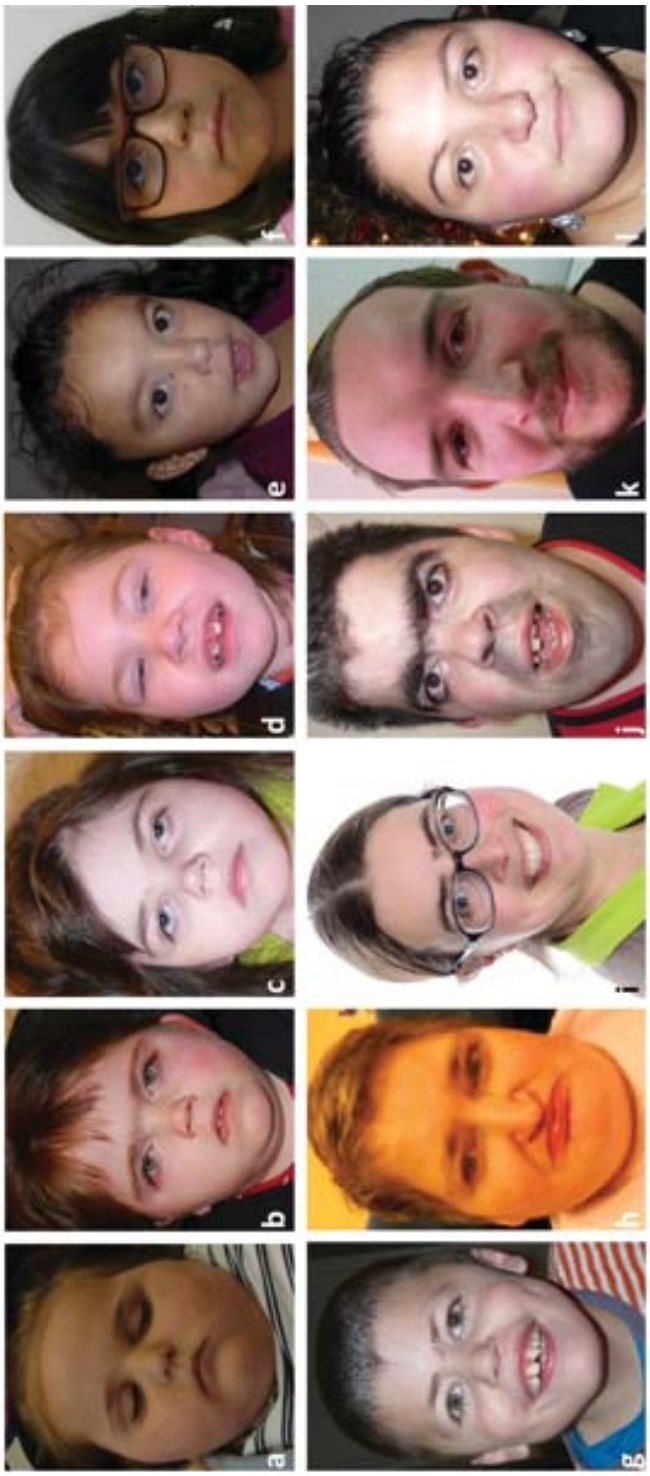

Figure 6.1 Faces of individuals with SMC1A variants from the Dutch cohort.
A. SMC1ANL007, B. SMC1ANL001, C. SMC1ANL002, D. SMC1ANL008, E. SMC1ANL015, F. SMC1ANL003 , G. SMC1ANL004 , H. SMC1ANL011 , I. SMC1ANL009, J. SMC1ANL005, K. SMC1ANL006 , L. SMC1ANL014. Note resemblances especially between faces depicted in A-D. Patient SMC1ANL014 (L) and SMC1ANL015 (E) are mother and daughter. Form a detailed description of facial morphology please see Table 6.1 and text.

to 37F. Median age of clinical diagnoses was 5 years (range: 0–46 years), median age of last examination was 11 years (range: 0–40 years). Median age of the NIPBL group was 14 years (range: 0–46 years), gender ratio was 34M to 33F.

Physical phenotypes

The faces of the Dutch patients are depicted in Figure 6.1. The main results of the present study are presented in Tables 6.1–6.2, 6.4–6.5. The data in the SMC1A group are compared to the 67 individuals with *NIPBL* variants.

The severity scores in CdLS-like, Rett-like and *NIPBL* positive individuals is depicted in Figure 6.2. In the text we only mention those data that are not presented in the tables.

The congenital cardiac malformations observed in individuals with SMC1A mutations consisted of pulmonic stenosis (n=3), atrial septal defects (n=3), persistent ductus arteriosus (n=2), ventricular septal defect (n=1), dextrocardia (n=1), aortic coarctation (n=1), pulmonary valve dysplasia (n=1) and left ventricular noncompaction with apical hypertrophy (n=1). Cryptorchidism was scored as a minor anomaly and was present in four of the 15 males (27%) with *SMC1A* variants; 31/34 males (91%) with *NIPBL* variants had cryptorchidism. Early pubic hair development was reported in four females with a pathological *SMC1A* variant.

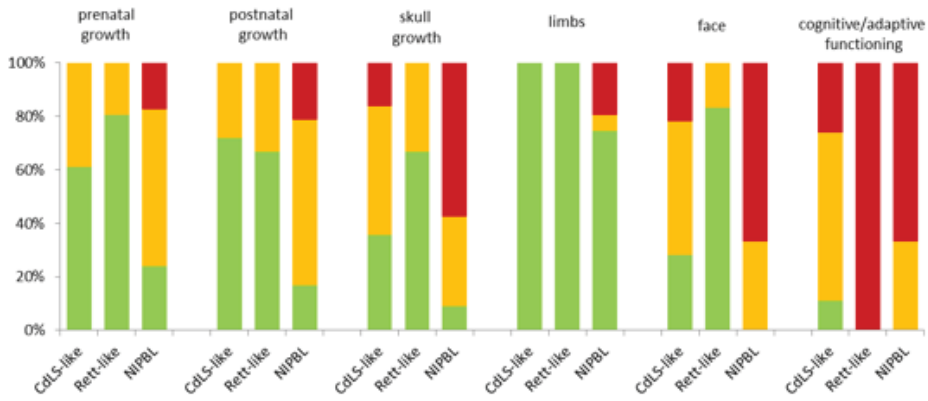

Figure 6.2 Histogram showing the total CdLS severity score (Bhuiyan et al., 2006) in the presently reported SMC1A individuals with a CdLS-like phenotype vs those with a Rett-like phenotype and compared to literature patients with *NIPBL* variants.
Green: lowest score for item; Yellow: middle score for item; Red: highest score for item. Note more severe growth impairment in NIBL group, absence of marked limb anomalies in the SMC1A groups, low resemblance of the Rett-like SMC1A subgroup to the CdLS-like subgroup and the NIPBL group, and less marked cognitive impairment in the CdLS-like SMC1A subgroup.

Table 6.1 General overview of the phenotype in individuals with *SMC1A* variants subdivided by types, compared to those with *NIPBL* variants reported in a Dutch and Polish cohort

	All (n=51)	Missense variants (n=36)	Other variants (n=15)	*NIPBL* literature (n=67)
Gender (M/F)	14 (27)/37 (73)	11 (31)/25 (69)	3 (20)/12 (80)	34 (51)/33 (49)
Growth				
Prenatal[a]				
Length at birth <-2SD	9/32 (28)	6/21 (29)	3/11 (27)	32/43 (74)
Weight at birth <-2SD	11/41 (27)	8/27 (30)	3/14 (21)	29/43 (67)
Head circumference <-2SD	8/24 (33)	5/18 (28)	3/6 (50)	39/43 (91)
Postnatal[b]				
Height <-2SD	24/38 (63)	17/27 (63)	7/11 (64)	37/43 (86)
Weight <-2SD	14/37 (38)	11/26 (42)	3/11 (27)	39/43 (91)
Head circumference <-2SD	23/36 (64)	18/26 (69)	5/10 (50)	54/62 (87)
Craniofacial morphology				
Brachycephaly	17/42 (40)	12/30 (40)	5/12 (42)	44/67 (66)
Low anterior/posterior hairline	30/43 (70)	23/31 (74)	7/12 (58)	57/67 (85)
Arched eyebrows	32/44 (73)	26/31 (84)	6/13 (46)	54/67 (81)
Synophrys	37/46 (80)	29/33 (88)	8/13 (62)	61/67 (91)
Long eyelashes	38/45 (84)	27/32 (84)	11/13 (85)	65/67 (97)
Depressed nasal bridge	20/43 (47)	14/30 (47)	6/13 (46)	57/67 (85)
Anteverted nostrils	26/46 (57)	21/33 (64)	5/13 (38)	58/67 (87)
Long, featureless philtrum[c]	27/43 (63)	20/30 (67)	7/13 (54)	54/67 (81)
Thin upper vermillion[c]	33/44 (75)	26/31 (84)	7/13 (54)	22/24 (92)
Downturned corners mouth	33/46 (72)	24/33 (73)	9/13 (69)	23/24 (96)
Palate (high arched; cleft)	11/37 (30); 10/45 (22)	8/26 (31); 7/32 (22)	3/11 (27); 3/13 (23)	35/67 (52); 20/67 (30)
Widely spaced teeth	13/44 (30)	8/31 (26)	5/13 (38)	18/23 (78)
Micrognatia	18/45 (40)	16/32 (50)	2/13 (15)	50/67 (75)
Low-set and/or malformed ears	18/45 (40)	15/32 (47)	3/13 (23)	45/67 (67)

Limbs				
Small hands	32/45 (71)	23/32 (72)	9/13 (69)	53/63[d] (84)
Proximally placed thumb	18/44 (41)	13/31 (42)	5/13 (38)	11/20 (55)
Clinodactyly 5th finger	21/45 (47)	17/32 (53)	4/13 (31)	42/63 (67)
Syndactyly	1/37 (3)	1/26 (4)	0/11 (0)	4/63 (6)
Small feet	29/44 (66)	20/31 (65)	9/13 (69)	65/67 (97)
Syndactyly 2nd–3rd toes	13/46 (28)	9/33 (27)	4/13 (31)	21/66 (32)
Skin				
Cutis marmorata	19/44 (43)	15/32 (47)	4/12 (33)	27/43 (63)
Hirsutism	37/47 (79)	28/34 (82)	9/13 (69)	37/43 (86)
Major and minor malformations				
Limb (major)	0/49 (0)	0/35 (0)	0/14 (0)	17/67 (25)
Heart (major and minor)	13/44 (30)	10/32 (31)	3/12 (25)	18/66 (27)
Genitourinary system (major; minor)[e]	4/42 (10); 9/40 (23)	2/30 (7); 7/29 (24)	2/12 (17); 2/11 (18)	0/67 (0); 46/67 (69)
Gut	3/44 (7)	3/32 (9)	0/12 (0)	6/24 (25)
CNS	5/43 (12)	4/31 (13)	1/12 (8)	

[a] In three prematurely born individuals (between 31–35 weeks) growth data were corrected for a gestational age of 40 weeks.
[b] Postnatal data are not available in one stillborn child.
[c] In three patients this could not be reliably scored due to surgery for clefting.
[d] Seven of the others had such marked limb reduction defects that it prevented evaluation of hand size.
[e] Major: uni/bilateral renal anomalies; minor: cryptorchidism; small penis; hypospadias; underdeveloped prepuce; small labia.
Note: Blank cell indicates that information was unavailable or uncertain. Between brackets percentages of the finding within each particular(sub)group.

Table 6.2 Natural history of physical, cognitive and behavioral development in individuals with *SMC1A* variants subdivided by types, compared to those with *NIPBL* variants reported in a Dutch and Polish cohort

	SMC1A			*NIPBL*
	All (n=51)	Missense variants (n=36)	Other variants (n=15)	All variants (n=67)
Physical health				
Birth				
Apgar at 1'				
<6	5/25 (20)	1/14 (7)	4/11 (36)	18/43 (42)
7–10	20/25 (80)	13/14 (93)	7/11 (64)	25/43 (58)
Apgar at 5'				
<6	2/25 (8)	0/14 (0)	2/11 (18)	11/43 (36)
7–10	23/25 (92)	14/14 (100)	9/11 (82)	32/43 (74)
Feeding problems	24/34 (71)	17/23 (74)	7/11 (64)	65/67 (97)
Seizures	20/44 (45)	13/32 (41)	7/12 (58)	10/66 (15)
Gastro-Esophageal Reflux Disease	25/42 (60)	17/30 (57)	8/12 (67)	47/66 (71)
Constipation	18/42 (43)	14/30 (47)	4/12 (33)	21/66 (32)
Visual impairment	20/38 (53)	15/29 (52)	5/9 (56)	29/66 (44)
Hearing impairment	16/39 (41)	12/30 (40)	4/9 (56)	43/66 (65)

Development				
Cognitive functioning[a]				
Dutch cohort[b] (n=13)				
Normal	1/8 (13)	1/6 (17)	0/2 (0)	
Mild disability	2/8 (25)	2/6 (33)	0/2 (0)	
Moderate disability	1/8 (13)	1/6 (17)	0/2 (0)	
Severe disability	1/8 (13)	1/6 (17)	0/2 (0)	
Profound disability	3/8 (38)	1/6 (17)	2/2 (100)	
International cohort[c] (n=39)				
Normal	2/20 (10)	1/12 (8)	1/8 (13)	0/58 (0)
Mild disability	4/20 (20)	2/12 (17)	2/8 (25)	4/58 (7)
Moderate disability	8/20 (40)	4/12 (33)	4/8 (50)	16/58 (28)
Severe disability	5/20 (25)	5/12 (42)	0/8 (0)	27/58 (47)
Profound disability	1/20 (5)	0/12 (0)	1/8 (13)	11/58 (19)
Sitting[d]	33/38 (87)	23/24 (96)	10/14 (71)	52/67 (78)
Milestone at 0–2 yrs.[d]	19/24 (79)	12/15 (80)	6/9 (67)	28/52 (54)
Milestone at 3–4 yrs.	3/24 (13)	2/15 (13)	1/9 (11)	17/52 (33)
Milestone at ≥5 yrs.	0/24 (0)	0/15 (0)	0/9 (0)	6/52 (12)
No milestone yet (≥5 yrs.)	3/24[e] (13)	1/15[e] (7)	2/9[e] (22)	1/52 (2)
Walking[c]	33/39 (85)	23/25 (92)	9/13 (69)	52/67 (78)
Milestone at 0–2 yrs.	17/30 (57)	13/22 (59)	4/8 (50)	3/52 (6)
Milestone at 3–4 yrs.	5/30 (17)	4/22 (18)	1/8 (13)	1/52 (2)
Milestone at ≥5 yrs.	4/30 (13)	3/22 (14)	1/8 (13)	11/52 (21)
No milestone yet (≥5 yrs.)	4/30[e] (13)	2/22[e] (9)	2/8[e] (25)	19/52 (37)
First words[c]	23/35 (66)	15/22 (68)	7/12 (58)	53/67 (79)
Milestone at 0–2 yrs.	7/20 (35)	4/14 (29)	3/6 (50)	4/53 (8)
Milestone at 3–4 yrs.	3/20 (15)	3/14 (21)	0/6 (0)	16/53 (30)
Milestone at ≥5 yrs.	1/20 (5)	1/14 (7)	0/6 (0)	0/53 (0)
No milestone yet (≥ 5yrs)	9/20[e] (45)	6/14[e] (43)	3/6 (50)	33/53 (62)

Table 6.2 continues on next page

Table 6.2 ***Continued***

	SMC1A				*NIPBL*	
	All (n=51)		Missense variants (n=36)		Other variants (n=15)		All variants (n=67)
Behavioral direct assessment							
Adaptive functioning							
Dutch cohort[b] (n=13)							
Communication							
Mild-moderate deficit	2/6 (33)		2/4 (50)		0/2 (0)		
Severe deficit	1/6 (17)		1/4 (25)		0/2 (0)		
Profound deficit	3/6 (50)		1/4 (25)		2/2 (100)		
Daily Living Skills							
Mild deficit	2/6 (33)		2/4 (50)		0/2 (0)		
Moderate-severe deficit	1/6 (17)		1/4 (25)		0/2 (0)		
Profound deficit	3/6 (50)		1/4 (25)		2/2 (100)		
Socialization							
Mild deficit	2/6 (33)		2/4 (50)		0/2 (0)		
Moderate-severe deficit	1/6 (17)		1/4 (25)		0/2 (0)		
Profound deficit	3/6 (50)		1/4 (25)		2/2 (100)		
Sensory processing	DD[f]	PD[f]	DD[f]	PD[f]	DD[f]	PD[f]	
Dutch cohort (n=13)							
Tactile sensitivity	4/6 (67)	1/6 (17)	2/4 (50)	1/4 (25)	2/2 (100)	0/2 (0)	
Taste/smell sensitivity	0/6 (0)	2/6 (33)	0/4 (0)	2/4 (50)	0/2 (0)	0/2 (0)	
Movement sensitivity	4/6 (67)	0/6 (0)	4/4 (100)	0/4 (0)	0/2 (0)	0/2 (0)	
Under responsive/seeks sensation	2/6 (33)	1/6 (17)	1/4 (25)	1/4 (25)	1/2 (50)	0/2 (0)	
Auditory filtering	0/6 (0)	2/6 (33)	0/4 (0)	2/4 (50)	0/2 (0)	0/2 (0)	
Low energy/weak	6/6 (100)	0/6 (0)	4/4 (100)	0/4 (0)	2/2 (100)	0/2 (0)	
Visual/auditory sensitivity	1/6 (33)	1/6 (17)	0/4 (0)	1/4 (25)	1/2 (50)	0/2 (0)	

Behavioral questionnaires				
Stereotypic movements	20/31 (65)	12/22 (55)	8/9 (89)	41/59 (69)
GERD behavior	23/31 (74)	16/22 (73)	7/9 (78)	
Self-injurious behavior	11/31 (35)	8/22 (36)	3/9 (33)	47/61 (77)

[a] Classification based on DC-LD, WHO and DSM-5.
[b] Based on validated testing by behavioral specialist.
[c] Physician reported data, no validated testing data available.
[d] Number of individuals (of total individuals of whom are data available) who has acquired this milestone during given period of age at the time of present study.
[e] Number of individuals (of total individuals of whom are data available) aged ≥ 5 years who has not acquired this skill at time of present study.
[f] DD = Definite Difference, PD = Probable Difference; some individuals could not be assessed on Taste/Smell sensitivity and/or Movement sensitivity due to PEG tube and not able to move independently.
Note: Blank cells indicate that information was unavailable or uncertain. Between brackets percentages of the finding within each particular (sub)group.

Milestones

While tabulating the milestones we left out *SMC1A* positive children below 5 years of age who were still too young to score with certainty whether they would or would not acquire the milestone before the age of 5 years. If a child ≥5 year old had not reached a milestone we indicated this.

Genotypes

Of the present series half (26/51) of patients have been published before. The nature and site of variants in the present series does not differ from those reported in literature (Table 6.3; Figure 6.3).

Reasons for molecular analysis

In the Dutch cohort, 5/15 (38%) of patients were clinically suspected of CdLS prior to molecular testing. For five patients CdLS was included in the differential diagnosis, but other diagnoses were thought to be more likely. For the remaining three patients CdLS was not clinically suspected at all. All patients coming from other countries were clinically suspected to have CdLS prior to molecular testing. The testing methods differed among

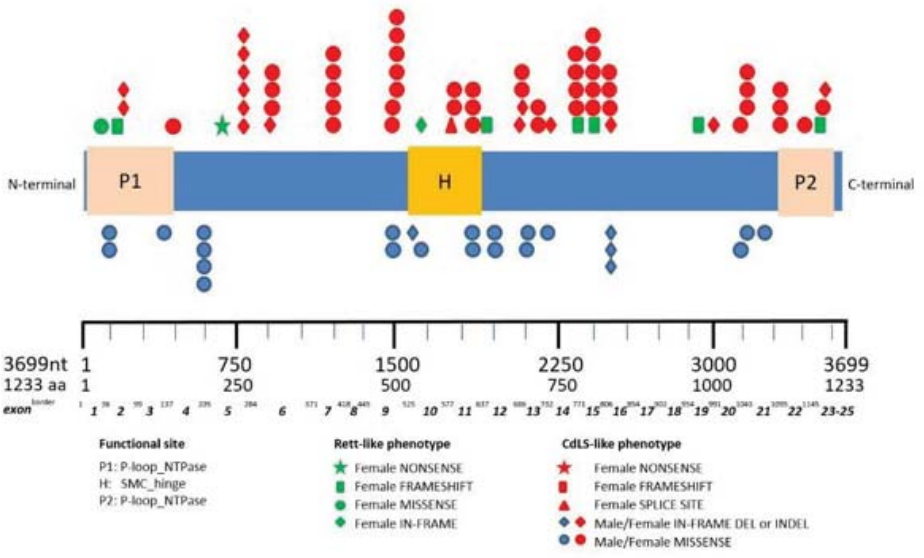

Figure 6.3 Variants in SMC1A reported in literature and in the present series, divided by gender and nature of the mutation.
Variants with a Rett-like phenotype are indicated in green. Please note variants are spread evenly over the whole gene, although more mutations are located between the SMC hinge and P-loop NTPase.

Table 6.3 Genotype in individuals with *SMC1A* variants from literature and in present seriesa

	Index (reference)	Targeted analysis	Exon	Nucleotide change	Amino acid change	Coding effect
	Literature					
1	BAB4135 Yuan, 2015[b]	-	2	c.121C>T	p.Leu41Phe	Missense
2	BAB4136 Yuan, 2015[b]	-	2	c.121C>T	p.Leu41Phe	Missense
3	Pt 3P Deardorff, 2007/ Yuan, 2015	+	2	c.173_187del	p.Val58_Arg62del	In-frame
4	Pt 2 Gervasini, 2013/ Parenti, 2014	+	2	c.173_187del	p.Val58_Arg62del	In-frame
5	Pt 4P Deardorff , 2007/ Yuan, 2015	+	3	c.397T>G	p.Phe133Val	Missense
6	Liu, 2009	+	3	c.421G>A	p.Glu141Lys	Missense
7	Pt 2 Borck, 2007	+	4	c.587G>A	p.Arg196His	Missense
8	Pt 5P Deardorff, 2007	+	4	c.587G>A	p.Arg196His	Missense
9	Pie, 2009	+	4	c.587G>A	p.Arg196His	Missense
10	Pie, 2009	+	5	c.802_804del	p.Lys268del	In-frame
11	Liu, 2009	+	5	c.802_804del	p.Lys268del	In-frame
12	Liu,2009	+	5	c.802_804del	p.Lys268del	In-frame
13	BAB3623 Yuan, 2015	-	5	c.802_804del	p.Lys268del	In-frame
14	Liu, 2009	+	5	c.916_918del	p.Ser306del	In-frame
15	Pt 3 Gervasini, 2013	+	7	c.1192C>G	p.Arg398Gly	Missense
16	Liu, 2009	+	7	c.1193G>A	p.Arg398Gln	Missense
17	Liu, 2009	+	7	c.1193G>A	p.Arg398Gln	Missense
18	Liu, 2009	+	7	c.1193G>A	p.Arg398Gln	Missense
19	Pt II3 Musio, 2006	+	9	c.1478A>C	p.Glu493Ala	Missense
20	Liu, 2009	+	9	c.1478A>C	p.Glu493Ala	Missense
21	Liu, 2009	+	9	c.1478A>C	p.Glu493Ala	Missense
22	Pt 6P Deardorff, 2007	+	9	c.1486C>T	p.Arg496Cys	Missense
23	Pt 7P Deardorff, 2007[b]	+	9	c.1487G>A	p.Arg496His	Missense
24	Pt 7S Deardorff, 2007[b]	+	9	c.1487G>A	p.Arg496His	Missense

Table 6.3 continues on next page

Table 6.3 ***Continued***

	Index (reference)	Targeted analysis	Exon	Nucleotide change	Amino acid change	Coding effect
25	Pt 8P Deardorff, 2007[b]	+	9	c.1487G>A	p.Arg496His	Missense
26	Pt 8S Deardorff, 2007[b]	+	9	c.1487G>A	p.Arg496His	Missense
27	Pt 9P Deardorff, 2007	+	9	c.1487G>A	p.Arg496His	Missense
28	Ansari, 2014	-	10	c.1585_1587del	p.Lys529del	In-frame
29	Wenger, 2016	-	10	c.1636_1638delATT	p.546del	In-frame
30	Hansen, 2013	-	10	c.1731G>A	p.Glu577Glu	Splice defect
31	Ansari, 2014	-	11	c.1757G>A	p.Arg586Gln	Missense
32	Lebrun, 2015	-	11	c.1911+1G>T	p.Thr638Valfs*48	Frameshift
33	Pt 17 Tzschach, 2015	-	12	c.1937T>C	p.Phe646Ser	Missense
34	Pt 1 Gervasini, 2013	+	12	c.1951G>A	p.Val651Met	Missense
35	Liu, 2009	+	12	c.2046_2048delAGA	p.Glu683del	In-frame
36	Liu, 2009	+	12	c.2077C>G	p.Arg693Gly	Missense
37	Pt 4 Gervasini, 2013/ Parenti, 2014	+	13	c.2078G>A	p.Arg693Gln	Missense
38	Pt 10P Deardorff, 2007	+	13	c.2131C>T	p.Arg711Trp	Missense
39	Liu, 2009	+	13	c.2131C>T	p.Arg711Trp	Missense
40	Pie, 2009	+	13	c.2132G>A	p.Arg711Gln	Missense
41	Hoppman-Chaney, 2011	+	13–16	c.2184_2563-268del	p.Leu729_Lys854delinsAspGluIle	In-frame
42	Liu, 2009	+	14	c.2342G>T	p.Cys781Phe	Missense
43	Limongelli, 2010	+	15	c.2351T>C	p.Ile784Thr	Missense
44	Pt 5 Gervasini, 2013/ Parenti, 2014	+	15	c.2351T>C	p.Ile784Thr	Missense
45	Pt 3 Fieremans, 2016	-	15	c.2351T>C	p.Ile784Thr	Missense
46	Pt 26 De Ligt, 2012/ Pt 13 Gillissen, 2014/ Pt1 Jansen, 2016	-	15	c.2364del	p.Asn788Lysfs*10	Frameshift
47	Ansari, 2014	-	15	c.2368C>T	p.Arg790Trp	Missense

48	Pt 11P Deardorff, 2007	+	15	c.2369G>A	p.Arg790Gln	Missense
49	Ansari, 2014	-	15	c.2369G>A	p.Arg790Gln	Missense
50	Pt 6 Gervasini, 2013	+	15	c.2369G>A	p.Arg790Gln	Missense
51	Pt 98 De Ligt, 2012/ Pt 48 Gillissen, 2014 / Pt2 Jansen, 2016	-	16–17	c.2421_2652del	p.Leu808Argfs*21	Frameshift
52	Liu, 2009	+	16	c.2446C>G	p.Arg816Gly	Missense
53	Mannini, 2009	+	16	c.2467T>C	p.Phe823Leu	Missense
54	Pt II4 Musio, 2006/ Parenti, 2014[b]	+	16	c.2493_2495del	p.Asp831_Gln832delinsGlu	In-frame
55	Pt III2 Musio, 2006/ Parenti, 2014[b]	+	16	c.2493_2495del	p.Asp831_Gln832delinsGlu	In-frame
56	Pt III3 Musio, 2006/ Parenti, 2014[b]	+	16	c.2493_2495del	p.Asp831_Gln832delinsGlu	In-frame
57	Pt III4 Musio, 2006 / Parenti, 2014[b]	+	16	c.2493_2495del	p.Asp831_Gln832delinsGlu	In-frame
58	Pt A Goldstein, 2015	-	18	c.2853_2856delTCAG	p.Ser951Argfs*12	Frameshift
59	BAB5452 Yuan, 2015	-	19	c.2974_2A>G	p.Asp992_Gln994del	In-frame
60	Liu, 2009	+	20	c.3146G>A	p.Arg1049Gln	Missense
61	Jang, 2015[b]	-	21	c.3178G>A	p.Glu1060Lys	Missense
62	Jang, 2015[b]	-	21	c.3178G>A	p.Glu1060Lys	Missense
63	Jang, 2015[b]	-	21	c.3178G>A	p.Glu1060Lys	Missense
64	Jang 2015[b]	-	21	c.3178G>A	p.Glu1060Lys	Missense
65	Pt 1 Borck, 2007	+	21	c.3254A>G	p.Tyr1085Cys	Missense
66	Pt 12P Deardorff, 2007	+	22	c.3364T>C	p.Phe1122Leu	Missense
67	Liu, 2009	+	22	c.3367C>T	p.Arg1123Trp	Missense
68	Pt 7 Gervasini, 2013/ Parenti, 2014	+	23	c.3497A>C	p.Asn1166Thr	Missense
69	Pat B Goldstein, 2015	-	24	c.3549_3552dupGGCC	p.Ile1185Glyfs*23	Frameshift
70	Pt 8 Gervasini, 2013/ Parenti, 2014	+	24	c.3565C>T	p.Leu1189Phe	Missense
71	Ansari, 2014	-	24	c.3574_3576del	p.Glu1192del	In-frame
72	Baquero, 2014)/Pie, 2016	+	1–25	Dup Xp11.22 region ~1.1Mb		

Table 6.3 continues on next page

Table 6.3 ***Continued***

	Index (reference)	Targeted analysis	Exon	Nucleotide change	Amino acid change	Coding effect
	Present series					
1	SMC1ANL001[c]	+	1	c.31A>T	p.Asn11Tyr	Missense
2	SMC1ANL002[c]	+	2	c.157dup	p.Thr53AsnfsX34	Frameshift
3	SMC1AUSA004 (Deardorff, 2007)		2	c.173_187del	p.Val58_Arg62del	In-frame
4	SMC1AUSA008 (Deardorff, 2007)		3	c.397T>G	p.Phe133Val	Missense
5	SMC1ASPA001 (Deardorff, 2007)	+	4	c.587G>A	p.Arg196His	Missense
6	SMC1AGER003	+	4	c.587G>A	p.Arg196His	Missense
7	SMC1AFR003 (Borck, 2007)	+	4	c.587G>A	p.Arg196His	Missense
8	SMC1ANL007 [c]	+	5	c.694G>T	p.Glu232*	Nonsense
9	SMC1ADEN001	+	5	c.802_804del	p.Lys268del	In-frame
10	SMC1ASPA002 (Pie, 2009)	+	5	c.802_804del	p.Lys268del	In-frame
11	SMC1AUK008	+	5	c.802_804del	p.Lys268del	In-frame
12	SMC1AUSA002 (Liu, 2009)		5	c.802_804del	p.Lys268del	In-frame
13	SMC1AFR005	+	6	c.919C>A	p.His307Asn	Missense
14	SMC1ADEN002	+	6	c.920A>T	p.His307Leu	Missense
15	SMC1AGER004/SMC1AARG001	?	7	c.1193G>A	p.Arg398Gln	Missense
16	SMC1AGER001/SMC1AAUSTR001	+	9	c.1475A>G	p.Gln492Arg	Missense
17	SMC1ADEN003[b]/SMC1AUSA007[b] (Deardorff, 2007)	+	9	c.1487G>A	p.Arg496His	Missense
18	SMC1ADEN004[b]/SMC1AUSA006[b] (Deardorff, 2007)	+	9	c.1487G>A	p.Arg496His	Missense
19	SMC1AUSA001 (Deardorff, 2007)		9	c.1487G>A	p.Arg496His	Missense
20	SMC1AUK002 (Ansari, 2014)	+	10	c.1585_1587 del	p.Lys529del	In-frame
21	SMC1AUK006	+	10	c.1607A>T	p.Lys536Met	Missense
22	SMC1AUSA012 (Wenger, 2016)	-	10	c.1636_1638delATT	p.546del	In-frame
23	SMC1AUSA010		11	c.1756C>T	p.Arg586Trp	Missense
24	SMC1AUK004 (Ansari, 2014)	+	11	c.1757C>T	p.Arg586Gln	Missense

25	SMC1ANL009[b]	+	11	c.1847C>A	p.Ala616Asp	Missense
26	SMC1ANL010[b]	+	11	c.1847C>A	p.Ala616Asp	Missense
27	SMC1ANL006	-	11	c.1904G>A	p.Arg635His	Missense
28	SMC1ANL014	-	11	c.1904G>A	p.Arg635His	Missense
29	SMC1ANL015	-	11	c.1904G>A	p.Arg635His	Missense
30	SMC1AGER002/SMC1ASWI001	+	13	c.2078G>A	p.Arg693Gln	Missense
31	SMC1AFR004	+	13	c.2090_2092dup	p.Glu697_Leu698delinsVal	In-frame
32	SMC1ANL005	+	13	c.2095C>T	p.Arg699Cys	Missense
33	SMC1AUSA005 (Deardorff, 2007)		13	c.2131C>T	p.Arg711Trp	Missense
34	SMC1ASPA003 (Pie, 2009)	+	13	c.2132G>A	p.Arg711Gln	Missense
35	SMC1AITA003 (Gervasini, 2013)	+	15	c.2351T>C	p.Ile784Thr	Missense
36	SMC1ANL011 (Jansen, 2016)	-	15	c.2364del	p.Asn788Lysfs*10	Frameshift
37	SMC1AUK001 (Ansari, 2014)	+	15	c.2368C>T	p.Arg790Trp	Missense
38	SMC1ASPA004 (Deardorff, 2007)	+	15	c.2369G>A	p.Arg790Gln	Missense
39	SMC1AUK007/SMC1AIND001 (Ansari, 2014)	+	15	c.2369G>A	p.Arg790Gln	Missense
40	SMC1AUK005/SMC1ATUR001	+	15	c.2369G>A	p.Arg790Gln	Missense
41	SMC1ANL008 (Jansen, 2016)	-	16	c.2421-?_2562+?del	p.Leu808Argfs*6	Frameshift
42	SMC1AUSA011 (Liu, 2009)		16	c.2446C>G	p.Arg816Gly	Missense
43	SMC1AFR001	+	16	c.2455A>C	p.Ile819Leu	Missense
44	SMC1AITA001[b] (Musio, 2006)	+	16	c.2493_2495del	p.Asp831_Gln832delinsGlu	In-frame
45	SMC1AITA002[b]	+	16	c.2493_2495del	p.Asp831_Gln832delinsGlu	In-frame
46	SMC1ANL004	+	21	c.3145C>G	p.Arg1049Gly	Missense
47	SMC1AFR0021 (Borck, 2007)	+	21	c.3254A>G	p.Tyr1085Cys	Missense
48	SMC1AUSA003 (Deardorff, 2007)		22	c.3364T>C	p.Phe1122Leu	Missense
49	SMC1ANL003[c]	+	22	c.3367C>T	p.Arg1123Trp	Missense
50	SMC1AITA004 (Gervasini, 2013)	+	23	c.3497A>C	p.Asn1166Thr	Missense
51	SMC1AUK003 (Ansari, 2014)	+	24	c.3574_3576del	p.Glu1192del	In-frame

[a] Annotation according to reference sequence NM_006306.3. [b] Familial cases. [c] Panel analysis (epilepsy, Rett syndrome); clinically the patients were not suspected as having CdLS, other diagnoses were thought to be more likely. Note: Blank cell indicates that information was unavailable or uncertain.

patients depending on local laboratory protocols, and included Sanger sequencing, panel analysis aimed at genes associated with CdLS, and panel analysis aimed at genes associated with intellectual disability/epilepsy.

Table 6.4 Severity scores in individuals with *SMC1A* variants subdivided by types compared to those with *NIPBL* variants reported in a Dutch and Polish cohort*

	SMC1A			*NIPBL*
	All (n=51)	Missense variants (n=36)	Other variants (n=15)	All variants (n=67)
Prenatal growth				
>2500g	26/41 (63)	17/28 (61)	9/13 (69)	15/63 (24)
1500–2500g	15/41 (37)	11/28 (39)	4/13 (31)	37/63 (59)
<1500g	0/41 (0)	0/28 (0)	0/13 (0)	11/63 (17)
Postnatal growth[a]				
>P75	27/38 (71)	19/27 (70)	8/11 (73)	11/66 (17)
P25–P75	11/38 (29)	8/27 (30)	3/11 (27)	41/66 (62)
<P25	0/38 (0)	0/27 (0)	0/11 (0)	14/66 (21)
Head growth				
>-2SD	15/37 (40)	10/27 (37)	5/10 (50)	6/66 (9)
-2SD to -4SD	17/37 (46)	12/27 (44)	5/10 (50)	22/66 (33)
<-4SD	5/37 (14)	5/27 (19)	0/10 (0)	38/66 (58)
Limb malformation[b]				
No	0/49 (0)	0/35 (0)	0/14 (0)	50/67 (75)
Partial	0/49 (0)	0/35 (0)	0/14 (0)	4/67 (6)
Severe	0/49 (0)	0/35 (0)	0/14 (0)	13/67 (19)
Face[c]				
Possible CdLS	18/51 (35)	9/36 (25)	9/15 (60)	0/67 (0)
Mild	24/51 (47)	18/36 (50)	6/15 (40)	10/67 (15)
Classical	9/51 (18)	9/36 (25)	0/15 (0)	57/67 (85)
Intellectual disability[d,e]				
Normal-borderline	3/32 (9)	2/20 (10)	1/12 (8)	0/66 (0)
Mild-moderate	16/32 (50)	10/20 (50)	6/12 (50)	22/66 (33)
Severe-profound	13/32 (41)	8/20 (40)	5/12 (42)	44/66 (67)
Total severity score[f]				
Mean (range)	9.4 (6–13)	9.7 (6–13)	9 (8–10)	13.5 (8–18)

* Between brackets percentages for the characteristic within each (sub)group.

[a] CdLS standard growth curves were used for postnatal height.

[b] No = no reduction defect; partial = partial reduction defects (absence 1/2 fingers); severe = severe reduction defects (absence 3 or more fingers or complicated oligo-/polydactyly).

[c] Possible CdLS; mild = mild type; classical = classical type.

[d] Classification based on DC-LD, WHO and DSM-5.

[e] Physician reported data, no validated testing data available.

[f] Total severity score = Σ(prenatal growth + postnatal growth + head growth + limb malformation + face + intellectual/adaptive functioning) (based on Bhuiyan et al., 2006).

DISCUSSION

SMC1A is known as a gene that can cause a cohesinopathy if mutated.[1] The entities tagged as cohesinopathies have been considered overlapping entities.[40] They share several physical and behavioral features, such as limited growth, several of the facial features, limb malformations, and intellectual disability. The cohesin complex and its regulators mediate sister-chromatid cohesion in dividing cells and are important for controlling gene expression.[41] Sharing of major features of the cohesinopathies supports the hypothesis that a disturbed cohesin function contributes to these characteristics.[22] There are also differences in the phenotypes caused by *SMC1A* and *NIPBL* pathological variants. Such differences support the argument that the phenotype is not only a result of the disturbed cohesin function, but also a result of other functions (moonlighting) of the cohesin genes.[42] One major difference in phenotype between the SMC1A and NIPBL group described here is the higher prevalence and more severe form of self-injurious behavior in the latter. The absence of this behavioral trait in patients with *SMC1A* variants with a Rett-like phenotype, and also in other cohesinopathies, such as individuals with CdLS due to variants in other genes and in individuals with Roberts syndrome,[43] suggests a moonlighting hypothesis for *NIPBL*. Indeed knock-out mouse models for *Nipbl* have shown that *Nipbl* affects transcription and global dysregulation of gene expression, and consequently does have functions different from the cohesin function and have shown evidence for different polypeptide chain functions of *NIPBL* products and for expression changes in genes with roles in neuronal functions that underlie the behavioral and neurological abnormalities observed.[44-45]

Patients with cohesinopathies share several physical signs and symptoms that have been implicated as cause of SIB,[46] and this argues against the self-injurious behavior being secondary to these physical conditions. Therefore, further studies into cohesinopathies and their associated genes, should not only be aimed at the cohesin and related functions, but should also take into account other potential functions of these genes.

The higher incidence of SIB in the NIPBL group could be due to the cognitive level, since cognitive functioning is overall more affected in the NIPBL group than in the SMC1A group. However, SIB seems to be absent in the Rett-like group and yet cognitive functioning appears even lower. Further developmental testing may indicate other cognitive and behavioral differences that may contribute to this. An association (if any) between the results of cognitive and developmental assessments and SIB, and results of the behavioral studies should be described in much detail and will therefore be published elsewhere [Mulder et al., in preparation].

Table 6.5 Characteristics in individuals with *SMC1A* variants with a Rett-like phenotype in present series and from literature

Patient	SMC1A NL001	SMC1A NL002	SMC1A NL007	SMC1A NL011	SMC1A NL008	Wenger et al. USA012	Lebrun et al.	Goldstein et al. Patient A	Goldstein et al. Patient B	Summary
Gender	F	F	F	F	F	F	F	F	F	0M/9F
Genotype										
Exon	1	2	5	15	16	10	11	18	24	
Nucleotide change	31A>T	157dup	694G>T	2364del	2421-?_2562+?del	1636_1638delATT	1911+1G>T	2853_2856delTCAG	3549_3552dupGGCC	
Amino acid change	Asn11Tyr	Thr53AsnfsX34	Glu232*	Asn788Lysfs*10	Leu808Argfs*6	546del	Thr638Valfs*48	Ser951Argfs*12	Ile1185Glyfs*23	
Type	missense	frameshift	nonsense	frameshift	frameshift	in-frame	frameshift	frameshift	frameshift	
Growth										
Prenatal growth	>2500g	>2500g	>2500g	>2500g	1500–2500g	>2500g	NA	>2500g	>2500g	1/8:1500–2500g 7/8: >2500g
Postnatal growth[a]	>P75	>P75	P25–P75	>P75	>P75	P25-P75	<P25	<P25	P25–P75	2/9: <P25 3/9 : P25-P75 4/9 : >P75
Head growth	>-2SD	>-2SD	-2/-4SD	-2/-4SD	>-2SD	-2/-4SD	-2/-4SD	>-2SD	>2SD	5/9: >-2SD 4/9: -2/-4SD
CdLS face	mild	possible	possible	possible	possible	possible	possible	possible	absent	
Arched eyebrows	-	-	-	-	-	-	-	-	-	0/9
Synophrys	+	+	-	-	-	-	+	-	-	3/9
Long eye-lashes	+	+	+	-	-	+	+	+	-	6/9
Long phil-trum	-	-	+	-	-	NA**	-	+	-	2/8

Thin upper vermillion	-	-	-	-	-	+	+	-	-	2/9
Down-turned corners mouth	+	+	+	+	-	+	-	+	-	6/9
Epilepsy										
Generalized epilepsy	+	+	+	+	+	+	+	+	+	9/9
Onset	2.5 m	5 m	4 m	9 m	2 m	2 m	1 m	4 m	17 m	8/9 <1yr
Refractory	+	+	+	+	+	+	+	+	-	8/9
Rett-like symptoms										
Regression	NA@	+	+	NA@	+	NA@	NA@	+	-	4/5
Intellectual disability	profound	profound	profound	severe	profound	severe-profound	severe-profound	profound	NA	8/8 severe-profound
Stereotypic hand movements	+	+	+	+	+	-	+	+	+	8/9
Hand wringing	+	+	+	+	-	-	+	NA	NA	5/7
Disturbed respiratory control	-	-	-	NA	+	NA	NA	NA	NA	1/4

+, present; -, absent; NA, not (reliably) available; m, month(s); yr, year(s); # CdLS standard growth curves; **could not be reliably scored due to microform cleft lip; @ could not reliably be scored due to early onset of seizures.

SMC1A variants are known to be associated with a CdLS phenotype. In comparing CdLS characteristics in the present study, the SMC1A group demonstrates a less disturbed growth compared to the NIPBL group. Prenatal growth parameters are below 2 SD in one-third of the SMC1A group, irrespective of the mutation type. In the NIPBL group prenatal growth parameters are below 2 SD in at least two-thirds of the group. Postnatal height and occipitofrontal circumference are decreased in two-thirds of the SMC1A group, which is less marked compared to the NIPBL group. However, weight is much more disturbed in the NIPBL group, possibly due to the much more frequent, more severe and more protracted feeding problems in this group.

All facial features that characterize CdLS can be present in individuals with *SMC1A* variants, but in a lower frequency compared to the NIPBL group. There are some exceptions: individuals with a missense *SMC1A* variant have the same frequency of periocular features as individuals in the NIPBL group, and also the prevalence of the thin upper vermillion is similar between the two groups. CdLS features that are more prevalent in the NIPBL group such as a small lower jaw and low-set and malformed ears occur more frequently in the group with a missense *SMC1A* mutation than in the group with other mutation types. However, the number of individuals in the latter group is small and results should be evaluated with care.

Limb reduction defects that are typical for CdLS and prevalent in 25% of the NIPBL group, are absent in the SMC1A group. Clinodactyly of the fifth finger occurs less frequently (X^2 $p = 0.038$) than in the NIPBL group, and small hands and a proximally placed thumb are also less frequent (statistically not significant). Feeding problems are more frequent in the NIPBL group (X^2 $p = 0.0001$), while gastroesophageal reflux disease and constipation are equally common in both groups. Seizures, however, are more frequent in the SMC1A group (X^2 $p = 0.0005$), and this is more marked in the group with non-missense *SMC1A* variants (statistically not significant).

A comparison of cognition and behavior is hampered by the lack of data in a considerable number of individuals in the international SMC1A group and the NIPBL group. The numbers of the in person tested individuals in the Dutch cohort are small and should be used with care. All tested individuals in the Dutch cohort have problems with sensory processing.

In summary, individuals with *SMC1A* variants show a phenotype that overlaps with CdLS. The frequencies of some signs and symptoms are lower than in individuals with *NIPBL* mutations. Major phenotypic distinctions are the absence of limb reduction defects and

increased prevalence of seizures in the SMC1A group. Another main difference is self-injurious behavior which is much more frequent and more severe in the NIPBL group.

The Dutch SMC1A group likely covers all individuals with *SMC1A* variants currently known in the Netherlands. The group includes both patients who were clinically diagnosed with CdLS, and those in whom a variant was unexpectedly detected through exome sequencing. We recognize two groups in the Dutch cohort: individuals with a phenotype similar to CdLS, and a group with an epileptic encephalopathy. Individuals with an epileptic encephalopathy have been previously reported as well.[26-34] In the Dutch cohort 5 of 13 (38%) individuals had an epileptic encephalopathy. In evaluating these female patients we were struck by the resemblance to females with progressed stages in Rett syndrome and their typical impaired ability to make contact and interact. All have severe or profound intellectual disabilities and four of the five Dutch females (five of the seven females of the total Rett-like group) showed hand movements such as 'hand wringing' (Table 6.5). Regression has been reported in literature[29,32] and is reported here in three of the five females (Table 6.5). In two other females epilepsy and developmental delay manifested at such young age that this may have masked any sign of regression. Other characteristics of the individuals with an epileptic encephalopathy were a lower birth weight and a lower postnatal height compared to the others in the SMC1A group. According to severity classification terminology (classical, mild, possible CdLS) their faces were assessed as possible CdLS, except in the youngest female who was assessed as mild CdLS. No face morphology was rated as classical CdLS. There is anecdotal evidence that individuals with *SMC1A* variants have a rounder face compared to individuals with *NIPBL* variants and this seems more marked in individuals with a Rett-like phenotype than in individuals with *SMC1A* variants in general (Figure 6.1).

We considered a cluster analysis of signs and symptoms to determine which set of phenotypical characteristics is more similar to each other in one sub-phenotype than in another, but the total numbers were too small to allow for meaningful results.

The exact phenotype of the subgroup of individuals with *SMC1A* variants with an epileptic encephalopathy and severe-profound intellectual disability has not emerged yet, but it is likely that more individuals will be recognized as exome sequencing is increasingly used worldwide. This may allow better insight whether the phenotypes are truly separate or rather ends of a spectrum. In the Netherlands, five of the thirteen patients known with *SMC1A* pathological variants have an epileptic encephalopathy phenotype (Table 6.5). Possibly this phenotype is much more common than anticipated. The mutations of individuals with the epileptic encephalopathy are spread all over the gene and a

clear correlation does not appear (Figure 6.3). All mutations are nonsense or frameshift mutations except one missense mutation (SMC1ANL001; Table 6.5), located at the first part of exon 1, in which functional studies have indicated it to cause a loss of function as well (Dr. Erwan Watrin, personal communication, 2017). To date there is no known exon 8 *SMC1A* mutation.

SMC1A incompletely escapes X-inactivation.[13,15-16,23,29,34] Since there is no altered level of *SMC1A* transcripts and mutant proteins maintain a residual function,[24] and a dominant negative effect is considered the pathogenic mechanism in females with a *SMC1A* variant, the level of allelic preferential expression might be one of the factors contributing to the wide phenotypic variability observed in these patients.[17] In the present study there is a remarkably distorted ratio of males and females with a *SMC1A* variant for non-missense variants. The small number of males with non-missense variants had in frame deletions. This seems to indicate that other types of mutations are not tolerated in males, likely leading to early miscarriages, and explaining the distorted gender ratio. We evaluated spontaneous abortions reported by the families: 22/49 (45%) families reported no known miscarriages, 3/49 (6%) families experienced a single miscarriage, and one (2%) family (with mutation c.3145C>G; p.Arg1049Gly) had 6 miscarriages for which no cause could be found (no data on the other 24 families). Although normal values for spontaneous miscarriages in the various populations are not available it seems likely the miscarriage rate in the families in total is not increased.

The present study has several limitations. First, the CdLS-like phenotype in the SMC1A group is very likely overestimated due to acquisition bias, as patients suspected to have CdLS were referred to CdLS specialists, whom we specifically invited to participate in the study. The specialists confirmed that all included individuals with *SMC1A* variants were suspected to have CdLS. We contacted the UK 100,000 genome project in order to obtain an estimate of the frequency of *SMC1A* mutations in a large group of individuals, but at present such a detailed question cannot be answered yet (Richard Scott, personal communication, 2016). Therefore, the phenotype presented here is mainly representative of the phenotype similar to CdLS and less of the epileptic encephalopathy “Rett-like” phenotype. Although numbers are small, prevalences of these two subphenotype groups in the Netherlands indicate that the latter phenotype might occur even more frequently than the former.

Furthermore, cross sectional data collection using binary categories to describe features hampers the reporting of gradations and changes over time. Moreover, as the somatic questionnaire was extensive, we had to deal with missing data from several patients.

These experiences underline the importance of using standardized, longitudinal databases.[47] Performing research with a large group of collaborating physicians may have influenced phenotype evaluations, especially with respect to facial morphology. As differences between the presently in person examined patients and patients evaluated by a group of others were small, it seems unlikely that this has played a major role.

Data on cognitive and adaptive functioning and the measures used are often missing in the medical file, and if these are available, different developmental and behavioral assessment instruments are typically used. We strongly advocate direct and indirect assessments of cognitive and adaptive functioning and behavior of affected individuals, performed by behavioral scientists, and that these always form an integrated part of an interdisciplinary evaluation.

We conclude that *SMC1A* variants can result in different phenotypes: a phenotype that overlaps with mild manifestations of CdLS and one that overlaps with Rett syndrome. Likely the increasing use of exome and genome sequencing will lead more frequently to identification of *SMC1A* variants in individuals not clinically suspected of CdLS. Large series of individuals recognized in this way should facilitate cluster analyses that may allow either separating distinct SMC1A phenotypes or merging these into one spectrum. Such better insights will allow better genetic counseling, allow health care professionals to answer the primary question of parents what it means if a *SMC1A* variant is found in their child.

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APPENDIX 6.1

Report form SMC1A study

PATIENT'S DATA

Name/initials
Gender M/F
DOB (dd-mm-yy)
SMC1A mutation
Age at clinical diagnosis

NEONATAL PERIOD

Gestational age
Weight at birth
Length at birth
Skull circumference at birth
Apgar score 1' 5'
Neonatal problems
Feedings problems in infancy

AUXOLOGICAL DATA

Age at (last) examination
Weight
Length/Height
Head circumference

NEURODEVELOPMENTAL DATA

Sitting independently
Walking independently
First words
First sentences
IQ
Age at IQ evaluation
Scale used

MAJOR MALFORMATIONS

Upper limb reduction defect (uni/bilat)
oligodactyly/phocomelia
Other upper limbs signs:
small hands
single palmer crease

small thumb
prox placed thumb
clinodactyly 5th finger
syndactyly 5th finger
short 4th metatarsal
limited elbow extension
Lower limbs signs
small feet
syndactyly toes 2+3
talipes
Congenital heart disorder (if, yes, describe)
Other malformations
diaphragmatic hernia
renal anomaly (uni/bilat)
intestinal malrotation
pyloric hypertrophy
bowel atresia
annular pancreas

DYSMORHIA

Brachycephaly
Low ant/post hairline
Arched eyebrows
Synophrys
Long eyelashes
Depressed nasal bridge
Anteverted nostrils
Broad nasal tip
Long/featureless philtrum
Thin upper vermillion
Downturned corners mouth
Palate (highly arched/normal)
Cleft palate/uvula
Micrognathia
Widely spaced teeth
Bluish tinge around eye/nose/mouth
Low set ears
Dysplastic ears
Short neck
Cutis marmorata
Hirsutism

SEIZURES

age of onset seizures
type of seizures
CNS anomalies
MRI
EEG anomaly without clinical seizures

GASTROESOPHAGEAL REFLUX (GER)

age of diagnosis
GER severity (mild, moderate, severe)
Barrett's esophagus
GER management (med, diet, surgery)

OTHER

Endocrine abnormalities
Hyper/hypotonia/spasticity
Genital (cryptorchism, small penis, hypospadias)
Small nipples/umbilicus
Hearing loss
Myopia
Glasses
Strabismus
Ptosis
Nystagmus
Cataract
Incontinence feaces/urine
Obstipation
Voice
Sensitivity to pain subjectively normal (tested?)
Cancer
Other medical problems

BEHAVIOR

If problems, please describe:
Age of onset of behavioural problems

7

Wel-doen en niet-schaden

Behandeling van zelfverwondend gedrag bij mensen met een verstandelijke beperking

Sylvia Huisman
Margreet Walinga
Raoul Hennekam

Submitted

Dames en Heren,

“Dokter, mijn dochter slaat zo hard op haar oor, dat er nauwelijks nog iets van haar oor over is. Alstublieft, laat dit stoppen. Er móet iets gebeuren!” Zelfverwondend gedrag bij mensen met een ernstige verstandelijke beperking betekent voor artsen een grote uitdaging. Aan de hand van casuïstiek presenteren we recente inzichten en handvaten voor een effectieve aanpak.

Patiënt A is een 25-jarige opgewekte vrouw met een zeer ernstige verstandelijke beperking en autisme bij het Cornelia de Lange syndroom. Als baby heeft ze uitgesproken voedingsproblemen. Het is moeilijk contact met haar te krijgen. Omgang met andere kinderen verloopt moeizaam. Ze kan urenlang bezig zijn met gidsen in reepjes scheuren. Geleidelijk ontstaan meervoudige, complexe gezondheidsproblemen: gastro-oesofageale reflux, met oesofagitis en recidiverende anaemieën, obstipatie, epilepsie, oorontstekingen en visusproblemen. Later zal ze gebitsproblemen, menstruatieproblemen, urineweginfecties en slaapproblemen krijgen. Door duwen en slaan van haar broertje en anderen is haar gedrag in de thuissituatie niet meer hanteerbaar. Op 8-jarige leeftijd wordt ze in een zorginstelling opgenomen.

Een jaar later begint ze te op haar tong, onderlip, vingers, handen en onderarmen te bijten. In die periode spelen reflux oesofagitis met ijzergebreksanemie, obstipatie en een sinusitis. Vanaf 14-jarige leeftijd staat het wrijven en drukken van haar rechter oor en wang over en op haar schouder op de voorgrond, met een grote, chronisch ontstoken wond aan haar oorschelp en wang tot gevolg. Daarnaast bonkt ze een periode met haar hoofd tegen harde voorwerpen en laat ze zichzelf hard tegen de grond of tegen de muur vallen. Er worden afwisselend medische en gedragsbehandelingen ingezet. Ook worden psychofarmaca en vrijheid beperkende middelen, zoals armkokers en Zweedse band toegepast. Het effect is onvoldoende, het ernstige zelfverwondend gedrag houdt aan. Begeleiders raken overbelast en wisselen vaak. De ouders van A zijn bezorgd, omdat ze zien dat het steeds slechter gaat met hun dochter en ontevreden, omdat verbinding met het team van begeleiders ontbreekt. Er is sprake van terugkerende handelingsverlegenheid, machteloosheid en gebrek aan onderling vertrouwen bij alle betrokkenen.

Als A 23 jaar oud is, wordt opnieuw het Centrum van Consultatie en Expertise (CCE) geraadpleegd. De CCE consulenten sporen het management aan om visie en beleid op zorg en behandeling voor mensen met ernstige verstandelijke beperkingen en complex gedrag te ontwikkelen. Gedragsdeskundige en arts voor verstandelijk gehandicapten (AVG) stellen met ouders en begeleiders een gezamenlijk, interdisciplinair behandelplan

op. Het integrale behandelplan is gericht op ontwikkelen van positief gedrag, het stimuleren van kwaliteit van bestaan, het bieden van wondzorg en het bewaken van gezondheid. De wonden helen. Ouders en A maken na lange tijd weer uitjes naar de McDonalds.

Patiënt B is een 12-jarig actief meisje met een ernstige verstandelijke beperking die alle belangrijke kenmerken toont van het Cornelia de Lange syndroom. Ze woont thuis en gaat overdag naar een kinderdagcentrum. Vanaf de geboorte zijn er ernstige voedingsproblemen met spugen en gastro-oesofageale reflux, waarvoor B twee maanden wordt opgenomen en met sondevoeding wordt gestart. Ook daarna blijven ziekenhuisopnames nodig vanwege voedingsproblemen, gastro-oesofageale reflux, spugen en luchtwegproblemen waaronder recidiverende pneumonieën. Op 2-jarige leeftijd wordt de neussonde vervangen door een PEG sonde. Op 6-jarige leeftijd krijgt B. gehoorapparaatjes.

Ze ontwikkelt stereotiepe bewegingen zoals tikken tegen het hoofd. Geleidelijk aan begint het zelfverwondend gedrag en op 8-jarige leeftijd wordt ze opgenomen in het ziekenhuis in verband met knijpen van de bovenarmen tot bloedens toe. Epilepsie wordt uitgesloten. Een jaar later begint het krabben aan eczeem aan haar rechter oor, dat door wrijven en slaan toenemend ernstig beschadigd wordt. Er vindt operatieve correctie plaats aan de oorschelp. ’s Nachts krijgt ze armkokers om het slaan en wrijven te verhinderen. Soms bonkt ze met haar achterhoofd op een hard voorwerp of harde achtergrond. Ouders maken zich grote zorgen en voelen zich machteloos.

Het CCE wordt geconsulteerd. Gedragsdeskundige, kinderpsychiater en AVG maken samen met ouders een integraal behandelplan. Communicatie en dagprogramma worden beter op B. afgestemd en gastro-oesofageale reflux en obstipatie worden behandeld. De behandeldoelen zijn gericht op het verminderen van zelfverwonding en op een zo normaal mogelijk leven van B en haar familie. Het lukt om gebruik van de armkokers af te bouwen. B. krijgt een extra indicatie voor extra begeleiding. Ouders krijgen weer vertrouwen en vinden hun kracht terug. Het oor herstelt, B. ontwikkelt zich gestaag en de familie geniet van vakanties met elkaar.

Patiënt C is een 37-jarige innemende man met een ernstige verstandelijke beperking op basis van het Cornelia de Lange syndroom. Vanaf de geboorte heeft hij last van spugen, gastro-oesofageale reflux met periodes van ijzergebreksanaemie, ondergewicht, obstipatie en onderste luchtweginfecties. Op de kleuterleeftijd krijgt hij anti-epileptica in verband met schokken, hoewel epilepsie niet is aangetoond.

Op zijn 8^{e} jaar begint het zelfverwondend gedrag en wordt hij opgenomen in een zorginstelling. Hij bijt zichzelf in de handen en onderarmen, bonkt met zijn hoofd tegen harde

voorwerpen en slaat zichzelf tegen zijn hoofd, oren en ogen. Het zelfverwondende gedrag neemt tijdens zijn puberteit verder toe. Hij maakt daarbij een angstige en ontstemde indruk. Verschillende psychofarmaca worden gegeven met onvoldoende resultaat. Als hij 13 jaar is, wordt zijn gebit deels verwijderd vanwege zeer ernstige bijtwonden. Hij raakt blind aan een oog en slechtziend aan het andere oog t.g.v. een netvlies loslating, beiden vanwege het slaan op zijn ogen. Hij is slechthorend en zijn oorschelpen raken ernstig vervormd door het slaan. Handelingsverlegenheid, machteloosheid en angst ontstaan bij zijn behandelaars en begeleiders. Vanwege de ernstige verwondingen worden steeds drastischer vrijheid beperkende maatregelen getroffen. Uiteindelijk draagt hij een helm, zit hij in een rolstoel met voorblad, draagt hij handschoenen met stootkussens, polsbanden en voetbanden. Ook 's nachts ligt hij vastgebonden in een hesje, polsbanden en een Zweedse band. Zodra zijn handen en voeten worden losgemaakt, begint hij zichzelf te slaan, te bijten en te bonken.

Na verhuizing naar een andere woning, vindt hij zijn nieuwe plek. Stapsgewijs ontwikkelen en evalueren gedragsdeskundige en AVG met ouders en begeleiders een gezamenlijk, interdisciplinair behandelplan. Zijn gezondheidsproblemen, voornamelijk gastro-oesofageale reflux en obstipatie, zijn beter onder controle. Vanwege de sterke wisselwerking tussen C. en zijn begeleiders wordt het leren omgaan met angst een van de belangrijkste pijlers van de behandeling. Het versterken van basisveiligheid en het bevorderen van kwaliteit van bestaan zijn de uitgangspunten voor beleid. Uiteindelijk kunnen alle vrijheid beperkende middelen succesvol worden afgebouwd. Hij geniet samen met zijn ouders van de wekelijkse bezoeken bij zijn ouders thuis.

Beschouwing

Zelfverwondend gedrag (ZVG) wordt gedefinieerd als 'abusievelijk, repetitief gedrag dat leidt tot zelf toegebrachte, aantoonbare beschadiging van het lichaam, zonder de intentie van suïcide of seksuele bevrediging. Het gedrag heeft de neiging tot persisteren.'[1] Karakteristieken van het ZVG zijn ontstaansleeftijd, vorm, plaats, frequentie, duur, intensiteit en gevolgen als lichamelijke beschadiging en als problemen in het dagelijks functioneren. Met deze karakteristieken kan het ZVG worden beschreven en gemeten.

ZVG komt bij mensen met een (zeer) ernstige verstandelijke beperking (ontwikkelingsleeftijd tot 0–3,5 jaar) vaak voor, maar kan ook bij mensen met een matige of lichte verstandelijke beperking optreden. Dat geldt in het bijzonder voor bepaalde syndromen, zoals het Cornelia de Lange syndroom (CdLS), waarbij ~60% van de mensen met dit syndroom ZVG toont.[1-3]

De gevolgen kunnen zeer ingrijpend zijn. Soms ontstaan er onherstelbare en zelfs levensbedreigende beschadigingen aan het lichaam. Het ZVG kan iemands functioneren en diens ontwikkeling ernstig belemmeren. Het gedrag veroorzaakt vaak grote machteloosheid, zowel bij de patiënt, de familie als bij de hulpverleners.

De praktijk

ZVG is geen diagnose, maar een verschijnsel van een onderliggend probleem dat zich uit via gedrag. Huisartsen, kinderartsen, internisten, (kinder)psychiaters, (kinder)neurologen en artsen voor verstandelijk gehandicapten (AVG) worden regelmatig bij ZVG geconsulteerd. Zij hebben een belangrijke taak in de diagnostiek en behandeling van medische problemen die onderliggend kunnen zijn aan of kunnen samenhangen met het ZVG.

Bij mensen met een ernstige verstandelijke beperking komen gezondheidsproblemen als gastro-oesofageale reflux ziekte, obstipatie, otitiden, gebitsproblemen en slaapproblemen veel vaker voor. Pijn kan een uitlokkende of onderhoudende rol spelen bij ZVG.[1,4-6] De gezondheidsproblemen, en daarmee de pijn, kunnen in het algemeen goed met medicatie, dieet en soms andere ingrepen behandeld worden. Terughoudendheid met psychofarmaca is op zijn plaats, want deze medicijnen zijn doorgaans niet of nauwelijks effectief.[7] Een gedragsmatige aanpak is vaak onontbeerlijk, want interacties met de omgeving spelen via operante conditionering vaak een uitlokkende en onderhoudende rol.[8] Echter, gedragsmatige interventies kunnen veel aan effectiviteit inboeten als pijn door een medische oorzaak blijft bestaan. Andersom kan ZVG persisteren als de medische oorzaak van de pijn adequaat is behandeld, maar het gedrag is geconditioneerd.

Daarom is bij aanhoudend ZVG aan te raden dat een gedragsdeskundige en AVG, soms aangevuld met een gespecialiseerde psychiater, met ouders en begeleiders een gezamenlijk, integraal behandelplan uitvoeren. Verwijzing kan via behandelcentra en poliklinieken voor mensen met een verstandelijke beperking of via het CCE. Soms zijn langdurige, interdisciplinaire behandeltrajecten geïndiceerd. Na het verminderen of verdwijnen van het ZVG is het cruciaal om succesvolle interventies, zeker op het gebied van ontwikkeling en kwaliteit van bestaan, en de randvoorwaarden, levenslang te bewaken.

Dames en Heren, de gevolgen van zelfverwondend gedrag kunnen uiterst ingrijpend zijn voor patiënten en hun families. Het gedrag kan tot handelingsverlegenheid leiden, ook bij artsen. Hoe kunnen artsen weldoen? Artsen kunnen bij ZVG het beste doen wat ze bij andere hulpvragen ook doen: diagnostiek en behandeling van medische problemen. En mocht dat niet afdoende zijn, dan is verwijzing naar een interdisciplinair behandelteam

van gedragsdeskundige en arts voor verstandelijk gehandicapten, soms aangevuld met een gespecialiseerde psychiater, geïndiceerd.

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8

‘Cri du coeur’ Self-injurious behavior

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Submitted

SELF-INJURIOUS BEHAVIOR

'My boy bangs his head so badly. It never stops, wounds don't heal, his face looks terrible. This *has* to end! Doctor, please! DO something!' When individuals with intellectual disability and their parents, are in such a desperate position, they are mostly faced with physicians with a lack of knowledge and experience regarding self-injurious behavior (SIB). The median SIB prevalence in this population is 30%, leading up to thousands of cries for help per year in the UK.[1] We want to ask attention for the one most effective solution: collaboration with behavioral specialists.

SIB can be defined as "non-accidental behavior resulting in demonstrable, self-inflicted physical injury, without intent of suicide or sexual arousal; typically, the behavior is repetitive and persistent".[1] SIB characteristics (prevalence, age of onset, topography, nature) vary between syndromes, indicating genetic influences in etiology and pathogenesis.[1] The physical damage can be life-threatening and the impact on daily functioning significant. Consequently SIB leads to compromised mental health in parents, high service needs and excessive health care costs.

SIB is a symptom of an underlying problem and can be a sign of or response to pain.[2] SIB is associated with common medical conditions (gastro-esophageal reflux disease, otitis media, constipation, dental disease).[3] Careful medical evaluation is required, as these health problems are amenable to treatment.

Psychologists and other behavioral specialists deal with SIB in their own way. They consider SIB from a completely different perspective and have shown that SIB is strongly associated with cognitive disabilities, co-morbid conditions (autism), social interaction and environmental events.[4,5] SIB can develop due to learning mechanisms that can be reinforced by external stimuli such as social interaction, or by internal stimuli such as pain. The implications for effective interventions are obvious: treatment of a physical cause may relieve the trigger, but the behavior may persist due to conditioned mechanisms. The opposite, lack of success of behavioral interventions if the physical trigger is not removed, is equally true.

Both physicians and behavioral specialists will keep failing patients with SIB if they omit integration of both perspectives. The bottom line is interdisciplinary collaboration. Of course, physicians should perform according to their usual high medical standards when consulted, as they do for any other request for medical help. But SIB also requires the expertise of behavioral specialists. Interdisciplinary collaboration is a conditio sine qua non to understand, treat and prevent the devastating self-harm. "United we stand."

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9

Summary and general discussion

SUMMARY

Chapter 1

Self-injurious behavior is a common and potentially devastating behavior in people with CdLS. Cure and prevention are not possible, since cause and pathogenesis are still unknown. The aim of this thesis is to evaluate SIB phenomenology, etiology and pathogenesis in order to develop advanced diagnostic and targeted treatment regimes.

During this interdisciplinary PhD trajectory CoDeLaGe (acronym for 'Cornelia de Lange Gedragsonderzoek'), we performed a translational study on SIB in people with CdLS and focused on somatic (genetic, physical, medical) factors in relation to SIB. We combined literature reviews and patient research. This thesis describes how we developed hypotheses on the role of somatic factors in SIB and what that means for future research.

Chapter 2

In the review of SIB phenomenology in people with intellectual disability of unknown etiology and in genetic syndromes, we highlight twelve genetic syndromes of which phenomenological data are available: Angelman Syndrome (AS), Cornelia de Lange Syndrome (CdLS), Cri du Chat Syndrome (CdCS), Down Syndrome (DS), Fragile X Syndrome (fraX), Lesch-Nyhan Syndrome (LNS), Lowe Syndrome (LS), Prader-Willi Syndrome (PWS), Rett Syndrome (Rett), Smith-Magenis Syndrome (SMS), Tuberous Sclerosis Syndrome (TSC), and Williams-Beuren Syndrome (WBS). Numerous authors have used various SIB definitions. The main elements in these definitions were self-initiated; directed towards the body; involves specific forms and body parts; contains repetition; can be chronometrically or chronographically quantified (frequency, duration, intensity), and its effects or extent of tissue damage can be classified. Disqualifiers are intent of suicide or sexual arousal. Hence, we propose to define SIB as non-accidental behavior resulting in demonstrable, self-inflicted physical injury, without intent of suicide or sexual arousal. Typically SIB is repetitive and persistent. SIB phenomenology can be characterized by topography (such as form, localization) and chronography (such as age of onset, frequency, duration). We summarize prevalence and main SIB characteristics across twelve etiologically distinct entities and identify influencing factors. SIB is associated with behavioral factors such as the level of intellectual disability, co-morbid conditions (such us autism, stereotypic behavior), environmental conditions (such as demand, denial, attention) and can be reinforced by internal or external stimuli due to an operant learning mechanism. However, the association with somatic (genetic, physical, medical)

factors has hardly been evaluated yet. Most publications on SIB fail to report on even basic physical examinations or medical evaluations of common medical conditions and potential physical causes of SIB, such as constipation, gastro-esophageal reflux disease (GERD), otitis media, and dental problems. We demonstrate that the prevalence of SIB in LNS, SMS, PWS, CdCS and CdLS is noticeably higher than in individuals with ID in general, and that characteristics such as age of onset and topographies differ widely across syndromes. Each syndrome is caused by a mutation in a different gene, and this allows detection of several pathways that may lead to SIB. Studying these with the behavioral consequences as specific aim will be an important step toward targeted early interventions and prevention. Therefore, we stress the importance of accurate and detailed physical and behavioral phenotyping using uniform definition and standardized methods.

Chapter 3

In Cornelia de Lange Syndrome (CdLS) six causative genes are known explaining ~55–65% of cases. We hypothesized that mosaicism might explain some of the remaining ~35–45% of cases without detectable mutation in DNA derived from lymphocytes. We obtained buccal swabs of 8 mutation positive and 13 mutation negative individuals with clinically diagnosed CdLS after informed consent. Buccal cells were screened for *NIPBL* mutations using Sanger sequencing techniques. Sufficient DNA for analysis could be obtained in 21/22 individuals. In all six tested individuals with a known *NIPBL* mutation and in two with a known *SMC1A* mutation, the mutation was confirmed in buccal cells. In 10 of the 13 tested individuals (77%) without detectable mutation in lymphocytes a *NIPBL* mutation could be detected in buccal cells. Clinically there were no significant differences between patients with a germ-line and mosaic *NIPBL* mutation. Somatic mosaicism for a *NIPBL* mutation is frequent (10/44; 23%) in clinically diagnosed CdLS individuals. Adding buccal swabs to CdLS diagnostics improves confirmation rates significantly (from 61% to 84%). DNA derived from buccal cells using a buccal swab is a reliable and efficient way to investigate whether a patient may have a somatic mosaicism if lymphocyte analysis has failed to show a mutation. Obtaining buccal swabs at the time the initial blood sample is obtained will facilitate adequate molecular analysis of clinically diagnosed CdLS patients.

Chapter 4

Individuals with rare disorders and their families are in great need of sufficient and reliable information. Reliable information means information of large groups of patients. In rare disorders with – by definition – small numbers, one should think big: involve

as many patients as possible from a single country or even from as many countries as possible all over the world. The internet pre-eminently marks an era with unprecedented opportunities for patient care, with particular benefit for individuals with rare disorders and their families. Their handicap of low numbers vanishes and even becomes a strength, as small, motivated and well-organized international support groups allow for fruitful collaborations for research. Support groups are extremely helpful in contacting groups of individuals with rare disorders. They are often organized internationally and can easily reach out to their members around the world. They have their own website and communicate via blogs, Facebook pages, or by e-mail. They manage a digital infrastructure, and have the trust of their members. These families are also the most important sources of information: nowhere is the number of bits of knowledge on development, health and behavior as large as with the individuals with the rare disorder and their families, given they experience the disorder 24/7. The sum of this knowledge is what all affected individuals like to know and constitutes a treasure trove of information. A digital survey was posted on the CdLS website asking families to indicate which research topic would be most important to them. The families prioritized self-injurious behavior, so such a research project was started. Participation of the CdLS families was extremely high and allowed a fast and effective study flow for online data collection via behavioral (translated in seven languages) and health questionnaires. The information gathered systematically over a long period of time will become an increasingly valuable treasure for everyone involved in care or research for this disorder. In analogy of Wikipedia ('wiki' is 'quick, quick' in Hawaiian and 'encyclopedia'), we have called our longitudinal database 'waihonapedia' from the Hawaiian word 'waihona' meaning 'treasure'. Waihonapedia requires a reliable diagnosis in all participating affected individuals, confirmed by biochemical, metabolic or molecular tests if possible. The waihonapedias will provide unprecedented information for everyone studying the rare disorder and everyone who plans interventions and would like to compare results to the natural history.

Chapter 5

Careful study and accurate description of behavior are important to understand behavioral challenges in individuals with CdLS. In this systematic review we present data from 43 eligible papers that studied behavior in CdLS. It highlights five areas of interest, namely developmental level, autism, SIB, physical conditions, and use of medication. Mutation analyses were only performed in six studies (14%). Participants were mostly categorized in the severe/profound developmental level. Methodology and quality were very heterogeneous, as well as reporting occurrence of autism. SIB

was reported in 15 papers. Physical conditions were reported in 21 studies, especially hearing and vision impairments and limb defects. Only nine studies mentioned details about medication. This review also considered methodological properties according to adjusted Cochrane quality criteria. Eight papers (19%) used only questionnaires for data collection, 34 papers (79%) used two or more methods (e.g. questionnaire, interview, and/or observation) of data collection, and 14 papers used a direct assessment tool (33%). Twenty studies used one or more comparison group(s) (47%). Comparison of presented results was hindered by variety in reported data, heterogeneous assessment tools and methodological differences. Improving our understanding of behavioral characteristics in CdLS requires uniform methodology. We propose a 'criterion standard' of items and instruments (cognition, adaptive functioning, autism, sensory processing, SIB, physical characteristics, level of support and living environment) that can ideally be used in assessment of behavior and development. Furthermore, we stress the importance of direct assessments besides questionnaires. This will improve understanding of behavior in the context of developmental level and daily functioning.

Chapter 6

CdLS is caused by variants in different genes that all encode proteins of the cohesin complex. The entities tagged as cohesinopathies have been considered overlapping entities. Sharing of major features (limited growth, several facial features, limb malformations, intellectual disability) across cohesinopathies supports the hypothesis that a disturbed cohesin function contributes to these characteristics. Contrariwise, if manifestations of the syndrome diverge, this may suggest different or additional functions of the cohesin genes, i.e. moonlighting.

We performed an international, interdisciplinary study on 51 individuals with *SMC1A* variants for physical and behavioral characteristics, and compared results to those in 67 individuals with *NIPBL* variants. *SMC1A* variants are known to cause a phenotype resembling CdLS. Individuals with *SMC1A* variants can resemble CdLS, but manifestations are less marked compared to individuals with *NIPBL* variants: growth is less disturbed, facial signs are less marked (except for periocular signs and thin upper vermillion), there are no major limb anomalies, and they have a higher level of cognitive and adaptive functioning.

Exome sequencing has allowed recognition of *SMC1A* variants in individuals who do not resemble CdLS. In the Dutch group five of 13 individuals (all females) had a phenotype that shows a remarkable resemblance to Rett syndrome: epileptic encephalopathy, severe or profound intellectual disability, stereotypic hand movements such as 'hand

wringing', and (in some) regression. Their missense, nonsense and frameshift mutations are evenly spread over the gene.

SIB is more frequent and more severe in the NIPBL group compared to the SMC1A group. The absence of this behavioral trait in patients with *SMC1A* variants and epileptic encephalopathy, and also in other cohesinopathies, such as individuals with CdLS due to variants in other genes and in individuals with Roberts syndrome, is in favor of the hypothesis that SIB may be caused by another gene function of *NIPBL*, i.e. moonlighting hypothesis. It also suggests that the level of intellectual disability is not a deciding factor in SIB in the NIPBL group. Gastro-esophageal reflux disease and constipation are equally common in the NIPBL and SMC1A groups. This argues against SIB being secondary to these physical conditions in the NIPBL group. Therefore, further studies into cohesinopathies and their associated genes, should not only be aimed at the cohesion and related functions, but should also take into account other potential functions of these genes.

We conclude that *SMC1A* variants can result in different phenotypes: a phenotype that overlaps with mild manifestations of CdLS and another that overlaps with Rett syndrome. It is likely the increasing use of exome and genome sequencing will lead more frequently to identification of *SMC1A* variants in individuals not clinically suspected of CdLS. Large series of individuals recognized in this way should facilitate cluster analyses that may allow either separating distinct SMC1A phenotypes or merging these into one spectrum. These higher-quality insights will allow for better genetic counseling, allow health care professionals to answer the primary question of parents of what it means if a *SMC1A* variant is found in their child.

Chapter 7 and 8

To give the attention needed to this topic we have put a lot of effort into publications intended for a broad medical audience. Most people visit mainstream medical services and do not have proper access to specialized care regarding SIB. We forwarded a *cri du coeur* of parents along with recent insights and tools for better treatment to opinion-stating and educational articles in both international and national peer-reviewed general medical journals. The main message for physicians is aimed at what they are trained for and do best: diagnostics and treatment of medical problems. In case that might not be sufficient and effective, they need to refer to easily accessible interdisciplinary teams in specialized centers.

GENERAL DISCUSSION

SIB can be a devastating problem for the individuals who harm themselves, and who may experience significant physical and psychological distress due to their SIB. It is devastating for the parents who see progressive damage to the one they love and feel they cannot provide the protection they want to offer as parents. It is devastating to caregivers who may feel ineffective and can experience this as a failure of their care. SIB often starts in early childhood and can aggravate into a destructive and persistent problem with profound repercussions for a person's health and quality of life. At this point most patients with ID and SIB have to find their way through mainstream medical services and visit their physicians for this behavior problem that – while common – is exceptionally complex. Managing SIB can be an enormous clinical challenge for physicians, because they often do not know how to approach the problem.

SIB is not a diagnosis, but a symptom of an underlying problem. SIB can be a sign of or a response to pain and is associated with health conditions such as gastro-esophageal reflux disease (GERD) and otitis media.[1-2] These health conditions are highly common in people with ID and can be treated effectively. SIB patterns seem to be related to the cause (pain or other factors), quality of pain (acute or chronic) and location of pain in children with severe intellectual disabilities.[3] The physician must be alert to symptoms of underlying medical conditions and carefully evaluate individuals with SIB, as medical conditions provoking or prolonging SIB may go unrecognized, undiagnosed and untreated, specifically due to the impaired communications skills in patients with ID.[2] Studies demonstrate that individuals who exhibit SIB show non-verbal signs of pain and that treatment of painful medical conditions can relieve SIB.[1,3-4] However, little is known about the relationship between pain and SIB and the area is intriguing and highly challenging to investigate.

In the general population, it is common knowledge that tissue injury results in activation of peripheral nociceptors and amplification of central nervous system pain pathways that serve as a disincentive for injurious behavior. In a negative feedback loop descending inhibitory neurons in the central nervous system attenuate spinal nociceptive processing that decreases pain sensation. In people with aberrant spinal nociceptive signaling, amplified external pain stimuli may be required to incite descending inhibitory signals. Furthermore, people with GERD may engage in SIB to excite descending inhibitory circuits to attenuate visceral pain.[5] Additionally, histological and physiological research comparing SIB and non-SIB sites suggests that individuals who engage in SIB have altered peripheral innervation and neuroimmune and inflammatory activity.[4] These studies sug-

gest that repeated tissue damage due to chronic SIB resembles the state of neuropathic pain. In analogy to neuropathic pain, in persisting SIB hyperalgesia may be mediated by dysregulation of inflammatory, immune and nociceptive systems, and cytokines may act on the brain creating sickness-like behavior and sensitize sensory afferents contributing to pain hypersensitivity.[6] Instead of the conventional hypothesis that sensory processing is reduced and pain is absent or blunted, these studies suggest that individuals who engage in SIB may have an increased pain sensitivity and decreased pain inhibitory regulation. Additional research is warranted to examine the anecdotal evidence for a neuropathy and the presumption of a high pain threshold in CdLS.

Pain sensitivity and pain modification are regulated by the peripheral and central nervous system and can be dysregulated in neurodevelopmental disorders. Pain experience is regulated by the brainstem and brain. Preclinical and clinical pain research in genetic syndromes, such as fraX syndrome and Rett syndrome, reflects differences in pain processing across syndromes indicating different underlying molecular mechanisms may impact the structural and functional development of the peripheral and central nervous system in general, and of the nociceptive and modification systems in particular.[7-10] Very little is known about peripheral and central nervous system in CdLS. This makes it even more unfortunate that we did not achieve the neurological testing pilot that we initially had planned in a small series: nerve conduction times for neuropathy testing; MRI for measuring position, volume, structure and function of (parts of) the brains; lumbar punctures for neurotransmitters. As a neurobiological follow-up study in CdLS is warranted, the cohort in this thesis allows both comparison across subgroups that are well-defined by genotype or phenotype, i.e. *NIPBL* versus *SMC1A* and CdLS-like versus Rett-like or comparison with other genetic syndromes.

Limitations of this thesis dealing with rare disorders such as CdLS, and a heterogeneous topic such as SIB, include ascertainment bias. Both in the reviews and patient research participants were mainly recruited through support groups and specialized (tertiary, expertise) centers. The reviews demonstrated that only a small part of participants had molecularly confirmed diagnoses, especially in CdLS studies. The acquisition of participants for the mosaicism and the SMC1A studies was via the support groups or CdLS specialists working at tertiary facilities or centers of expertise. CdLS-like phenotype in the SMC1A group under study is likely overestimated due to acquisition bias, as patients suspected of CdLS were referred to CdLS specialists, whom we specifically invited to participate in the study. Furthermore, there were limitations regarding cross-sectional data collection using binary categories to describe features, which hampers the reporting of gradations and changes over time. Moreover, as the somatic questionnaire was

extensive, we had to deal with missing data from several patients. These experiences underline the importance of using standardized, longitudinal databases.[11] Performing research with a large group of collaborating physicians may have influenced phenotype evaluations, especially with respect to facial morphology. As differences between the presently in-person examined patients and patients evaluated by a group of others were small, it seems unlikely that this has played a major role. Data on development and behavior are often missing in the medical file, and if these are available, different assessments or instruments are typically used. For that reason a comparison of level of functioning and behavior is hampered in the international SMC1A group and the NIPBL group. We strongly advocate direct and indirect assessments of cognitive and adaptive functioning, and behavior using standardized instruments and performed by behavioral specialists.[12] Furthermore, we argue for recording these test results in medical files as they are guiding in communication and treatment of patients with ID.

Social sciences have made immense and impressive advances in understanding SIB. Psychologists and other behavioral specialists consider SIB from a selective perspective focusing on the behavior actor, operation, interactions, and their properties. They have shown that SIB is strongly associated with cognitive disabilities, co-morbid conditions (autism), social interaction and environmental events.[13-14] They have also demonstrated that SIB can develop due to a learning mechanism that is reinforced by external or internal stimuli. Although these social scientific insights have contributed to sound behavioral analytic techniques and efficacious behavioral interventions, SIB is persistent in a significant subgroup, suggesting an incomplete perspective and approach. On the other hand, in medical sciences very little attention has been paid to SIB, while there is increasing interest in somatic substrates in behavior and growing evidence that SIB is associated with pain.[3-4,15-18] The implications of one-sided and biased perspective for effective interventions are obvious: treatment of a physical cause may relieve the trigger, but the behavior may persist due to conditioned mechanisms. The opposite, lack of success of behavioral interventions if the physical trigger is not removed, is equally true. Both physicians and behavioral specialists will keep failing patients with SIB if they omit integration of both perspectives. In this thesis we conclude that there are hardly any studies available which evaluate SIB from both angles and unify these perspectives toward identifying underlying cause and informing treatment. Typically, social sciences have disregarded somatic substrates as an important cause of SIB, and medical sciences have ignored the behavioral machinery in a similar way. The obvious next step is to focus on how biological and behavioral mechanisms coincide and interact to cause and maintain SIB. By adding a genetic mindset combining genotypic with phenotypic

data to delineate somatic substrates, the different studies in this thesis contribute to consecutive hypotheses and recommendations for future research and new horizons for treatment development in CdLS and other entities.

Current developments are greatly driven by new diagnostic technologies such as next-generation sequencing (NGS) that will facilitate diagnosis extensively. NGS as a diagnostic tool will yield variants in many genes, e.g. *SMC1A*, and the meaning of these variants can only be understood in relation to clinical findings. To make a diagnosis we need accurate physical and behavioral phenotyping to analyze the consequences of these variants: next generation sequencing demands next generation phenotyping.[19] In the SMC1A physical study we made a first step to answer the primary question of parents of what it means if a *SMC1A* variant is found in their child. Furthermore, phenotypes may be caused by the actions of more than one gene, and epigenetic and environmental influences. To unravel the impact of these polygenic and multifactorial influences, continuous and consistent phenotyping, and iterative analyses are required. Understanding of molecular findings and mechanisms will allow more and better personalized medical care for all disorders, not least rare disorders.[19] Personalized medicine is the paradigm for (near) future mental and physical healthcare. Genetics determines personal liability, but metabolism defines the consequences of genetics plus environmental influences. Advances in DNA technologies, understanding of molecular biology and experience in dissecting phenotypes are essential requirements to make a leap forward to personalized healthcare. If we understand more of molecular etiologies of disorders and we extend molecular mechanisms to metabolic pathways, tailored therapy appears on the horizon (Figure 9.1). The bottom line is that SIB research demands an open mind and a firm scientific, interdisciplinary base.

Reflecting on the past six years of this PhD trajectory, one of the major eye openers for me was how attackable this interdisciplinary base has been, how understated molecular mechanisms are and how studying phenomenology from different angles can invigorate the foundation for integrated research on etiology and pathogenesis. To be frank, I had to accustom myself to this way of somatic reasoning and allowing for molecular mechanisms as the ground for SIB etiology: with the body in mind. By all means physicians and behavioral specialists have to change the way they think and act. Physicians should perform a complete physical evaluation and behavioral specialists a complete behavioral evaluation. Their all-inclusive findings will be the basis of an integrated analysis and intervention plan (Figure 9.2).

Separated from the Dutch mainstream physical and mental health care systems there is a third care system that gradually professionalizes and specializes the care for people

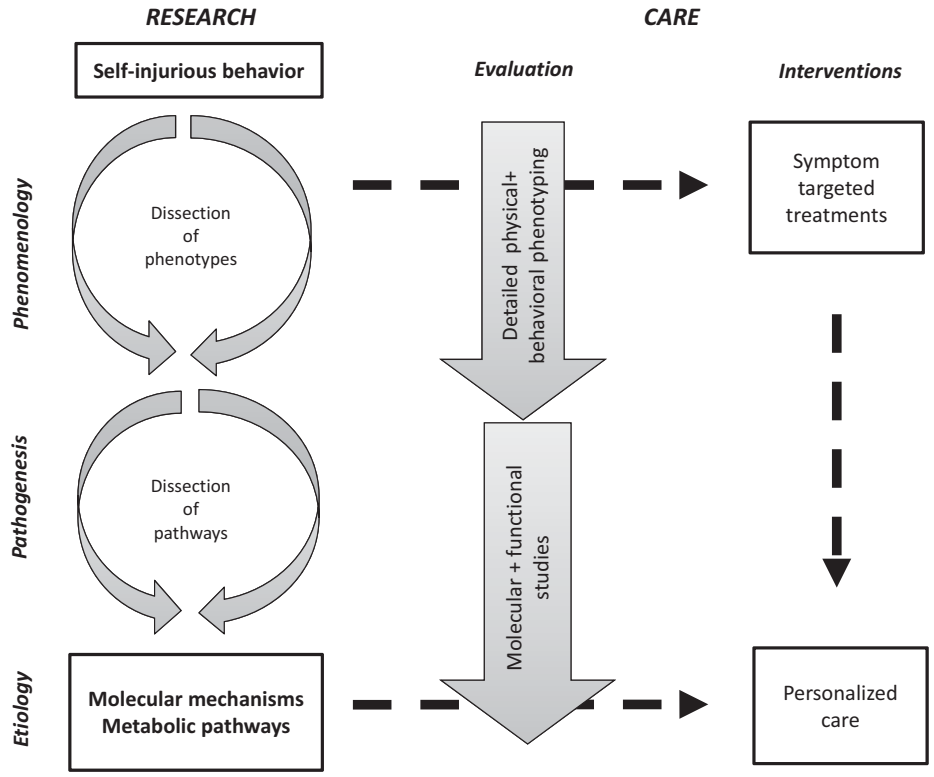

Figure 9.1 Model for developing SIB research and SIB personalized care.

with ID in which behavioral specialists and physicians for people with ID (ID physicians) increasingly take the lead and consistently build bridges towards the mainstream health care systems. We need a critical mass of these professionals to invigorate research and development. ID physicians should limit their general practice activities in favor of expanding their outpatient clinics capacity to offer properly accessible expertise on referral by physicians in mainstream services, if needed. Care centers for people with intellectual disabilities are privileged to have a large body of behavioral specialists, who often have an advisory role and who authorize care plans. More of these behavioral specialists should position themselves as experts and obtain training in behavior assessments and functional analysis, boosting the quality of behavioral interventions for people with SIB. For the sake of syndrome-specific expertise and SIB-specific expertise that are needed, a substantial portion of these ID physicians and behavioral specialists should specialize and combine diagnostics, treatment with research in tertiary centers or centers of expertise. Only then will we be able to improve developmental opportu-

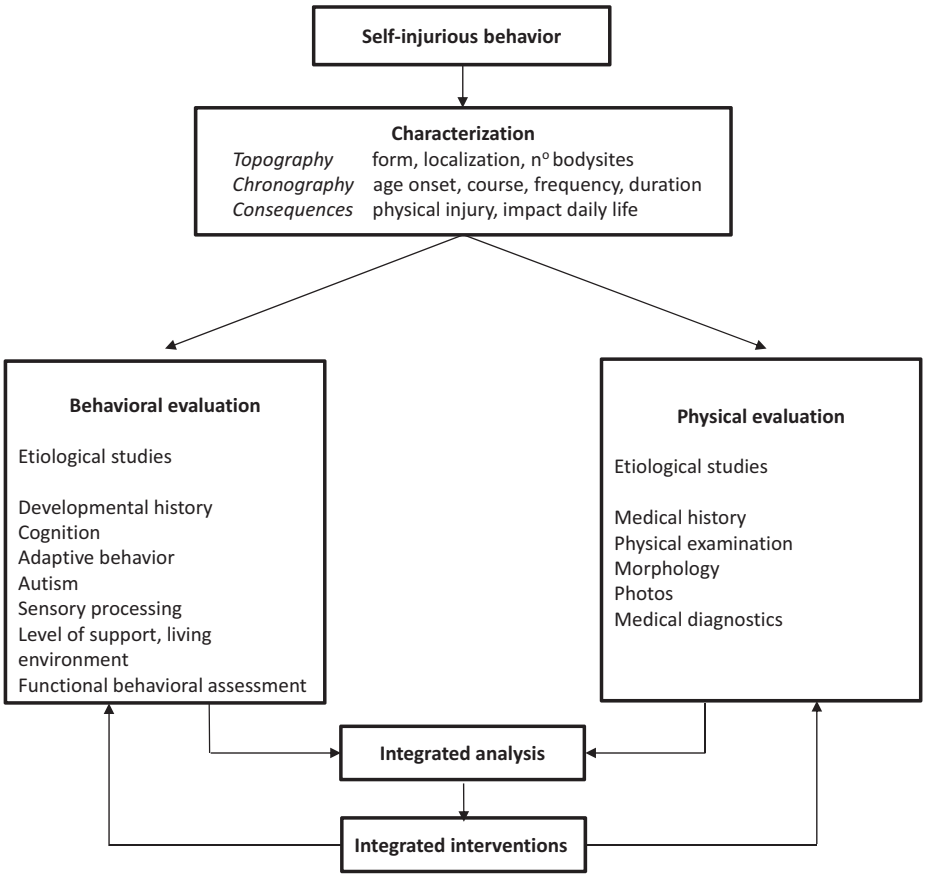

Figure 9.2 Interdisciplinary SIB work-up.

nities and health, and to prevent social stigmatization and (re)institutionalization at a young age.

The basic concept of looking into differences in SIB characteristics between etiologically distinct entities and combining this with coinciding physical or behavioral conditions is new and promising to SIB research. Cross genetic syndrome comparison, cross gene comparison, cross mutation (type, site) comparison is challenging, but may lead to better clues for somatic substrates in the etiology and pathogenesis of SIB. Approaching SIB from a molecular context is one of the core concepts and assets in this 'With the body in mind' thesis. During this PhD trajectory we started with some initial hypotheses on SIB in CdLS that we reviewed along the way (Figure 9.3). In the end we generalized the hypotheses scheme for genetic syndromes (Figure 9.4).

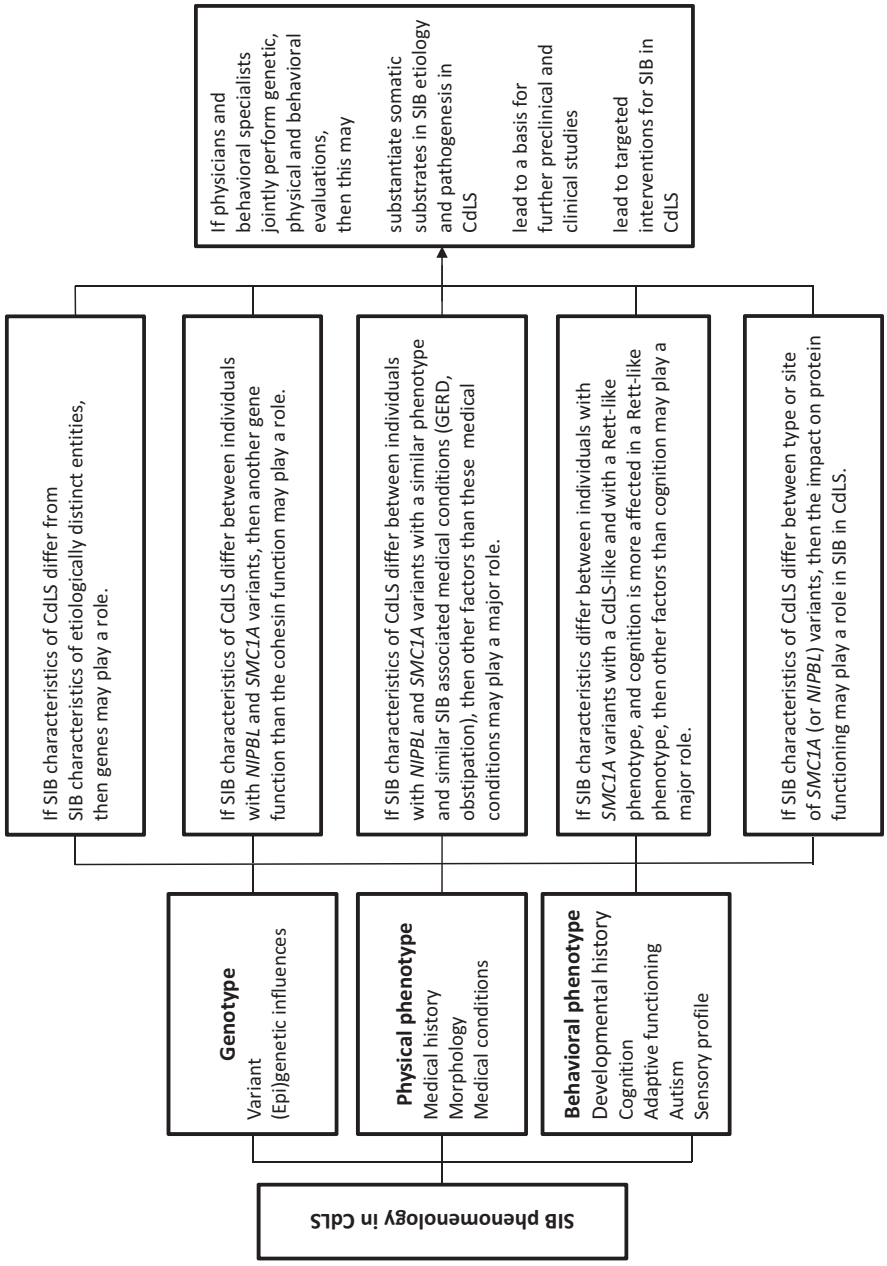

Figure 9.3 Hypotheses scheme SIB in CdLS.

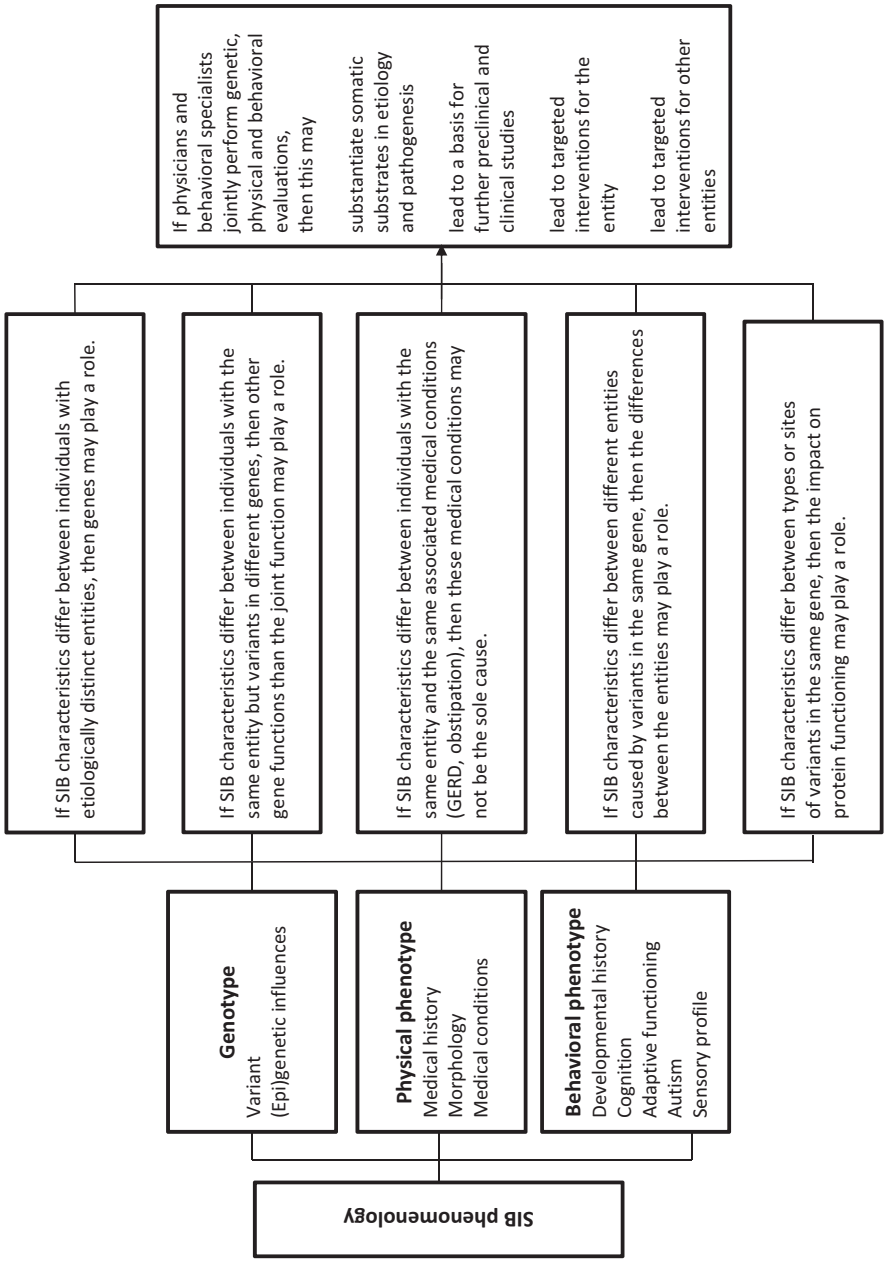

Figure 9.4 Hypotheses scheme SIB in genetic entities.

In this general discussion we targeted SIB and navigated 'with the body in mind' from a macro level to a micro level and back. We highlighted the importance of careful medical evaluation of health conditions provoking or prolonging SIB that may go unrecognized, undiagnosed and untreated in addition to accurate behavioral evaluation. We demonstrated – on a macro level – that SIB prevalence in several well-known genetic ID syndromes is noticeably higher than in individuals with ID in general and that other characteristics such as age of onset and topographies also differ widely across syndromes, which are -on a micro level- each caused by a different gene with a different action when mutated. Pathogenetic mechanisms behind these differences remain to be elucidated. It may be many different pathways can cause SIB. One may also hypothesize that these genes may have more than one action, one causing the syndrome and another causing SIB. Studying these multifunctional, 'moonlighting' proteins may show a common pathway to SIB.[21] The absence of SIB as a behavioral trait in individuals with *SMC1A* variants resulting in a Rett-like phenotype, and in individuals with other cohesinopathies, such as Roberts syndrome, and such as CdLS due to variants in the other cohesin genes, suggests a moonlighting hypothesis for *NIPBL*. Next generation phenotyping will be of utmost importance for further comprehensive phenotype – genotype studies and functional analyses as an important step towards targeted early interventions and effective prevention.

The main recommendations of this thesis are an interdisciplinary approach, accurate description of SIB phenomenology and careful evaluation of physical and behavioral phenotype in molecular confirmed individuals, that are essential in further etiological studies, especially if we add complementary approaches. Etiological studies of disorders have the tendency to focus on detection of disorder-causing mutations in affected individuals. Instead of traditional genetic studies that focused on the identification of disease-causing mutations in afflicted individuals, Chen et al. (2016) postulated a complementary approach to detect healthy individuals resilient to highly penetrant genetic disorders, so-called genetic superheroes. They indicated that detection of resilient individuals may provide clues to uncover protective variants that could inversely help to elucidate pathogenic mechanisms and new therapeutic strategies.[20] Accordingly, we could investigate why some people with CdLS caused by *NIPBL* variants do not engage in SIB, while most of them do.

In this thesis we started off with a hypotheses scheme that delineates a conceptual frame work of genetic, physical and behavioral determinants to deduce somatic substrates for SIB in CdLS (see Figure 1.1, General introduction). We initially aimed at developing a flow chart for diagnostic and management strategies. However, we soon realized

there was a lack of basic data so we decided to adapt and focus on description of SIB phenomenology and standardized evaluation of physical and behavioral phenotypes as the basis of an integrated analysis and intervention plan for daily practice (Figure 9.2). Furthermore, we refined the hypotheses scheme to substantiate somatic substrates in the etiology and pathogenesis of SIB in CdLS and other genetic entities (Figures 9.3–9.4), and we presented a perspective on how next generation phenotyping is fundamental to targeted therapeutic interventions and personalized care in the future (Figure 9.1).

Unfortunately, due to delays relating to ICT problems, we were not able to complete the SMC1A behavioral paper in time for this thesis. The SMC1A behavioral paper is complementary to the SMC1A physical paper in this thesis reflecting a mirroring approach to SIB in which we jointly analyze data on genotype, physical phenotype and behavioral phenotype. The paper will be one of the jewels of Paul Mulders' thesis. Study results of the mosaicism report, of the physical and behavioral SMC1A papers and both reviews in this thesis will also be used in the International Guidelines for Management in CdLS that will be published next year.

We hope people with SIB such as Dennis, their parents, carers, physicians, behavioral specialists and researchers may benefit from the results of this thesis.

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Samenvatting

INLEIDING (HOOFDSTUK 1)

"Dokter, mijn dochter slaat zo hard op haar oor, dat er nauwelijks meer iets van haar oor over is. Dit moet meteen stoppen. Doet u a.u.b. iets!"

In mijn dagelijks werk als Arts voor Verstandelijk Gehandicapten (AVG) ontmoet ik veel patiënten met zelfverwondend gedrag (ZVG), en hun families. Bij het Cornelia de Lange syndroom (CdLS) komt ZVG nog vaker (~55–60%) voor dan bij mensen met een verstandelijke beperking in het algemeen (~30%). Het ZVG kan leiden tot onherstelbare en zelfs levensbedreigende beschadigingen aan het lichaam. Het gedrag kan iemands functioneren en ontwikkeling ernstig belemmeren. Het veroorzaakt vaak grote machteloosheid, zowel bij de patiënt, de ouders als bij de hulpverleners. De gevolgen zijn soms zo ernstig, dat patiënten en hun ouders eraan 'kapotgaan'. Het waren de ouders die aandrongen op wetenschappelijk onderzoek: voor betere bekendheid, voor betere diagnostiek en voor betere behandeling.

Cornelia de Lange syndroom (CdLS) is vernoemd naar Cornelia de Lange, een kinderarts in Amsterdam, die het beeld in 1933 beschreef. CdLS is een zeldzame aandoening, veroorzaakt door een verandering in het erfelijk materiaal. Er zijn 6 genen bekend die CdLS veroorzaken. Deze genen coderen voor het cohesincomplex, een eiwitring die een belangrijke rol speelt bij de celdeling. Een verandering in één van de genen heeft consequenties voor aanleg en ontwikkeling van weefsels en organen. Mensen met CdLS zijn klein en hebben een typisch uiterlijk met o.a. doorlopende wenkbrauwen, lange wimpers en een wipneusje. Ze hebben kleine handen en voeten, en soms ontbreken er vingers, handen of delen van de armen. Ook aanlegstoornissen van andere organen, zoals het hart, komen vaker voor. Mensen met CdLS hebben een verstandelijke beperking en zijn kwetsbaar voor het ontwikkelen van gedragsproblemen, met name zelfverwondend gedrag.

Dit proefschrift beschrijft het CoDeLaGe (acroniem *Co*rnelia *de La*nge *Ge*dragsonderzoek), een onderzoek naar zelfverwondend gedrag bij het Cornelia de Lange syndroom. De onderzoeksvragen zijn:

1. Wat zijn de verschijningsvormen van het zelfverwondend gedrag?
2. Wat zijn de oorzaken?
3. Wat zijn de ontstaanswijzen?
4. Hoe kunnen oorzaken en ontstaanswijzen worden beïnvloed ten behoeve van doelgerichte behandeling en preventie van zelfverwondend gedrag bij het Cornelia de Lange syndroom?

ZELFVERWONDEND GEDRAG BIJ GENETISCHE SYNDROMEN (HOOFDSTUK 2)

Literatuuronderzoek laat zien dat er verschillende definities voor zelfverwondend gedrag (ZVG) worden gebruikt. Een eenduidige definitie is echter belangrijk voor patiëntzorg en wetenschappelijk onderzoek. Op basis van een analyse van de gebruikte definities, stellen we de volgende definitie voor: 'abusievelijk (onopzettelijk), repetitief (zich herhalend) gedrag dat leidt tot zelf toegebrachte, aantoonbare beschadiging van het lichaam, zonder de intentie van suïcide (zelfdoding) of seksuele bevrediging. Het gedrag heeft de neiging tot persisteren (voortduren).' De ernst van ZVG wordt bepaald door de lichamelijke beschadiging en de problemen voor het dagelijks functioneren. ZVG kan beschreven en gemeten worden aan de hand van karakteristieken zoals ontstaansleeftijd, vorm, plaats, frequentie en duur. De ontstaansleeftijd van ZVG in CdLS lijkt 4–8 jaar, maar er is weinig onderzoek naar gedaan. Hoewel bij CdLS veel ZVG-vormen vóórkomen, lijkt het met de hand op gezicht en hoofd slaan het meest typisch. ZVG bij CdLS houdt vaak aan. Vergelijking van prevalentie (percentage mensen met CdLS op een bepaald moment met ZVG) en andere ZVG-karakteristieken laat opvallende verschillen tussen genetische syndromen zien. Dit pleit voor een genetische invloed bij de oorsprong en de ontstaanswijze van ZVG. Tot op heden zijn genetische of somatische (lichamelijke) determinanten van ZVG echter nauwelijks onderzocht. Gedragswetenschappers hebben aangetoond dat ZVG geassocieerd is met factoren zoals ernst van de verstandelijke beperking, autisme en stereotiepe bewegingen. Ook werd duidelijk dat er een wisselwerking is tussen ZVG, sociale omgang en omgeving. ZVG kan ook een signaal of uiting zijn van pijn. Geïntegreerde studies naar genetische, lichamelijke en gedragsfactoren zijn nog niet verricht. Onderzoek van ZVG bij syndromen en de genen die deze syndromen veroorzaken, zal ons inzicht kunnen geven over de rol van genetische factoren in oorzaken en ontstaanswijzen van ZVG.

MOSAÏCISME BIJ CDLS (HOOFDSTUK 3)

Onderzoek naar de rol van genetische factoren begint bij het aantonen van een verandering in het erfelijk materiaal. De CdLS-diagnose is heel lang op basis van uiterlijke kenmerken gesteld. Sinds medio jaren '90 is het mogelijk om de klinische diagnose met DNA-onderzoek te bevestigen. Opvallend genoeg kon maar bij 55–65% van de mensen met CdLS een genverandering worden gevonden. We bedachten dat de DNA-verandering mogelijk niet in witte bloedcellen, maar wel in andere lichaamscellen aanwezig was. Dat heet mosaïcisme. In de Nederlandse groep mensen bij wie eerder geen DNA-verandering

kon worden aangetoond, vonden we met wangslijmvliesonderzoek bij 10/13 (77%) alsnog een verandering in het *NIPBL*-gen. Mosaïcisme komt bij CdLS relatief vaak voor: 10/44 (23%). Met wangslijmvliesonderzoek steeg het aantal bevestigde CdLS-diagnoses van 61% naar 84%. Een monduitstrijkje blijkt een betrouwbare, efficiënte én weinig belastende manier van DNA-afname. Bij vermoeden van het CdLS is het monduitstrijkje inmiddels stap 1 in de diagnostiek. Een bevestigde diagnose is tegenwoordig een voorwaarde voor allerhande onderzoek bij mensen met CdLS.

WAIHONAPEDIA: SCHAT AAN INFORMATIE VAN OUDERS (HOOFDSTUK 4)

Meer informatie voor een beter begrip over ZVG bij zeldzame genetische aandoeningen is nodig, maar ook een uitdaging. Het internet biedt ongekende kansen voor mensen met een zeldzame aandoening en hun families. Hun handicap van de beperkte aantallen wordt een meerwaarde, omdat kleine, internationale, gemotiveerde familieverenigingen zich uitstekend lenen voor samenwerking met onderzoekers. De verenigingen hebben een eigen website en de families communiceren via email, blogs of Facebook. Ouders zijn de belangrijkste bronnen van informatie voor elkaar, maar ook voor onderzoekers. De som van hun stukjes kennis en ervaring vormt een schat aan informatie voor alle mensen met de zeldzame aandoening. Naar analogie van Wikipedia ('wiki' – 'snel-snel' in het Hawaiiaans en 'encyclopedia') noemen we deze database 'Waihonapedia' ('waihona' – 'schat' in het Hawaiiaans). De CdLS-vereniging is actief met Waihonapedia. Via een digitale vragenlijst hebben ouders het onderwerp ZVG gekozen voor wetenschappelijk onderzoek. Dit draagt bij aan een hoge onderzoekdeelname en een effectief studiebeloop via online vragenlijsten over ontwikkeling, gezondheid en gedrag. Uitkomsten worden naar de families teruggekoppeld, waaruit nieuwe onderzoeksvragen ontstaan. Als ouders de vragenlijsten door de jaren opnieuw invullen, ontstaat een longitudinale database met informatie over natuurlijk beloop bij zeldzame aandoeningen, ook ten behoeve van interventiestudies. Waihonapedia vereist wel dat alle deelnemers een betrouwbare, liefst genetisch bevestigde diagnose van de zeldzame aandoening hebben.

GEDRAGSONDERZOEK BIJ CDLS (HOOFDSTUK 5)

Een beter begrip van gedrag bij CdLS begint bij nauwkeurige beschrijving en zorgvuldige beoordeling van gedrag. We bestudeerden de literatuur over gedragsonderzoek

naar ZVG, autisme en/of cognitie bij mensen met CdLS. We vonden 43 artikelen en brachten in kaart hoe het gedragsonderzoek was uitgevoerd. De meeste deelnemers met CdLS hebben een ernstige tot zeer ernstige verstandelijke beperking. Slechts in 6 studies (14%) is sprake van een genetisch bevestigde diagnose. Onderzoeksmethodes en kwaliteit van de onderzoeken verschillen sterk, evenals de manier waarop autisme wordt beoordeeld en ingedeeld. ZVG wordt gerapporteerd in 15 artikelen. In 21 artikelen worden lichamelijke aandoeningen gemeld, met name problemen met zien en horen, en afwijkingen aan de ledematen. In 8 studies (19%) worden alleen vragenlijsten gebruikt, in 34 onderzoeken (79%) 2 of meer methodes (bv. vragenlijst, interview en/of observatie) en in 14 studies (33%) worden deelnemers door de onderzoeker zelf onderzocht. Vergelijking van de diverse onderzoeksresultaten is niet mogelijk, vanwege de verschillen in onderzoeksmethodes. We stellen daarom voor om, naast genetisch onderzoek, een standaardset aan testen en instrumenten in te zetten voor onderzoek naar cognitie, adaptief functioneren, sensorische prikkelverwerking, autisme, ZVG, lichamelijke en zintuigbeperkingen, mate van ondersteuning, en leefomgeving. Zo zullen we beter in staat zijn om gedrag bij mensen met een verstandelijke beperking en een zeldzaam syndroom te leren begrijpen tegen de achtergrond van de genetische diagnose en het niveau van ontwikkeling en van functioneren.

CDLS: EEN SYNDROOM MET VERSCHILLENDE OORZAKEN (HOOFDSTUK 6)

CdLS wordt veroorzaakt door varianten in verschillende genen. Als de kenmerken van het syndroom niet hetzelfde zijn, geeft dat informatie over de functie van die verschillende genen. Veranderingen in het *NIPBL*-gen (~70–75%) en in het *SMC1A*-gen (~5%) vormen de meest voorkomende oorzaak van CdLS. In de tot nu toe grootste, internationale groep van 51 mensen met een *SMC1A*-verandering vergeleken we de CdLS-verschijnselen met een controlegroep van 67 mensen met een *NIPBL*-verandering. Er bestaat overlap in de CdLS-kenmerken (groei, opvallende gezichtskenmerken, aanlegproblemen handen en armen, verstandelijke beperking), maar de kenmerken bij een *SMC1A*-verandering zijn doorgaans milder. De overlap in deze CdLS-kenmerken pleit ervoor dat deze kenmerken veroorzaakt worden door een gedeelde genfunctie, namelijk een verstoorde cohesinfunctie. De Nederlandse SMC1A-groep omvat ook mensen van wie CdLS aanvankelijk niet werd vermoed, maar bij wie wel een *SMC1A*-verandering werd gevonden via exome sequencing (een DNA-techniek waarbij de nucleotidevolgorde van alle delen die coderen voor eiwitten in één keer wordt afgelezen). Een deel van deze mensen heeft lichte

CdLS-verschijnselen, maar het andere deel laat meer een syndroom van Rett-achtig beeld zien: therapieresistente epilepsie, zeer ernstige verstandelijke beperking en stereotiepe handbewegingen. ZVG komt veel minder vaak en veel minder ernstig voor bij de SMC1A-groep en is afwezig bij mensen met een syndroom van Rett-achtig beeld. Dit verschil pleit ervoor dat ZVG veroorzaakt wordt door een andere genfunctie van *NIPBL* (moonlighting) en pleit ertegen dat de ernst van de verstandelijke beperking een belangrijke rol speelt bij ZVG in de *NIPBL*-groep. Omdat het vóórkomen van gastro-oesofageale refluxziekte (GORZ) en obstipatie vergelijkbaar is in de *NIPBL*-groep en de *SMC1A*-groep pleit dat ertegen dat GORZ een belangrijke rol speelt bij ZVG in de *NIPBL*-groep. Deze studie biedt eerste voorzichtige antwoorden op de vraag van ouders: wat betekent het voor mijn kind dat hij een *SMC1A*-variant heeft? Tevens leidt de studie tot hypotheses over de genetische invloeden bij ZVG in CdLS.

CRI DU COEUR (HOOFDSTUK 7 EN 8)

Zelfverwondend gedrag verdient meer aandacht bij dokters. Daarom hebben we artikelen over dit onderwerp geschreven voor een breed dokterspubliek. Hoewel ZVG een veel voorkomend gedragsprobleem is, kan het heel ingewikkeld zijn voor dokters die weinig ervaring hebben met gedragsproblematiek bij mensen met een verstandelijke beperking. Onder gedragsproblematiek kan een medisch probleem schuilgaan. Het belangrijkste is daarom dat dokters vooral doen, wat ze bij andere hulpvragen ook doen en waar ze goed in zijn: diagnostiek en behandeling van medische problemen. Als dat onvoldoende effectief is, is verwijzing naar teams in gespecialiseerde centra geïndiceerd, waar gedragsdeskundigen en artsen nauw samenwerken met ouders en begeleiders.

BESPREKING

ZVG is geen diagnose, maar een verschijnsel van een onderliggend probleem dat zich uit via gedrag. Genetische, lichamelijke en gedragsmatige factoren spelen een rol. Pijn, veroorzaakt door veel voorkomende gezondheidsproblemen (gastro-oesofageale refluxziekte, obstipatie, otitiden, gebitsproblemen), kan een uitlokkende of onderhoudende rol spelen bij ZVG. Deze gezondheidsproblemen kunnen in het algemeen goed met medicatie, dieet en soms andere ingrepen behandeld worden. Daarnaast is een gedragsmatige aanpak onontbeerlijk, want interacties met de omgeving spelen via operante conditionering (geleerd gedrag) ook vaak een uitlokkende en onderhoudende rol. Echter, gedragsmatige interventies kunnen veel aan effectiviteit inboeten als pijn door

een medische oorzaak blijft bestaan. Andersom kan ZVG persisteren als de medische oorzaak van de pijn adequaat is behandeld, maar het gedrag is geconditioneerd. Het is niet verwonderlijk dat een gecombineerde aanpak daarom het beste werkt. In het stroomschema hebben we de bevindingen uit het promotieonderzoek verwerkt in een interdisciplinair stappenplan.

Pijn, prikkelverwerking, stereotiepe bewegingen, ontstemming en angst hangen samen met ZVG, maar onduidelijk is precies hoe. Helaas is het niet gelukt ook het zenuwstelsel mee te nemen in het patiëntgebonden deel van het promotieonderzoek: het meten van zenuwgeleidingstijden met het oog op een neuropathie, het meten van neurotransmitters (signaalstoffen van het zenuwstelsel) via een lumbaalpunctie in verband met mentale klachten en een MRI van de hersenen voor een beeld van de ligging, grootte en structuur van de hersendelen. Dat vraagt om een vervolgonderzoek.

Oorzaak en ontstaanswijze van ZVG zijn nog niet uitgekristalliseerd. Dit proefschrift biedt op basis van beschrijving en vergelijking van verschijningsvormen van ZVG, lichamelijke kenmerken en gedragskenmerken, aanknopingspunten voor en hypotheses over genetische invloeden en daarmee moleculaire mechanismen bij ZVG in CdLS. Voor verder onderzoek naar genetische en somatische (lichamelijke) oorzaken en ontstaansmechanismen is interdisciplinaire samenwerking tussen dokters en gedragsdeskundigen (gedragswetenschappers, psychologen, orthopedagogen) onontbeerlijk. De eerste stap is samen terug naar de basis waar we goed in zijn: dokters beschrijven lichamelijke kenmerken, gedragsdeskundigen beschrijven gedragskenmerken bij mensen met ZVG, een verstandelijke beperking en een aangetoonde genverandering. Vervolgens kunnen de hypotheses over genetische invloeden nader getoetst worden. Daarvoor zijn zo groot mogelijke groepen mensen met CdLS met en zonder ZVG nodig en dat vereist nauwe samenwerking met internationale collega's en ouders. Bij aanname van de hypotheses, is er een sterkere onderbouwing voor aanvullend fundamenteel onderzoek, zoals functieonderzoek van genen en dieronderzoek. Via deze weg kunnen mechanismes worden ontrafeld ten behoeve van doelgerichte behandeling en preventie van ZVG bij mensen met CdLS.

De onderzoeksresultaten in dit proefschrift worden ook gebruikt voor de internationale richtlijnen voor diagnostiek en behandeling bij mensen met CdLS, die volgend jaar gepubliceerd worden. We hopen dat de ontwikkelingen ten goede komen aan de mensen met ZVG, hun ouders, begeleiders, dokters, gedragsdeskundigen en onderzoekers.

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Geachte prof. Hennekam, Beste Raoul, ik zie me nog bij je aankloppen eind 2010. Ik wist wat ik wilde, maar niet hoe het moest. Mijn ideeën pasten goed in wat je translationeel onderzoek noemde, een aanvulling op de andere onderzoekslijnen op mijn vakgebied. Je feedback waarom dit soort onderzoek belangrijk is, zowel voor de ontwikkeling van de zorg als van het vakgebied, heeft me gesterkt. We deelden meteen de overtuiging hoe essentieel het is dat verschillende disciplines met elkaar samenwerken en elkaars taal leren spreken. Dat gold ook voor ons:

Raoul: Om zelfverwondend gedrag beter te begrijpen is onderzoek naar de etiologie en pathogenese nodig. Daar hoort ook functioneel onderzoek bij.

Sylvia: Over de oorzaak en ontstaanswijze van zelfverwondend gedrag is al veel bekend vanuit de gedragswetenschappen. En er wordt door gedragswetenschappers al veel functioneel of functie-onderzoek gedaan: naar aard en niveau van functioneren, naar functie van gedrag.

Raoul: Nee, ik bedoel somatisch onderzoek.

Sylvia: Er is ook gekeken naar de rol van medische aandoeningen, met name refluxziekte en zo.

Raoul: Nee, ik bedoel onderzoek naar de biologische functies van genen, dus naar metabole pathways, muisonderzoek en zo.

Sylvia: De gedragswetenschappers spreken ook over etiologie en hebben daar modellen voor ontwikkeld.

Raoul: Ja, maar voor een oorzaak is een somatisch substraat nodig… dat biedt nieuwe aanknopingspunten voor behandeling en preventie.

Sylvia: We hebben een integrale aanpak nodig, waarin we genetische, lichamelijke en gedragsfactoren in samenhang bekijken.

Raoul en Sylvia: Laten we beginnen met wat er al bekend is over de fenomenologie, de kenmerken en verschijningsvormen van het zelfverwondend gedrag en van de mensen bij wie dit gedrag voorkomt. En van daaruit hypotheses formuleren over oorsprong en ontstaanswijze.

En toen begonnen we, een traject met talloze memorabele momenten: jouw tomeloze aansporing voor mijn herhaalde weifeling bij de scope van 'het SIB review', de voor mijn gevoel oneindig aantal versies van het manuscript en het grote genoegen toen het – uiteindelijk – werd geaccepteerd; het 'kicken' toen het wangslijmvliesonderzoek mosaïcisme aantoonde (en de implicaties jou meteen veel duidelijker waren dan mij) en de haast om het te publiceren ('Want als wij het kunnen bedenken, kunnen anderen het ook'!); samen op zoek naar de term 'waihonapedia'; volhouden tot SMC1A n=50; het 'bouncen' voor de beste formuleringen in pogingen om een 'cri du coeur' stuk in de beste, breed gelezen tijdschriften te krijgen. Het stimuleerde, inspireerde me en verruimde mijn blik. "Het wordt mooi!" en "Trek maar een fles wijn open!" waren je gevleugelde woorden als we weer een mijlpaaltje hadden bereikt. En altijd was ik onder de indruk van je ongeëvenaard denk- en werktempo, scherpe analytische vermogen, vanzelfsprekende overtuiging, pragmatisch strategisch denken, onbegrensd optimisme. En altijd met de patiënt in het vizier.

En zo introduceerde je me gaandeweg in de wereld van Cornelia de Lange, pionier op vele vlakken: van haar onconventionele verschijning als mens en dokter tot haar klinische blik in combinatie met haar wetenschappelijke kijk; ook zíj had buitengewone interesse voor kinderen met een opvallend uiterlijk en een typische ontwikkeling (ik zeg bewust 'typische' en niet 'atypische' ontwikkeling). In feite deed ze aan 'phenotyping avant la lettre', een discipline waar je je zo hard voor maakt, met name nu de DNA-technologie een vlucht heeft genomen en de betekenis van het vinden van varianten steeds meer afhankelijk is van de manier waarop we kunnen 'phenotyperen'. Hartelijk dank, Raoul, voor alles, ik kon me geen betere promotor wensen.

Geachte dr. van Balkom, Beste Inge, dat jij mijn copromotor werd, heeft zo moeten zijn! Met expertise uit een aanpalend vakgebied en ervaring na een enigszins vergelijkbaar promotietraject jaren geleden (ik was erbij in Groningen, niet wetende dat je mijn copromotor zou worden!), voelde ik me gesteund en bij alles was je snel bereid te helpen, met de nadruk op snel: bij de vertalingen van de gedragsvragenlijsten, als er per ommegaande een formulier geregeld moest worden of bij de zorgvuldige feedback op de manuscripten. We hebben gediscussieerd, maar ook veel gelachen, o.a. over de staat van de (geestelijke) gezondheidszorg en de krachten die 'echte' kwaliteit bepalen

danwel ondermijnen. Met een schaterlach en een kwinkslag weet je overtrokken zaken binnen de juiste proporties brengen.

Beste Paul en Sigrid, wat een plezier om met jullie op te trekken tijdens het onderzoek. Sigrid, als begeleider van Paul ben je ook nauw betrokken geweest bij mijn promotie onderzoek. Dank voor je constructieve feedback op de manuscripten, waarbij je steeds scherp was op toon en accenten om de interdisciplinaire boodschap zo goed mogelijk voor het voetlicht te brengen. Paul, wat hebben we door ons gezamenlijk promotietraject al veel mogen beleven, in binnen- en buitenland. Trefwoorden: varken, Indonesisch, bier en cocktails, Skype, warmte van families, consultations. Als we samen naar speciale kinderen en volwassenen kijken, ervaar ik kracht en verbondenheid, omdat we vanuit verschillende invalshoeken hetzelfde kijken, beschrijven en betekenis geven. We zien ook meestal hetzelfde en zoniet: dan gaan we nog beter kijken. Onze input is complementair en leidt vanzelfsprekend tot integrale hypotheses en toetsende interventies. Juist deze ervaringen met jou maken mijn overtuiging nog stelliger dat interdisciplinaire samenwerking ons verder gaat helpen in het beantwoorden van zelfs de moeilijkste vragen van ouders en hun kinderen. Zo wil ik werken! Ik koester de spreuk: 'If you want to go fast, go alone. If you want to go far, go together' (Afrikaans gezegde).

Dear members of the committee, Prof. dr. F.J. Kaiser, Prof. dr. C. Oliver, Prof. dr. D.A.J.P. Denys, Prof. dr. J.B. van Goudoever, Prof. dr. M.A. Grootenhuis, Dr. D.A.M. Maes-Festen, it is an honor for me that you were willing to judge my PhD thesis on its scientific merits and join the PhD defence committee in such a wide-ranging interdisciplinary company. Thank you very much for reviewing my thesis, some of you even during your holidays due to suddenly arising deadlines! Dear Chris and Frank, l would like to extend a special thank-you to you for travelling to Amsterdam, for attending the ceremony and for presenting at the symposium. It means a lot to me.

De Prinsenstichting heeft mij een plek voor ontwikkeling en ontplooiing geboden. Mijn dank gaat uit naar het management, maar vooral naar ons team van AVG collega's Madelon, Susanne, Christina Miranda, Ilse en Karla, A(N)IOS AVG Myrthe, Maria, Lianne, verpleegkundige Ina, en assistentes Yvonne, Aniska, Patricia, Anna en Debby en vele anderen, die het promotietraject mogelijk maakten. Ik hoop met het promotietraject een brug te slaan tussen academie en onze zorginstelling, maar die brug heeft een stevige structuur en veel onderhoud nodig ten behoeve van toekomstige collega's – gedragsdeskundigen en artsen – die ook met wetenschappelijk onderzoek de zorg en kwaliteit van leven van mensen met een verstandelijke beperking willen verbeteren.

Ik zie uit naar het symposium Gedrag in Genetische Syndromen: interdisciplinaire samenwerking noodzakelijk! en wil in het bijzonder Gerard, Désirée en de mensen achter de schermen bedanken voor alle steun en inzet bij de organisatie ervan.

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'In rare disorders, you need to think globally!' Dank aan mijn dierbare collega's van de Scientific Advisory Committee CdLS World, voor hun steun en medewerking, maar vooral ook het plezier dat we delen bij het werk dat we doen. Alle lof en dank aan de nationale en internationale collega's, die hielpen om zoveel mogelijk gegevens te verzamelen. Dear SAC colleagues, many thanks for your generous help and I look forward to continuing our collaboration in future research projects and SAC activities. Hopefully many will follow!

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Om met de woorden van Cornelia de Lange te spreken en te eindigen: Het werk dat ons wacht…

Curriculum vitae
Portfolio
Publications

CURRICULUM VITAE

Sylvia Huisman was born in Amstelveen on June 14th 1971, almost a century to the day since Cornelia de Lange (June 24th 1871-January 28th 1950) was born. From an early age Sylvia was an inquisitive person and had a natural affinity for the sciences. Although her interests during her formative years were varied, medicine was a calling ever since her school days. After graduating from grammar school in 1989, Sylvia was accepted into Medical School at the Free University of Amsterdam. Before embarking on her medical training, she spent her freshman year at the University of Oregon USA on a NACEE scholarship, studying a.o. American studies, Russian and astronomy. During Medical School in Amsterdam she met Remko, her husband today, and the both of them travelled to Yogyakarta Indonesia and wrote their undergraduate scientific thesis on Dengue hemorrhagic fever. They both graduated summer 1997, a century after Cornelia de Lange wrote her dissertation 'Vergelijkende Aschanalyses' (1897).

1998 marked the start of her first medical career at Prinsenstichting, a center for people with intellectual disabilities (ID). During one of her first consultations she met a man with Cornelia de Lange Syndrome (CdLS) who engaged in serious self-injurious behavior (SIB). Professor Raoul Hennekam regularly visited the Prinsenstichting as a clinical geneticist and once Margriet van Duinen (one of the paranimfs) joined him as a student. Inspired by her mentor Frans Ewals (the other paranimf) in the developing field of ID medicine, Sylvia started the new specialist training program for physicians for people with ID at the Erasmus Medical Center in Rotterdam in 2000. Margriet and Sylvia met again and have become close colleagues and friends ever since.

Frans, Sylvia and other colleagues collaborated with Mieke van Leeuwen, a representative of Dutch support groups, and together they wrote a series of syndrome brochures for parents to forward information about CdLS and other rare ID syndromes to their general practitioners and dentists. Mieke introduced Sylvia to the CdLS support group, and finding the work hugely rewarding, Sylvia became medical advisor to the group. For the past two years she has served as a president of the Scientific Advisory Committee of CdLS World.

Over the years Frans, Margriet, Raoul and Sylvia have strived to tackle the challenges and capitalize on the opportunities to improve the delivery of ID medicine. Bridging the gap between the world of daily care and the world of academic cure was one of the main topics. Sylvia was very motivated to start a PhD trajectory and visited Raoul for advice in late-2010. It only took two conversations with Raoul to identify what research was

needed in order to improve care, with Raoul in a supervisory role. Responses gathered via an online questionnaire revealed the CdLS support group prioritized the SIB topic for research in 2011.

Sylvia will defend her thesis *With the Body in Mind* in November 2017, ninety years after Cornelia de Lange wrote her inaugural address 'Het werk dat ons wacht' ('The work that is awaiting us', 1927).

Since March 2017 Sylvia has also been part-time engaged as an ID physician at the Emma Children's Hospital (AMC) in Amsterdam, the same hospital in which Cornelia de Lange worked most of her career.

Sylvia does not believe in fate, but she does trust serendipity!

Remko and Sylvia are the happy parents of daughter Rosanne (12) and son Jesse (7), who are an absolute delight in their busy (medical) lives!

PORTFOLIO

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AVG, Department of Pediatrics, AMC, Amsterdam

Education and specialist training

2000–2003:	AVG specialist training, Erasmus MC, Rotterdam
1990–1997:	Medical Degree, VUmc, Amsterdam
1989–1990:	NACEE scholarship, University of Oregon, USA

Work – clinical

2017– :	AVG, Department of Pediatrics, AMC, Amsterdam
2013– :	Consultant physician Center for Consultation and Expertise, areas of expertise: Self-injurious behavior, Cornelia de Lange syndrome
2007– :	BOPZarts Prinsenstichting, Purmerend
2003–2016:	AVG detached assignments (Odion, Cordaan, Esdege-Reigersdaal, Lijn5)
2003– :	AVG Prinsenstichting, Purmerend
2000–2003:	Registrar (AIOS) AVG, Prinsenstichting, Purmerend
1999–2000:	Registrar (ANIOS) Internal medicine, BovenIJ Ziekenhuis, Amsterdam
1998–1999:	Registrar (ANIOS) AVG, Prinsenstichting, Purmerend

Work – teaching

2016– :	CCE training course Self-Injurious behavior in people with severe-profound ID
2016– :	Training course Dieticians for patients with ID
2007– :	Module ID Medicine (Geneeskunde voor mensen met een verstandelijke beperking), General Practitioners Erasmus MC and VUmc
2007–2008:	Committee for developing AVG specialist training scheme
2006– :	AVG trainer (AVG-opleider)
2004–2009:	Educational student program 'De patiënt met een verstandelijke beperking', ErasmusMC
2004–2006:	Educational student program 'Gezondheidszorg in de grote stad, Zorg aan verstandelijke gehandicapten', AMC
2000– :	Coach and examinator medical students (co-assistenten) AMC and VUmc

Awards

2012:	Hanna Oorthuys award

Courses and training

PhD courses AMC

2016:	Genetic Epidemiology	1.1 ECTS
2013:	Clinical data management	0.3 ECTS
2013:	Practical biostatistics	1.1 ECTS
2013:	Clinical Epidemiology	0.6 ECTS
2013:	Oral Presentation in English	0.8 ECTS
2013:	Scientific writing in English for publication	1.5 ECTS
2012:	BROK course	1.1 ECTS
2012:	Systematic Reviews	0.7 ECTS
2012:	PsychINFO	0.1 ECTS
2012:	Web of science	0.1 ECTS
2012:	PubMed	0.1 ECTS
2012:	The AMC world of science	0.7 ECTS

Other

2009:	NVAVG Science course
2007:	Didactic course AVG specialist training scheme
2007:	'Evidence based richtlijnontwikkeling' (EBRO) course
2000:	Postgrade-course 'Workshops & casuïstiek'

Administrative positions

NVAVG

2016– :	NVAVG committee Education in ID medicine in the medical curricula
2016– :	NVAVG committee Legislation and regulations
2011–2013:	Project group *Anticipatory Decision-making Resuscitation* (addendum NVAVG Guideline *End-of-life decision-making for people with ID*)
2011–2012:	Project group Zorgaanbod van de AVG
2004–2012:	Project group PlatformVG-NVAVG
2004–2011:	Steering group NVAVG guidelines
2004–2010:	NVAVG board
2004–2008:	Project group Psychofarmaca

CdLS support group

2015– :	President of SAC International CdLS Federation
2011– :	Member Scientific Advisory Committee (SAC) of the international CdLS Federation
2011– :	Professional director National CdLS Support group

PUBLICATIONS

International peer-reviewed journals

Huisman S, Walinga M, Hennekam R. Wel-doen en niet-schaden. Behandeling van zelfverwondend gedrag bij mensen met een verstandelijke beperking. Submitted.

Huisman S, Mulder P, Van Balkom I, Piening S, Hennekam R. Self-Injurious Behavior. Submitted.

Huisman S, Mulder P, Kuijk J, Kerstholt M, Van Eeghen A, Leenders A, Van Balkom I, Oliver C, Piening S, Hennekam R. Self-Injurious Behavior. Neurosci Biobehav Rev. 2017 doi: 10.1016/j.neubiorev.2017.02.027. [Epub ahead of print]

Kline AD, Krantz ID, Deardorff MA, Shirahige K, Dorsett D, Gerton JL, Wu M, Mehta D, Mills JA, Carrico CS, Noon S, Herrera PS, Horsfield JA, Bettale C, Morgan J, Huisman SA, Moss J, McCleery J, Grados M, Hansen BD, Srivastava S, Taylor-Snell E, Kerr LM, Katz O, Calof AL, Musio A, Egense A, Haaland RE. Cornelia de Lange syndrome and molecular implications of the cohesin complex: Abstracts from the 7th biennial scientific and educational symposium 2016. Am J Med Genet A 2017;173:1172-85.

Huisman S, Mulder PA, Redeker E, Bader I, Bisgaard A, Brooks A, Cereda A, Cinca C, Clark D, Cormier-Daire V, Deardorff MA, Diderich K, Elting M, Van Essen A, FitzPatrick D, Gervasini C, Gillessen-Kaesbach G, Girisha KM, Hilhorst-Hofstee Y, Hopman S, Horn D, Isrie M, Jansen S, Kaiser FJ, Kaur M, Kleefstra T, Krantz ID, Lakeman P, Landlust A, Lessel D, Michot C, Moss J, Noon SE, Oliver C, Parenti I, Pie J, Ramos FJ, Rieubland C, Russo S, Selicorni A, Tümer Z, Vorstenbosch R, Wenger TL, Van Balkom I, Piening S, Wierzba J, Hennekam RC. Phenotypes and genotypes in individuals with SMC1A variants. Am J Med Genet A 2017. doi: 10.1002/ajmg.a.38279. [Epub ahead of print]

Mulder PA, Huisman SA, Hennekam RC, Oliver C, van Balkom ID, Piening S. Behaviour in Cornelia de Lange syndrome: a systematic review. Dev Med Child Neurol 2017;59:361-6.

Baas M, Huisman S, van Heukelingen J, Koekkoek G, Laan HW, Hennekam RC. Building treasures for rare disorders. Eur J Med Genet 2015;58:11-3.

Zevenbergen C, Klootwijk W, Peeters RP, Medici M, de Rijke YB, Huisman SA, Goeman H, Boot E, de Kuijper G, de Waal KH, Meima ME, Larsen PR, Visser TJ, Visser WE. Functional analysis of novel genetic variation in the thyroid hormone activating type 2 deiodinase. J Clin Endocrinol Metab 2014;99:E2429-36.

Alders M, Mendola A, Adès L, Al Gazali L, Bellini C, Dallapiccola B, Edery, Frank U, Hornshuh F, Huisman SA, Jagadeesh S, Kayserili H, Keng WT, Lev D, Prada CE, Sampson JR, Schmidtke J, Shashi V, Van Bever Y, Van der Aa N, Verhagen JM, Verheij JB, Vikkula M, Hennekam RC. Evaluation of clinical manifestations in patients with severe lymphedema with and without CCBE1 mutations. Mol Syndromol 2013;4:107-13.

Huisman SA, Redeker EJW, Maas SM, Mannens MM, Hennekam RCM. High rate of mosaicism in patients with Cornelia de Lange syndrome. J Med Genet 2013;50:339-44.

Vis JC, De Bruin-Bon HA, Bouma BJ, Huisman SA, Imschoot L, van den Brink K, Mulder BJ. Adults with Down syndrome have reduced cardiac response after light exercise testing. Neth Heart J 2012;20:264-9.

Vis JC, de Bruin-Bon RH, Bouma BJ, Backx AP, Huisman SA, Imschoot L, Mulder BJ. 'The sedentary heart': physical inactivity is associated with cardiac atrophy in adults with an intellectual disability. Int J Cardiol 2012;158:387-93.

Vis JC, de Bruin-Bon RH, Bouma BJ, Huisman SA, Imschoot L, van den Brink K, Mulder BJ. Congenital heart defects are under-recognised in adult patients with Down syndrome. Heart 2010;96:1480-4.

Vis JC, Thoonsen H, Duffels MG, de Bruin-Bon RA, Huisman SA, van Dijk AP, Hoendermis ES, Berger RM, Bouma BJ, Mulder BJ. Six-minute walk test in patients with Down syndrome: validity and reproducibility. Arch Phys Med Rehabil 2009;90:1423-7.

Vis JC, Duffels MG, Winter MM, Weijerman ME, Cobben JM, Huisman SA, Mulder BJ. Down syndrome: a cardiovascular perspective. J Intellect Disabil Res 2009;53:419-25.

Other publications

Huisman S, Maes-Festen D, Mastebroek M, Mergler S, Soudant S, Tack I, Veeren H, Walinga M. Onderwijs: een van de drie pijlers van de VG geneeskunde. TAVG 2017;35:55-7.

Henderikse B (Red.). Zelfverwonding. Hdst. 3 & Hdst. 5. Centrum voor Consultatie en Expertise. Van Schaik Grafimedia, Oudewater 2017.

Schermer M, Ewals F, Weisz M. Ethische dilemma's in de zorg voor mensen met een verstandelijke beperking. Casus 17 & 20. Koninklijke van Gorcum, Assen, 2016.

Braam W, Van Duinen-Maas MJ, Festen DAM, Van Gelderen I, Huisman SA, Tonino MAM, Medische Zorg voor patiënten met een verstandelijke beperking. Prelum, Houten, 2014.

Kuijk J, de Buck L, Huisman S. Overmatig speekselverlies bij mensen met een verstandelijke beperking: van oorzaak naar behandelmogelijkheden. TAVG 2012;30:71-5.

Ewals F, Huisman S. Van zorgtekort naar behandelindicaties: het dienstenpakket van de AVG. TAVG 2008;26:54-60.

Buntinx WHE (Red.). Professionaliteit in de hulpverlening aan mensen met verstandelijke beperkingen. Hdst. 5. Professionaliteit van de AVG. Garant, Antwerpen-Apeldoorn, 2007.

Ewals F, Huisman S. Het domein van de AVG. TAVG 2005;23:3-10.

Huisman SA. Luchtwegproblemen bij ernstig verstandelijk gehandicapten: systematische benadering biedt uitkomst. Modern Medicine 2003;27:880-2.

Huisman S, Ewals F. Op en top AVG in de toekomst, een vervolgopiniestuk. TVAZ 2002; 20:16-8.

Ewals F, Huisman S, Veraart W, Meijer M. Een andere tijd vraagt om een andere AVG, een opiniestuk. TVAZ 2002;20:5-6.

Huisman SA. Een pilotonderzoek naar luchtweginfecties bij mensen met MCG problematiek. TVAZ 2001;19:9-11.

Roeterdink CH, Huisman SA. Obstipatie bij verstandelijk gehandicapten: een groot probleem. TVAZ 2000;18:6-8.

Huisman SA. Draindysfunctie: een atypisch verhaal? TVAZ 1999;17:21-3.