From the Department of Clinical Science and Education,
Södersjukhuset, Karolinska Institutet,
Stockholm, Sweden

CONGENITAL UPPER LIMB ANOMALIES – STUDIES OF EPIDEMIOLOGY AND HAND FUNCTION

Anna Gerber Ekblom

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To Holger, Arvid, Adam and Harald

and to all children with a hand difference

ABSTRACT

Objectives: This thesis has three interrelated aims:
(1) To describe the epidemiology of congenital upper limb anomalies (CULA) in Stockholm County, Sweden, in order to augment the few existing population studies of CULA (paper I);
(2) To measure the incidence of different categories of CULA while using and evaluating a recently proposed new classification scheme (*Oberg, Manske and Tonkin (OMT) Classification*) based on more current knowledge of limb development than the previously used *International Federation of Societies for Surgery of the Hand (IFSSH) Classification* is based on (paper II); and
(3) To investigate the relationship between measurements of *body function and structure* with both *activity* and *participation* in children and adults with radial longitudinal deficiency (RLD) by using the *International Classification of Functioning and Health (ICF)* framework, in order to shed light on what aspects of physical limb function and structure actually affect individuals' daily life activity (papers III and IV).
Methods: 562 children born with a CULA were identified through registry studies. Incidence and relative frequency of different types of anomalies were calculated. Distribution of gender, affected side, associated non-hand anomalies and occurrence among relatives were investigated (paper I and II). In twenty children (paper III) and 20 adults (paper IV) with RLD, *Body function and structure* was evaluated by measures of range of motion, grip strength, key pinch, sensibility and radiographic parameters. *Activity* was evaluated by Box and Blocks test, Assisting Hand Assessment (AHA) and Sollerman Hand Function test and p*articipation* by Children Hand-use Experience Questionnaire (CHEQ), Quick-DASH and SF-12. Statistical correlations between assessments of *body function and structure, activity* and *participation* were examined.
Results: The incidence of CULA in Stockholm, Sweden, 1997 to 2007, was 21.5 per 10,000 live births (paper I). All CULA could be classified using the OMT classification. The largest main category was *Malformations* (429 cases), followed by *Deformations* (124 cases), *Dysplasias* (10 cases) and *Syndromes* (14 cases) (paper II). In children with RLD (paper III), significant relationships were found between measurements of *activity* and range of motion of digits as well as between measurements of *participation* and range of motion of wrist. In adults with RLD (paper IV), significant relationships were found between measurements of *activity* and grip strength, key pinch and range of motion of elbow and digits. In adults, measurements of *participation* showed significant relationships with grip strength, forearm length and range of motion of elbow and digits. However, radiographic measurements of radial wrist deviation did not show a significant relationship with measurements of *activity* or *participation* in children or in adults with radial longitudinal deficiency.
Conclusions: The incidence of CULA in one Swedish region confirms the findings in the only previous comparable total population study. The OMT classification proved useful and accurate and with further refinements can replace the IFSSH classification. In children and adults with RLD, grip strength, key pinch, forearm length and elbow and digital motion seem to be more important for the individual´s levels of activity and participation than the radial angulation of the wrist. The current treatment principle of surgical correction of the angulated wrist could therefore be questioned.

SAMMANFATTNING

Mål: Denna avhandling har tre relaterade målsättningar:
(1) Att genom en epidemiologisk kartläggning av medfödda avvikelser inom hand och arm i Stockholms Län, Sverige, öka kunskapen inom detta område (delarbete I);
(2) Att beräkna förekomsten av de olika typerna av avvikelser inom hand och arm med utgångspunkt från en ny klassifikation av hand-/arm-missbildningar (*Oberg, Manske and Tonkin (OMT) Classification*) som, till skillnad från den tidigare mest använda klassifikationen, *the International Federation of Societies for Surgery of the Hand (IFSSH) Classification*, utgår från dagens kunskap om armens embryologiska utveckling (delarbete II); och
(3) Att, med utgångspunkt från *Klassifikation av funktionstillstånd, funktionshinder och hälsa, WHO, (ICF)*, undersöka sambandet mellan *kroppsfunktion och struktur* och *aktivitet* och *delaktighet* bland barn och vuxna med medfödd underutveckling av tumsidan av hand och underarm, radial längsgående reduktionsmissbildning (RLD), för att därigenom bättre belysa vilka aspekter av den kroppsliga funktionsnedsättningen hos dessa individer som påverkar individens dagliga liv (delarbete III och IV).
Metoder: 562 barn med medfödda avvikelser inom hand och arm identifierades i medicinska register. Förekomst av de olika typerna av avvikelser beräknades liksom könsfördelning, påverkad sida, associerade missbildningar och förekomst av missbildning av arm eller ben i släkten (delarbete I och II).
I delarbete III undersöktes 20 barn, och i delarbete IV 20 vuxna, individer med medfödd underutveckling av tumsidan av hand och underarm (RLD). Individerna undersöktes med avseende på rörelseomfång, styrka, känsel, röntgenparametrar, handfunktionstester och enkäter. Relationen mellan k*roppsfunktion och struktur* och *aktivitetsnivå* och *delaktighet* i dagligt liv utvärderades.
Resultat: Förekomsten av medfödda avvikelser inom hand och arm i Stockholm, Sverige, 1997 till 2007, var 21,5 per 10,000 levande födda barn (delarbete I). Alla avvikelser var möjliga att klassificera i enlighet med OMT klassifikationen. Den största huvudgruppen var *Malformations* (429 fall), följt av *Deformations* (124 fall), *Dysplasias* (10 fall) och *Syndromes* (14 fall) (delarbete II).
Bland barn med RLD påvisades samband mellan *aktivitet* och fingrarnas rörelseomfång och mellan *delaktighet* och rörelseomfång i handleden (delarbete III). Bland vuxna personer med RLD påvisades samband mellan *aktivitet* och greppstyrka, nyckelgrepp, och rörelseomfång i armbåge och fingrar och även mellan *delaktighet* och greppstyrka, underarmslängd och rörelseomfång i armbåge och fingrar (delarbete IV). Varken bland barn eller vuxna med RLD kunde något statistiskt säkerställt samband påvisas mellan röntgenmått på vinkling av handleden och *aktivitet* eller *delaktighet*.
Slutsatser: Förekomsten av avvikelser inom hand och arm bland nyfödda barn i en region i Sverige var jämförbar med resultatet i den enda jämförbara tidigare total-populationsstudien. OMT klassifikationen är adekvat och med förbättring kan den bli en välbehövlig ersättning för IFSSH klassifikationen.
För barn och vuxna med RLD är styrka, underarmslängd och rörelseomfång i armbåge och fingrar troligen är av större betydelse för aktivitet och delaktighet än vinkling av handleden. Den nu rådande behandlingsprincipen att kirurgiskt räta upp handleden kan därför behöva omprövas.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Ekblom AG, Laurell T, Arner M
Epidemiology of Congenital Upper Limb Anomalies in 562 Children Born in 1997 to 2007: A Total Population Study from Stockholm, Sweden
The Journal of Hand Surgery (Am.) 2010;35A:1742–1754.

II. Ekblom AG, Laurell T, Arner M
Epidemiology of Congenital Upper Limb Anomalies in Stockholm, Sweden 1997 to 2007: Application of the OMT Classification
Submitted

III. Ekblom AG, Dahlin LB, Rosberg HE, Wiig M, Werner M, Arner M
Hand Function in Children with Radial Longitudinal Deficiency
BMC Musculoskeletal Disorders 2013 Mar 28;14(1):116.
DOI: 10.1186/1471-2474-14-116.

IV. Ekblom AG, Dahlin LB, Rosberg HE, Wiig M, Werner M, Arner M
Hand Function in Adults with Radial Longitudinal Deficiency
Submitted

CONTENTS

LIST OF ABBREVIATIONS

AER	Apical Ectodermal Ridge
AHA	Assisting Hand Assessment
AHA-PAD	Assisting Hand Assessment, version for Prosthesis, Amputation and Deficiency
AROM	Active Range of Motion
BL	Body Length
BMP	Bone Morphogenic Protein
CHEQ	Children´s Hand-use Experience Questionnaire
CULA	Congenital Upper Limb Anomalies
HFA	Hand Forearm Angle
HFP	Hand Forearm Position
HWO	Vilkki Severity Grading for Radial Dysplasia (Hand Wrist Other)
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} revision
ICF	International Classification of Functioning, Disability and Health, WHO 2001
ICF-CY	International Classification of Functioning, Disability and Health, version for Children and Youth, WHO 2007
IFSSH	International Federation of Societies for Surgery of the Hand
mH	Modified Vilkki Severity Grading for Radial Dysplasia (Hand)
mHFP	Modified Hand Forearm Position
NBHW	The National Board of Health and Welfare (Socialstyrelsen)
OMT	Oberg, Manske and Tonkin
PEDI	Pediatric Evaluation of Disability Inventory
PZ	Progression Zone

Quick DASH	Short version of Disabilities of the Arm Shoulder and Hand Outcome Measure
RLD	Radial Longitudinal Deficiency
SF-12	Medical Outcomes Study 12-item Short-Form Health Survey
SHDR	Swedish Hospital Discharge Register (Svenska Slutenvårdsregistret)
SHH	Sonic hedge hog morphogenic protein
SMBR	Swedish Medical Birth Register (Svenska Födelseregistret)
SRCM	Swedish Register on Congenital Malformations (Svenska Missbildningsregistret)
STI	Shape-Texture-Identification test
TAM Digits	Total Active Range of Motion of digits
TAM Elbow	Total Active Range of Motion of elbow
TAM Shoulder	Total Active Range of Motion of shoulder
TCFL	Total Carpal Forearm Length
TFA	Total Forearm Angle
UB	Ulnar Bow
UL	Ulnar Length
VATER	Syndrome of non-random association of birth defects including vertebral anomalies, anal atresia, trachea-esophageal fistula, esophageal atresia, renal (kidney) and/or radial anomalies
WNT7A	Wingless Type 7A morphogenic protein
WRD	Wrist Radial Deviation
ZPA	Zone of Polarizing Activity

GLOSSARY

Anomaly	a deviation from normal, especially of a bodily part
Anterior	situated toward the front of the body
Birth defect	a physical or biochemical defect that is present at birth and may be inherited or environmentally induced
Deformation	an insult that occurs after normal formation which changes structure and form
Disruption	a destructive process that alter a structure after it has formed normally
Distal	being located away from the center of the body
Dorsal	located near, on, or toward the back or posterior part of the human body
Dysmorphology	the scientific study of abnormal structure and form in animals, plants or humans
Dysplasia	abnormal cellular organization within a tissue resulting in structural changes in size and shape
Ectoderm	the outermost of the three primary germ layers of an embryo that is the source especially of nervous system, epidermis, hair and nails
Epidemiology	the scientific study of diseases and how they are found, spread and controlled in groups of people
Hypoplasia	a condition of arrested development in which an organ or part remains smaller than normal
Incidence	the number of new cases of a disorder in a population of individuals during a specified time interval (e.g. number of cases/year)
Longitudinal deficiency	an underdevelopment of the limb mainly extending along or relating to the long axis of the limb
Malformation	abnormal formation of body part or tissue.

Mesoderm	the middle of the three primary germ layers of an embryo that is the source especially of bone, muscle, connective tissue and dermis
Pollicization	the reconstruction or replacement of the thumb especially from part of the index finger
Posterior	situated at or toward the hind part of the body
Prevalence	the proportion of individuals in a population who have a disorder at a specific point of time
Proximal	located toward the center of the body
Radial	located on the same side of the forearm as the radius or the same side of the hand as the thumb
Reduction deformity	an anomaly caused by underdevelopment (reduction) of structures
Transverse deficiency	an underdevelopment of the limb mainly extending at right angle to the long axis of the limb
Ulnar	located on the same side of the forearm as the ulna or the same side of the hand as the little finger
Ventral	located near, on, or toward the front or anterior part of the human body

Sources: 1) MedLine Plus Medical Dictionary, U.S. National Library of the Medicine and National Institutes of Health and 2) Cambridge Dictionaries Online 3) Epidemiology in Medicine, Hennekens CH, Buring JE, ed Mayrent SL. Philadelphia: Lippincott Williams & Wilkins, 1987.4) Morphogenesis and Dysmorphogenesis, Jones KL. In: Smith´s recognizable patterns of human malformations. Philadelphia, Saunders Elsevier, 2006.

1 PROLOGUE

My interest in research had it´s starting point in all the questions that were put to me as a hand surgeon by the many parents I met who had just given birth to a child with a hand difference. How common is this? Why did this happen to our child? Did we do anything wrong? How can you treat this? Maybe the most important question was; What will the future hold for my child?

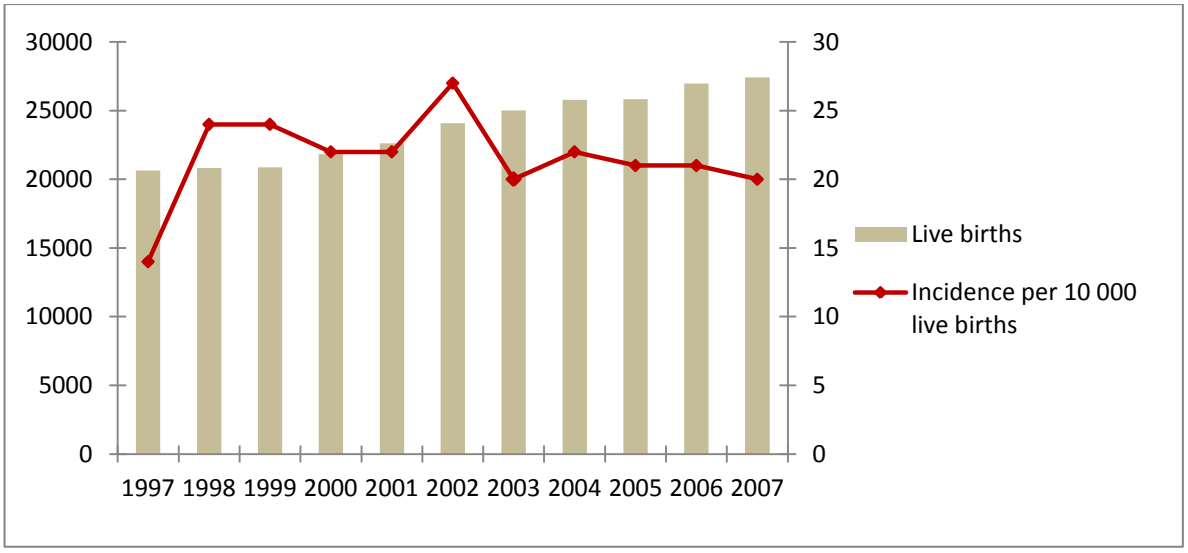
It is of vast importance to the parents and their ability to help and encourage their child in handling the surrounding world, that we as health care professionals can provide true and informative answers. In trying to find these answers I found that knowledge about congenital upper limb anomalies was sparse. The urge to be able to answer at least a few of these questions was the seed of my research projects.

What is the true incidence of the different types of congenital upper limb anomalies?
How common are associated non-hand anomalies and familial occurrence of hand differences?
How do children and adults with radial dysplasia cope in daily life?
Do we as hand surgeons address the problem that is most important to the individual with a hand difference?

2 THESIS AT A GLANCE

I. Epidemiology of Congenital Upper Limb Anomalies in 562 Children Born 1997 to 2007: A Total Population Study from Stockholm, Sweden

Aim: To classify and describe the epidemiology of congenital upper limb anomalies in the total population of Stockholm County between 1997 and 2007.
Methods: Registry studies (Registries held by the National Board of Health and Welfare and hospital based medical registries), medical records and radiographs. International Federation of Societies for Surgery of the Hand (FSSH) classification.
Conclusion: The incidence of congenital upper limb anomalies (CULA) was 21.5 per 10,000 live births. The results can be used as a reference for CULA in a total population.

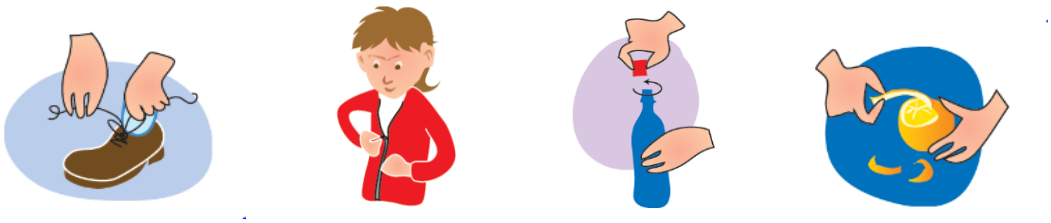


II: Epidemiology of Congenital upper Limb Anomalies in Stockholm, Sweden 1997 to 2007; Application of the OMT Classification

Aim: To apply the newly proposed Oberg, Manske and Tonkin classification of congenital upper limb anomalies on the same population studied in paper I in order to measure the incidence of congenial upper limb anomalies and to evaluate the new classification system´s usefulness.
Methods: Registry studies. OMT classification.
Conclusion: The OMT classification provides a useful framework for classification of CULA based on current understanding of limb development. Further refinements of the classification are proposed. The results can be used as a reference of CULA in a total population.

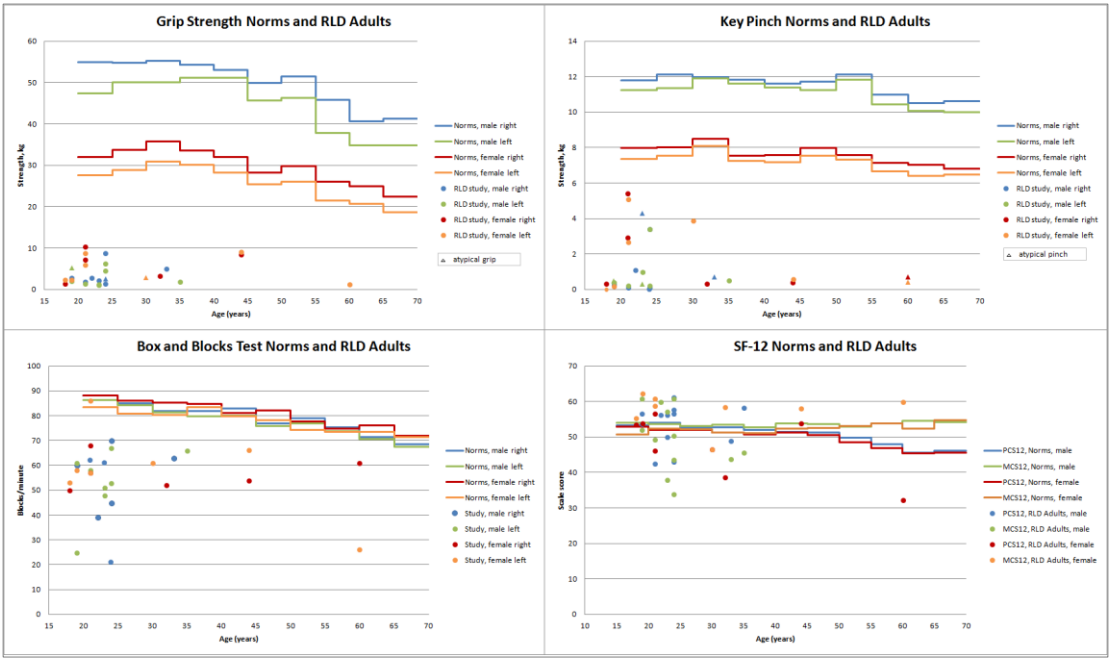
III: Hand Function in Children with Radial Longitudinal Deficiency

Aim: To investigate what aspect(s) of the limb anomaly has the most effect on activity and participation in children with radial longitudinal deficiency (RLD).
Methods: 20 children age 4-17 years, RLD Bayne II-IV, range of motion, grip strength, sensibility, radiographic parameters, Box and Block test, AHA-PAD, PEDI, CHEQ
Conclusion: In children with radial longitudinal deficiency total range of motion of digits and wrist may be of more cardinal importance to the child´s activity and participation than the angulation of the wrist.



IV: Hand Function in Adults with Radial Longitudinal Deficiency

Aim: To investigate what aspect(s) of the limb anomaly has the most effect on activity and participation in adults with radial longitudinal deficiency (RLD).
Methods: 20 individuals age over18 years, RLD Bayne II-V, range of motion, grip strength, key pinch, sensibility, radiographic parameters, Box and Block test, Sollerman hand function test, Quick DASH, SF-12
Conclusion: In adult individuals with radial longitudinal deficiency grip strength, key pinch, forearm length, and elbow and digital motion seem to be more important to the individual´s activity and participation than the radial angulation of the wrist.



3 CONGENITAL UPPER LIMB ANOMALIES

3.1 BACKGROUND

This thesis has as its focus a rare and relatively unstudied group of diagnoses – Congenital upper limb anomalies (CULA). These diagnoses encompass a wide variety of malformations, deformations and dysplasias of the hand and arm. Most of these anomalies are minor and do not affect individuals´ participation in school, work related activities or in social life. A few congenital anomalies of the upper limb, however, are more extensive and can restrict an individual's activities in daily life considerably. The hand is not only a tool for manipulating the world around us, but also plays an important role in our communication through touch and gestures. Since our hands are almost always visible, both to ourselves and to others, a congenitally different hand is a challenge to the individual that must be coped with. Therefore, even a minor hand difference can be important from a psychological point of view.

In approximately 3% of all live births an immediately detectable congenital anomaly is found (1, 2). Anomalies of the upper and lower limb represent a minor part of these. Previous research has found that limb defects affect approximately 5-6 children per 10,000 births (3-5). Upper limb deficiencies are much more common than lower limb deficiencies, representing 3/4 of the cases (4, 5). In 12-50% of cases, the limb anomaly is associated with other structural congenital anomalies (3, 4, 6). Since the thalidomide tragedy many countries and centers cooperate in collecting data on birth defects (International Clearinghouse Birth Defects Surveillance and Research). The surveillance of birth defects facilitates early detection of changes in incidence rate and pattern of malformations.

Rapidly increasing knowledge of the molecular and physiological mechanisms guiding normal limb development has facilitated our understanding of the mechanisms behind deviant limb development. The structure of the anomalies can be understood from disturbances of the normal developmental process. The recent rise in knowledge has also led to a lack of concordance between the currently used classification system of congenital upper limb anomalies and what we now know about limb development. In order to more accurately categorize types of upper limb anomalies, a new classification scheme for CULA has been proposed (7, 8).

Accurate systems of classification are crucial for creating a common language for description of these disorders as well as for comparative studies of treatment and epidemiology. Epidemiologic studies of congenital upper limb anomalies are important not only for health care planning and for monitoring possible changes in incidence over time, but also for enabling comparison between regions in order to identify underlying, potentially preventable, factors.

3.2 UPPER LIMB DEVELOPMENT

Around the fourth week after gestation the upper limb buds are visible at opposite sides of the main body axis of the embryo (9). These limb buds are protrusions of lateral plate mesoderm covered with a thin layer of ectoderm. The continuing development of the limb buds proceeds along three axes: proximal - distal, anterior - posterior (radio-ulnar) and dorsal - ventral. The growth and patterning along each axis is controlled by signaling centers, i.e. populations of cells that excrete morphogens. Morphogens are signaling molecules that signal patterning information to local cells and organize the developmental process (7). Well-known examples of morphogens in the limb bud are sonic hedgehog (SHH) and fibroblast growth factor.

An ectodermal thickening at the dorsal-ventral boundary of the limb bud, the apical ectodermal ridge (AER), interacts with a zone of undifferentiated cells in the underlying mesoderm, the progression zone (PZ), and by signaling loops maintains continuing proximal-distal outgrowth of the limb bud (7). As cells leave the PZ they start to differentiate. According to the progress zone model, the length of time the cells spend in PZ determines proximo-distal identity (10). The longer the time, the more distal structures are formed (9). The patterning along the anterior- posterior (radial-ulnar) axis is regulated by the zone of polarizing activity (ZPA), a population of cells located in the posterior (ulnar) limb mesoderm. By secretion of the morphogen sonic hedgehog (SHH), ZPA controls the differentiation between the ulnar and radial side structures of the forearm and hand. The AER and ZPA interact in a reciprocal signaling feedback loop that maintains SHH expression during proximal to distal outgrowth of the limb bud. Another morphogen, wingless-type MMTV integration site family member7A (WNT7A), is involved in the dorsalization of the underlying mesoderm. WNT7A excreted from the dorsal ectoderm interacts with the ZPA by maintaining the secretion of SHH. Hence, ZPA links all three axes of development and differentiation during limb outgrowth (7) (Figure 1).

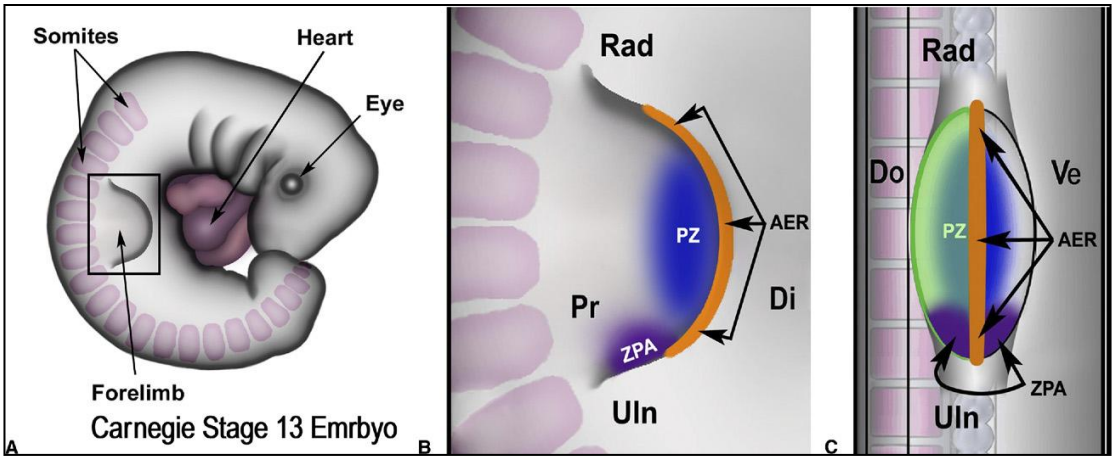


Figure 1. Upper limb bud

From Oberg et al. (7), with permission from the publisher.

The hand plate, a broadening and flattening of the distal part of the limb bud, is visible around the fifth week after gestation. SHH, secreted from ZPA, by interaction with other morphogens, regulates the number and identity of the digits. The SHH induces a gradient of bone morphogenic protein (BMP) along the radio-ulnar border of the hand plate which contributes to the identity of the becoming digits. The BMP induces programmed cell death, apoptosis, in the interdigital space, which leads to separation of the digits (7) (Figure 2).

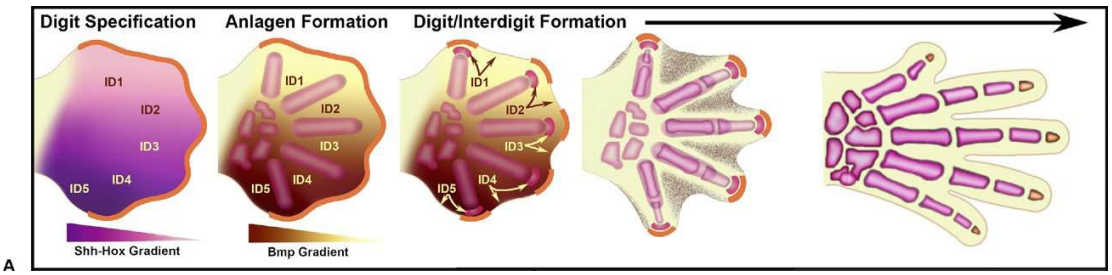


Figure 2. Formation of the digits.

Adapted from Oberg et al. (7), with permission from the publisher

By the 7th week after gestation the fingers are completely separated and ossification of the radius and ulna begins. By the 8th week after gestation ossification of the metacarpals and phalanges start (11). By the 13th week finger nails are present. At about three months of fetal age all tissues in the upper extremity have completed their differentiation and this is followed by further growth of all tissues. Ossification of the cartilage and skeletal growth continues in the fetus as well as after birth and does not cease until the closure of the epiphyseal growth plates in adolescence. The timeline of upper limb development is presented in Table 1.

If the complex process of limb development in the early embryonic stages is disturbed, it results in an abnormal formation of the limb. Most congenital anomalies of the upper limb occur in the embryonic period between the third week and the 7th week (13). More rare are insults to the limb bud after the third gestational month, causing disruption of a, hitherto, normal formation of the limb (7).

The terminology of dysmorphology provides a framework for discussions on the etiology of congenital limb anomalies. A *malformation* is an abnormal formation of body part or tissue. A d*eformation* refers to an insult that occurs after normal formation, and when it is due to destructive processes that alter a structure it can also be termed a *disruption*. A *dysplasia* refers to abnormal cellular organization within a tissue resulting in structural changes in size and shape. (14).

Table 1.

Timeline of Upper Limb Development	
Days after gestation	*Developmental Events*
26	Upper limb bud forms
31	Limb bud curves
33	Hand plate forms
	Subclavian/axillary/brachial arteries form
36	Nerve trunks enter upper limb
	Chondrification of humerus and forearm
	Glenohumeral cavitation begins
41	Digital rays visible
	Chondrification of rays
	Ulnar artery forms
44	Chondrofication of proximal phalanges
	Radial artery forms
	Pectoralis muscles splits in two heads
47	Chondrofication of middle phalanges
	Initial separation of digits
	Digital cavitation/joint formation begins
50	Chondrofication of distal phalanges
	Digital separation
54	Humerus ossifies
	Digital separation complete
56	Ossification of distal phalanges

Adapted from Al-Qattan et al. (12), with permission from the publisher

3.3 SYSTEMS OF CLASSIFICATION

A classification system of a disorder tends to be adapted to the aim of its use. Limb anomalies have thus been classified differently by pediatricians, geneticists and hand surgeons. Early classifications of limb anomalies emanated from the morphology of the deformities. Already in 1949, Birch-Jensen (15, 16) classified reduction deformities of the upper limb by categorizing them as radial or ulnar defects, split hands or amputations. Shortly thereafter, in 1951, O`Rahilly, (17) proposed a classification of long bone deficiencies that categorized the anomalies as terminal or intercalary defects, using Greek and Latin terminology. The extended and revised version of the Frantz and O´Rahilly classification (18) was the first widely accepted and used classification system for limb deformities (19).

In 1968, Swanson et al. (20) proposed a new comprehensive classification system based on the then current understanding of embryologic failure. In a revised form (21), this classification system was adopted by the International Federation of Societies for

Surgery of the Hand (IFSSH) in 1984. In 2000, Knight and Kay presented an extended version of this classification system (22).

In the IFSSH classification upper limb anomalies are divided into seven major categories. In contrast to earlier classification systems, the IFSSH classification not only includes reduction deformities, but also malformations due to aberrant differentiation of tissues, duplications, overgrowth, undergrowth, deformation due to constriction ring syndrome and generalized abnormalities and syndromes (Table 2).

Table 2.

IFSSH Classification of Congenital Upper Limb Anomalies (21, 22)	
	Category
I	Failure of formation
II	Failure of differentiation of parts
III	Duplication
IV	Overgrowth
V	Undergrowth
VI	Constriction ring syndrome
VII	Generalized abnormalities and syndromes

Each main category is in turn subdivided with regard to the anomaly´s level (proximal to distal), and side (radial to ulnar), and with regard to the type of tissue (vascular, neurologic, connective, skeletal) affected by the anomaly. When classifying a specific anomaly, it should be allocated to the main category containing the predominant deformity.

The IFSSH classification is still the internationally accepted and most widely used classification system. It is a useful tool for classifying most congenital upper limb anomalies and enables comparison between studies from different times and regions. The IFSSH classification has some obvious drawbacks though, since some anomalies fit in several categories and some do not fit in any category (22, 23). Because of this, the distribution of relative frequencies among the seven categories in the IFSSH classification is highly related to the classification strategies used by the authors. How to classify, especially complex cases along the spectrum of symbrachydactyly, cleft hand, central polydactyly and syndactyly, have been subjects of debate (22, 24-28). The seventh category, Generalized abnormalities and syndromes, is, to even greater extent, influenced by classification strategies and runs the risk of being used when no other category is appropriate. Furthermore, our current knowledge of limb development does not agree with the IFSSH classification system (7).

While awaiting an updated classification system for congenital upper limb anomalies, the IFSSH classification was used in paper I.

In 2010, Oberg, Feenstra, Manske and Tonkin (7) proposed a new updated classification scheme for CULA based on current understanding of limb development,

the OMT classification. An assessment of this OMT classification system was published in 2013 and a refined and extended version of the system was proposed by the authors (8) (Table 3).

The OMT classification is divided in four main categories; *Malformations*, *Deformations*, *Dysplasias* and *Syndromes.*

The *Malformations* category consists of conditions caused by an abnormal limb formation and is divided according to the extent and localization of developmental failure; *Failure of axis formation/differentiation – entire upper limb* and *Failure of axis formation/differentiation – hand plate*.
Each of the two subgroups is further subdivided according to the three axes of limb development;

1. Proximal-distal axis,
2. Radial - ulnar (antero-posterior) axis,
3. Dorsal-ventral axis
4 . Unspecified axis.

The *Deformations* category consists of conditions caused by a deformation or disruption of normal limb development and is divided into three groups: Constriction ring sequence, Trigger digits and "Not otherwise specified".

The *Dysplasias* category includes conditions associated with cellular atypia or tumour formation and is divided into Hypertrophy and Tumorous conditions.

The fourth main category, *Syndromes*, includes generalized syndromes that also affect the upper limb.

The refined and extended version of the OMT classification (8) was used in paper II.

Table 3.

OMT Classification of Congenital Upper Limb Anomalies (8)	
	Category
1	Malformations
	A. Failure of axis formation/differentiation - entire upper limb
	B. Failure of axis formation/differentiation - hand plate
2	Deformations
	A. Constriction ring sequence
	B. Trigger digits
	C. Not otherwise specified
3	Dysplasias
	A. Hypertrophy
	B. Tumorous conditions
4	Syndromes

3.4 EPIDEMIOLOGY

Prevalence refers to the proportion of individuals in a population who have a disorder at a specific point of time. The *incidence* refers to the number of new cases of a disorder during a specified time interval (e.g. number of new cases/year). In the case of birth defects the prevalence at birth and incidence are equal. The *incidence rate* of birth defects is usually expressed as number of cases per number of births per year. Furthermore, it is important to define if *births* is equal to live births as well as stillbirths or live births only. In this thesis the term incidence was chosen and incidence rate is expressed per live births.

Even though epidemiologic studies are important both for health care professionals and for the affected families there are few epidemiologic studies concerning congenital upper limb anomalies. Furthermore, the few studies that do exist are difficult to compare since they rely on both different classification systems and different classification strategies. Some studies, for example, include only reduction deformities (4, 15, 29, 30) while others regard the upper and lower extremity as a common group (3, 5, 29, 31, 32). Hospital-based studies from highly specialized centers present somewhat different relations between the categories compared to studies based on total populations (23). The methods of data collection are also important for the accuracy of the incidence figures. Some studies have a poorly defined reference population and thereby incidence figures are extrapolated from clinical visits and local populations (33, 34).

Because of the differences in methodology and perhaps due to different populations as well, incidence of CULA vary in the studies that have been done to date. One of the first total population studies on congenital upper limb anomalies is a Danish cross-sectional survey from 1943-1947 (15). In that study only limb deficiencies were included and the incidence was estimated to be 1.55 per 10,000 births. In a more recent study from Finland in 2011, the national incidence of upper limb deficiencies were 5.25 per 10,000 live births and in 60% of cases associations with other malformations were found (35). In the study by Conway et al. 1956 (33), that included other types of CULA than limb deficiencies, the incidence of CULA was estimated to be16 per 10,000 live births. In a study of data from the Edinburgh Register of the Newborn, 1964-1968, Rogala et al. (36) found the incidence of CULA to be 30 per 10,000 births, including stillbirths. In the large multicenter study by Lamb et al. (34), based on the IFSSH classification, the incidence of CULA for the period 1976-1978 was 18 per 10,000 live births. In both the study from Conway et al. (33) and the study from Lamb et al. (34) the incidence figures were an estimate from clinical visits and local populations. The only previous total population study of CULA based on the IFSSH classification is a study from Western Australia by Giele et al. (37). The incidence of CULA in that study was 19.7 per 10,000 live births.

In the IFSSH classification the first three categories; Failure of formation, Failure of differentiation and Duplications, represent the vast majority of upper limb anomalies. Overgrowth, Undergrowth, Constriction ring syndrome (Amniotic band syndrome) and Generalized abnormalities and syndromes are much rarer.

No total population study of CULA based on the OMT classification has, to my knowledge, previously been published.

3.5 ETIOLOGY

It has been estimated that in approximately 10% of congenital malformations the identified cause is environmental, in 15-25% genetic and in 65-75% the cause is unknown (38). Despite the rapidly increasing knowledge of genetic causes of congenital malformations, the etiology of most CULA is still unknown. Disturbances in limb development can be caused by both genetic and environmental factors or by the interaction of both.

Examples of genetic causes of limb malformation include chromosomal aberrations, genedosealterations and mutations of single genes. Probably mutations in genes or regulatory elements that control limb development are the cause of many limb anomalies but, as yet, few CULA have been linked to a specific gene mutation. For some diagnoses, the inheritance pattern is well known (e.g. cleft hand and foot with autosomal dominant inheritance). For others, de novo mutations are the cause (e.g. Apert´s syndrome and mutation in the gene *FGFR2*) (40). In some known syndromes, the gene mutation is identified (e.g. Holt – Oram and *TBX5* mutation) (41), but in the majority of cases of CULA the etiology is still unknown.

Environmental factors that can cause congenital anomalies are for example exposure to drugs, radiation, congenital infections and maternal disorders (39). The environmental factors can either induce an alteration of limb development resulting in an abnormal limb formation (e.g. drugs), or cause a disruption or deformation of an otherwise normal limb development (e.g. amniotic band strangulation, external pressure in utero).

4 RADIAL LONGITUDINAL DEFICIENCY

4.1 BACKGROUND

Radial longitudinal deficiency, often referred to as radial club hand, is a rare congenital condition characterized by an underdevelopment and malformation of the radial side structures of the forearm and hand. The anomaly, first described by Petit in 1733 (42), is characterized by a significant shortening of the forearm, radial angulation of the wrist, impaired range of digital motion and limited strength in pinch and grip. In addition, the thumb is always affected with a varying degree of hypoplasia or aplasia.

Since the 19th century there has been an evolution of surgical methods to correct the radial angulation of the wrist with the aim of improving function and appearance. In spite of this, the long-term results of surgery are discouraging with a high rate of late deformity recurrence and impaired ulnar growth (43-45). Functional improvements have been difficult to verify (46-48) and the routine use of surgical correction of the radially deviated wrist in individuals with RLD is currently debated.
Current knowledge about the relationships between, on the one hand, different physical aspects of the deformity in RLD (body function and structure) and, on the other, activity and participation among individuals with RLD, is sparse.

The International Classification of Functioning, Disability and Health, WHO 2001 (ICF) (49) provides a comprehensive framework for the description of disability that allows us to explore these relationships. To give a broader picture of individuals with RLD the ICF framework can be used to cover the three different aspects of disability - body function and structure, activity and participation.

4.2 CLASSIFICATION

4.2.1 Classification of radial longitudinal deficiency

During the 20th century several classifications of radial longitudinal deficiency were proposed. Heikel (50) was the first to divide RLD into three categories: total aplasia, partial aplasia and hypoplasia of the radius. In 1976, the International Federation of Societies of Surgery of the Hand (IFSSH) classified RLD as *Failure of formation of parts, longitudinal - radial*. In 1987, Bayne and Klug (51) expanded this classification, dividing RLD into four categories in reference to the radiographic characteristics of the radius. In the Bayne and Klug classification of RLD, Type I is a radius more than 2mm shorter than the ulna, Type II is a hypoplastic radius, Type III is a partially absent radius and Type IV a totally absent radius. In 1999, this classification was modified and expanded and deficiencies of the thumb and radial side of the carpus were included (52). In this modified classification Type N represents hypoplasia/aplasia of the thumb without carpal or radial deficiencies and Type 0, in addition to thumb deficiencies, includes carpal anomalies and may also include radio-ulnar synostosis or congenital dislocation of the radial head. The most recent expansion of the classification added

severe proximal radial longitudinal dysplasia, which represents absence of the proximal humerus in combination with total absence of the radius and radial-sided hand deficiencies; thus, Type V (53). (Table 4) This modified Bayne and Klug classification was used in paper III and IV (Figure 3).

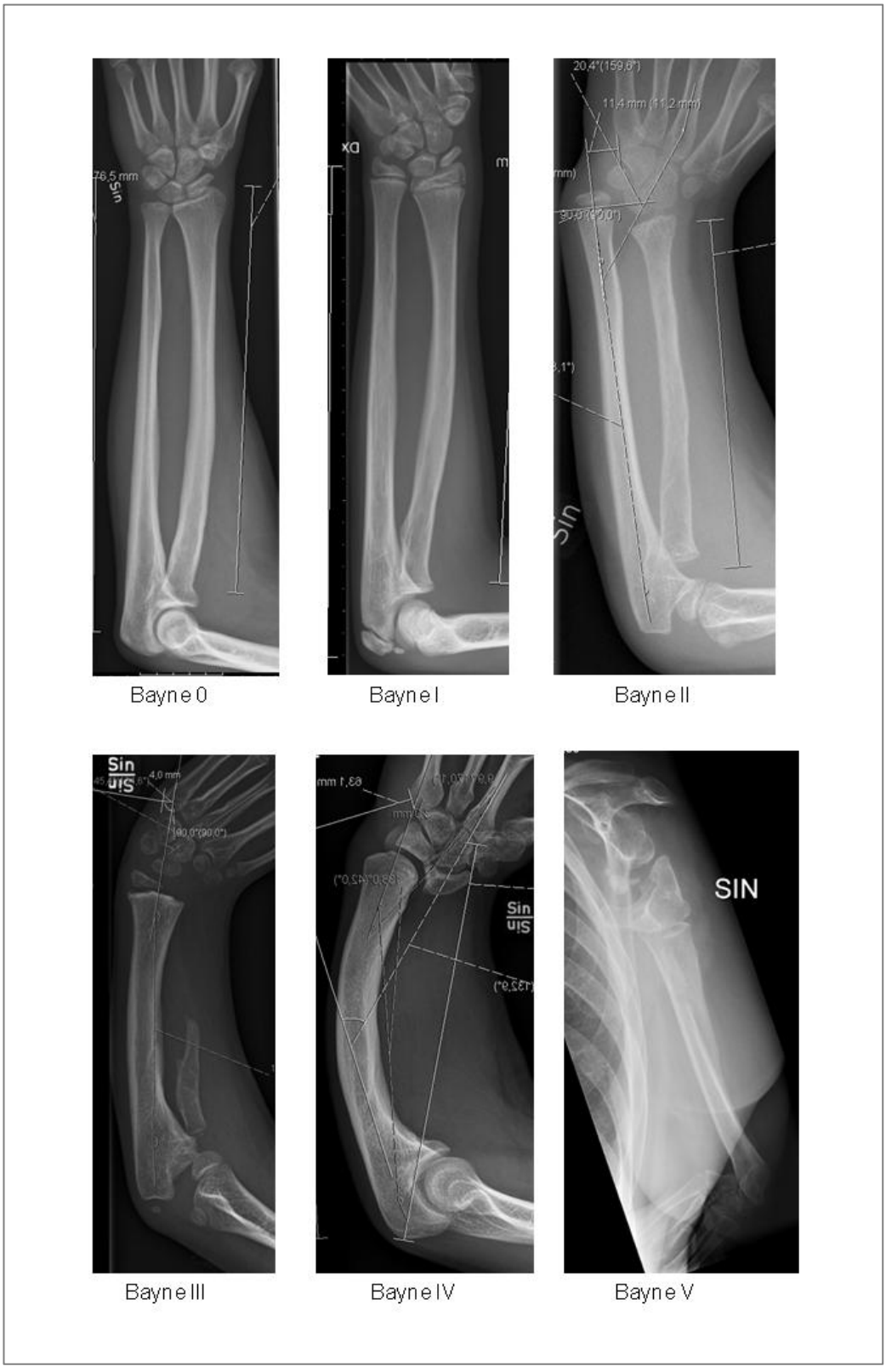


Figure 3. Radiographs of RLD Bayne Type 0, I-V

Table 4.

Modified Bayne and Klug Classification of RLD (51-53)					
Type	*Thumb*	*Carpus*	*Distal radius*	*Proximal radius*	*Humerus*
N	Hypoplastic or absent	Normal	Normal	Normal	
0	Hypoplastic or absent	Absence, hypoplasia or coalition	Normal	Normal, radio-ulnar synostosis or congenital dislocation of radial head	
I	Hypoplastic or absent	Absence, hypoplasia or coalition	Radius > 2mm shorter than ulna	Normal, radio-ulnar synostosis or congenital dislocation of radial head	
II	Hypoplastic or absent	Absence, hypoplasia or coalition	Hypoplasia	Hypoplasia	
III	Hypoplastic or absent	Absence, hypoplasia or coalition	Partial absence of the radius Physis absent	Variable hypoplasia	
IV	Hypoplastic or absent	Absence, hypoplasia or coalition	Absent	Absent	
V	Hypoplastic or absent	Absence, hypoplasia or coalition	Absent	Absent	Anomalous or absent

4.2.2 Classification of thumb deficiencies

In RLD the thumb is always affected with a varying degree of hypoplasia or total aplasia. However, thumb hypoplasia also can occur in isolation (54). The Blauth classification system is the most frequently used way of classifying thumb deficiencies (55). In this system, Type I represents minor hypoplasia of the thumb ray. In Type II the thumb is hypoplastic and unstable with a narrowing of the first web space. In Type III, the hypoplastic thumb has, in addition, intrinsic and extrinsic musculotendinous deficiencies as well as skeletal hypoplasia. Type IV comprises a so-called floating thumb and Type V represents a totally absent thumb. In 1995, Manske et al. (56) proposed a subdivision of Type III thumb deficiencies, where Type IIIA has a stable carpometacarpal joint, in contrast to Type IIIB, where the thumb base is unstable due to a deficient base of the first metacarpal (Table 5).

Table 5.

Modified Blauth Classification of Thumb Hypoplasia (56)						
Type	*Thumb Size*	*First Web*	*Intrinsic muscles*	*Extrinsic muscles*	*Ligaments*	*Bones & Joints*
I	Normal or small	Normal	APB and OP hypoplastic	Normal	Normal	All bones present, may be hypoplastic
II	Normal or small	Distal and tight	APB and OP hypoplastic or absent	Normal or nearly normal	MP UCL lax	All bones present and hypoplastic
IIIA	Small	Distal and tight	APB and OP absent or severely hypoplastic	Abnormal: FPL and/or EPL absent or connected or pollex abductus	MP UCL and possibly RCL lax	All bones present and hypoplastic
IIIB	Small	Distal and tight	APB and OP absent or severely hypoplastic	Abnormal: FPL and/or EPL absent or connected or pollex abductus	MP UCL and possibly RCL lax	Proximal metacarpal absent
IV	Very small		APB, OP,FPB and adductor absent	Absent	Absent	Metacarpal, trapezium and scaphoid absent
V	Absent	Absent	APB, OP, FPB and adductor absent	Absent	Absent	Phalanges, metacarpal, trapezium and scaphoid absent

APB= abductor pollicis brevis, OP= opponens pollicis, MP= metacarpophalangeal joint, UCL=ulnar collateral ligament, RCL= radial collateral ligament, FPL= flexor pollicis longus, EPL= extensor pollicis longus, FPB= flexor pollicis brevis

4.3 INCIDENCE

The incidence rate of RLD is estimated to be 0.2 to 1.64 per 10,000 live births (3, 4, 15, 31, 36, 57). The variation could be due to different populations, divergent classification strategies and/or differences in data collection. RLD comprises approximately 4% of all CULA (58). About 40 - 70% of individuals with RLD have a bilateral involvement (3, 29, 31, 57). In unilateral cases the right side is more frequently affected (29, 31, 35, 59). On close examination though, an individual with unilateral RLD often has a slightly hypoplastic thumb on the "unaffected" side. There is a slight preponderance of males (57, 60) in RLD.

4.4 EMBRYOLOGY AND ETIOLOGY

The etiology of RLD is still not fully understood. In experimental studies on rats, administration of a teratogenic agent in the early embryonic stage induces radial ray deficiency similar to RLD in humans (61). Damage to the AER in the chicken limb bud has also been found to induce radial ray deficiency (62, 63). Intake of the drug thalidomide by the mother during early pregnancy (postmenstrual day 38-54) has been associated with severe limb anomalies, especially RLD (64). Also maternal intake of antiepileptics has been associated with RLD (65-67). In many cases of isolated unilateral RLD without associated non-hand anomalies, neither genetic nor environmental causes have yet been identified. In individuals with a bilateral RLD, association with non-hand anomalies are more common and the RLD is often part of a recognized pattern of non-random associations of congenital malformations (VATER) or a known syndrome (TAR, Holt-Oram, Fanconi) (65). Many of these syndromes are recognized as genetic disorders.

4.5 ANATOMIC PATHOLOGY

The more severe types of RLD are characterized by a short and bowed forearm, radial angulation of the wrist, limited digital range of motion and a varying degree of thumb hypoplasia or aplasia. In RLD not only the skeletal structures are anomalous, but also muscles, tendons, vessels and nerves on the radial side of the hand and forearm are deviant. In the more pronounced cases the whole limb may be involved. Knowledge of the structural changes of the anatomy in RLD is important for understanding the corresponding functional impairments in these individuals and also for planning treatment strategies.

The *skeletal anomalies* in RLD can involve the entire upper extremity. In the more severe cases of RLD the humerus can be affected with an abnormal glenoid and absent or anomalous proximal part (53). The elbow motion is often limited, especially in flexion. The radius is either shorter than normal, hypoplastic, partially absent or totally absent. Ulnar length is only 40-60% of age related norms and the ulna is often radially bowed (44, 50). In cases of partial or total absence of the radius a fibrous cord is sometimes present, possibly, representing a developmental remnant of the radius. This “fibrous anlage” can further aggravate the radial deviation of the wrist and ulnar bow. Due to the lack of radial support of the wrist in RLD Type I-V the wrist is radially deviated. When the distal radius is absent the carpus is often volarly displaced, the ulnar head subluxated and the radial deviation even more pronounced. The scaphoid and trapezium are almost always absent in the more severe types of RLD and often anomalous in the less severe cases (17) (50, 68).

RLD always includes varying degrees of hypoplasia or total aplasia of the thumb ray (54). The fingers tend to have a more limited range of motion on the radial side of the hand. The metacarpophalangeal joints are restricted in flexion and hyperextended, whereas the proximal interphalangeal joints have flexion contracture deformities.

The *muscle anomalies* in RLD are related to the degree of skeletal anomalies. In RLD Type V, when the proximal humerus is affected, the shoulder muscles may be anomalous. The biceps is often abnormal, but the triceps is usually present and normal in RLD. In the forearm, muscles normally originating from the lateral epicondyle of the humerus, the radius and interosseous membrane are frequently deviant. The pronator teres is often anomalous and the pronator quadratus absent. The radial wrist extensors are rudimentary and often fused with the brachioradialis muscles and their insertion in the ulna and carpus may be aberrant. The flexor carpi radialis is often absent, if present, it is hypoplastic and fused with the flexor digitorum profundus. The wrist extensor and flexor on the ulnar side are usually normal. In individuals with TAR-syndrome an aberrant muscle, the brachiocarpalis, with its origin on the anterolateral aspect of the proximal humerus and insertion in the radial side of carpus, is frequently present (69). The flexors of the fingers are commonly fused and abnormal and the finger extensors are often deficient and fused with the radial wrist extensors (50, 59). The flexor digitorum profundus to the index finger is frequently absent or deficient, which may influence decisions regarding pollicization of this finger to create a thumb (68). Furthermore, thumb extrinsic and intrinsic muscles are also abnormal or absent (54).

Nerve anomalies in RLD are common. The radial nerve often terminates at the elbow and the median nerve supplies the muscles in the anterior compartment of the forearm. The sensibility of the radial side of the hand is also supplied by the median nerve. This so-called "median-radial nerve" is frequently located just beneath the skin on the radial side of the wrist, which is important to bear in mind in surgery. The ulnar nerve is usually normal (59).

Vascular anomalies are also often present in RLD. The arteries on the radial side of the forearm and hand are abnormal but the ulnar artery is usually normal. The radial artery is absent in almost half of cases and otherwise hypoplastic. The interosseous arteries are usually well-developed and sometimes replace the ulnar and radial arteries. The deep palmar arch is small or missing in more than 90% of cases, but persistent median artery is often found. The radial digital artery to the thumb and index finger is sometimes absent (59, 70).

4.6 FUNCTIONAL IMPAIRMENT

The extensive anatomical abnormalities in the more severe types of RLD significantly impair hand function. The ulno-carpal joint is unstable and the range of wrist motion is limited. The lack of radial support of the wrist together with the tethering forces of the anomalous radial-side soft tissues results in a considerable radial deviation of the wrist. In the most severe cases, the radial deviation is over 90 degrees. Furthermore, the force of the wrist and finger flexors overpowers the extensors and the carpus becomes volarly displaced. The radial bowing combined with reduced ulnar length result in a short forearm and impaired reach for these individuals (50, 59, 71). If elbow flexion is limited, the individual is dependent on radial wrist deviation to reach the mouth. In these cases straightening of the wrist is contraindicated (68). Grip strength is also considerably limited by the deficient forearm muscles. The sub-functional or absent

thumb, together with the limited range of motion of the fingers, especially on the radial side, further reduces grip strength and manual dexterity. Holding a glass, turning a key or performing a power grip can be very difficult for individuals with these anomalies. When the thumb is absent or non-functional a lateral pinch between the two ulnarmost digits is often preferred and the index finger may be pronated to better meet the ulnar fingers, thereby acting as a substitute for a thumb. Two types of prehension, not usually seen in the normal hand, are found in individuals with RLD: a lateral pinch between any two fingers and a spherical grip between the index and little finger (72).

In unilateral cases of RLD the affected hand assists the normal hand in bimanual activities. When both arms are affected the functional impairments are much more pronounced. Many single-handed activities must then be performed with both hands and some bimanual activities may be difficult to accomplish.

4.7 TREATMENT PRINCIPLES

4.7.1 No treatment

In children with milder forms of RLD, such as Type I-II, and with a functional thumb and good wrist function, no treatment of the wrist is indicated. In individuals with additional severe associated conditions treatment of the hand and arm may be of lesser importance and therefore not prioritized. A very limited range of elbow motion is a contraindication to surgical wrist correction since the radial angulation of the wrist facilitates reach to the mouth (51, 73). Older individuals have often adapted well to their disability and have usually developed dexterity and independence in activities of daily life. In these individuals the preferred grip is often the interdigital grip between the two ulnarmost fingers and if the wrist is straightened these digits will be placed in an unfavorable position. Furthermore, surgical wrist correction in older children is more difficult and has an increased risk of epiphyseal damage (51). If the index finger has very limited motion and is not used in manipulation tasks, the results of a pollicization procedure are less favorable (74-77) and therefore the procedure might be refrained from.

4.7.2 Manipulation and splinting

In individuals with RLD Type I-II with a mild radial deviation of the wrist stretching and splinting during childhood can be sufficient to retain a straight wrist position. Even in children with more severe radial wrist angulation stretching and splinting during the first period of life is frequently used to oppose the angulating forces on the wrist prior to surgery (78). After surgical wrist correction the child is usually prescribed continuous splinting of the wrist. The length of period varies, but many children use night splinting throughout growth (73).

4.7.3 Surgical correction

The common aims of wrist surgery in RLD are to stabilize the carpus on top of the ulna and thereby improve function and appearance of the arm by correcting the radial

angulation, to increase functional length of the limb and to improve wrist position for later pollicization.

The first reported surgical correction of the radially deviated wrist in RLD was carried out by Sayre in 1893 (79). Since then several different types of surgical procedures for deformity correction have been described. Many of the early procedures involved ulnar osteotomy and bone grafts (59, 80, 81). The two surgical procedures that are still the most frequently used are centralization and radialization.

In *centralization* the carpus is centered on top of the ulnar head. Commonly, after soft tissue release a partial resection of the carpal bones is made and a slot for the distal ulna is created. The distal ulna is then introduced in the carpal slot and the wrist is stabilized with an intramedullary pin introduced in the third metacarpal bone (68, 82). Long-term results after this notched centralization technique have been disappointing, however, with reduced wrist motion and affected ulnar growth. This has led to the development of a modified centralization technique without resection of carpal bones (51, 83). Even with this non-notched centralization technique there is a verified impaired ulnar growth and a high rate of late deformity recurrence (43-45, 84).

In an attempt to improve the unsatisfying results after centralization, in 1985 Buck-Gramcko proposed the *radialization* technique for wrist correction in RLD (84). In radialization the wrist deformity is slightly overcorrected and the radial side of the carpus is centered on top of the ulna. In this procedure the tethering structures on the radial side of the wrist are released or resected and the radial forearm muscles are transposed to the ulnar side of the wrist to balance the wrist in the straightened position. An intramedullary pin inserted through the index metacarpal stabilizes the wrist in a short postoperative period (Figure 4). Unfortunately, late deformity recurrence is also frequent in radialization (85). At present neither centralization nor radialization has proved to be superior to the other (43). If the ulnar bow is prominent, additional corrective *ulnar osteotomy* is an efficacious procedure to correct the ulnar deformity (43).

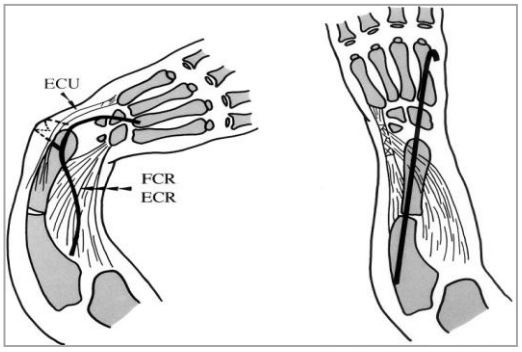


Figure 4. Radialization procedure

From Geck et al. (43) with permission from the publisher.

In 1998, Vilkki proposed the use of a *vascularized second metatarsophalangeal joint transfer* for wrist stabilization (86). This technically demanding procedure has shown encouraging results regarding wrist deformity recurrence, ulnar growth and wrist mobility (87, 88). As yet, this technique has mainly been used by one surgeon and further comparative studies between this procedure and centralization/radialization are needed.

The current practice of using *soft tissue distraction* with an external fixator before wrist correction facilitates surgical reduction of the wrist deformity in individuals with RLD (85, 89, 90). Also *bone lengthening with callus distraction* can be used to lengthen either an existent radius in RLD Type I-II or a short ulna (91, 92).

In spite of improvements of surgical techniques late deformity recurrence is frequent after surgical wrist correction. In severe cases of recurrent radial angulation *ulnocarpal arthrodesis* to achieve alignment of the wrist has been proposed (93).

In individuals with an absent thumb or a non-functional thumb with an unstable thumb base *pollicization* is the current treatment practice. In this procedure the index finger is transposed on its neurovascular bundle to create a new thumb. The technique described by Buck-Gramcko in 1971 (94) with refinements is still widely used. Long-term results after pollicization in individuals with a congenitally deficient thumb have shown increased strength in pinch and grasp as well as improved hand function in daily life (74, 95, 96).

4.8 ASSOCIATED ANOMALIES

In about 50-60% of RLD cases other congenital malformations are present as well (3, 30). These malformations include cardiac, gastrointestinal, pulmonary, genitourinary, neurologic and skeletal malformations. Due to the fact that these anomalies often occur together the acronym, VATER association has developed. It includes vertebral anomalies, anal atresia, tracheo-esophagal fistula and renal and/or radial defects (97, 98). In 20% of RLD cases a VATER association is found (57). VATER has in later years been expanded to also include anomalies of the heart (Cor) and limbs (VACTERL). RLD is also associated with several well described syndromes. These syndromes involve blood dyscrasias, cardiac anomalies, craniofacial defects and chromosomal defects (99). The clinically most important syndromes related to RLD are Fanconi anemia, Trombocytopenia-absent radius (TAR) and Holt-Oram.

Fanconi anemia is an autosomal recessive disorder characterized by a progressive bone marrow failure leading to aplastic anemia. The pancytopenia develops progressively and clinical onset is usually between 5-10 years of age. These children frequently have other associated anomalies and furthermore have an increased risk of developing malignancies (100). Eighty percent of children with Fanconi have a thumb hypoplasia and 15% have a radial hypoplasia or aplasia (65). The possibility of treatment by bone marrow transplant has considerably improved the survival rate in these children (101).

Trombocytopenia-absent radius syndrome (TAR) is characterized by bilateral radial aplasia with present thumbs in combination with neonatal trombocytopenia and leukocytosis (102). Platelet counts increase with age and are usually normalized by the age of five. Children with this syndrome may also have cardiac, renal and additional skeletal anomalies (103).

Holt-Oram syndrome is an autosomal dominant disorder with variable expression caused by a mutation in *TBX5*. It is characterized by congenital heart disease in combination with an upper limb anomaly that includes RLD (104). In 3% of cases of RLD a Holt-Oram syndrome is found (57).

Due to the severity of the associated malformations and syndromes all children presenting with RLD should be thoroughly investigated for additional anomalies.

4.9 ICF AND ICF-CY

The International Classification of Functioning, Disability and Health (ICF) is a classification system developed by the World Health Organization (WHO) in 2001 to enable more nuanced measurements and understandings of how individuals cope with disability (49). It is based on the notion that disability must be understood not as an attribute of a person, but as the result of complex interactions between a health condition and contextual factors in an individual´s life (105) (Figure 5).

Focusing thus on an individual´s ability to function in everyday life rather than on specific health impairments per se, the ICF measures disability in three domains: (1) *body function and structure*, referring to measurable physiological functions and anatomical structures, (2) *activity*, referring to how impairments in body function and structure limit an individual´s execution of activities, and (3) *participation*, referring to how limitations in activity level can in turn lead to restrictions in the individual´s ability to participate in, for example, school, work or social activities.

The International Classification of Functioning, Disability and Health, version for Children and Youth (ICF-CY), WHO 2007 (106), is based on the ICF and adapted to the developing child and the influence of its surrounding environment.

The ICF-CY framework was used in paper III and the ICF in paper IV.

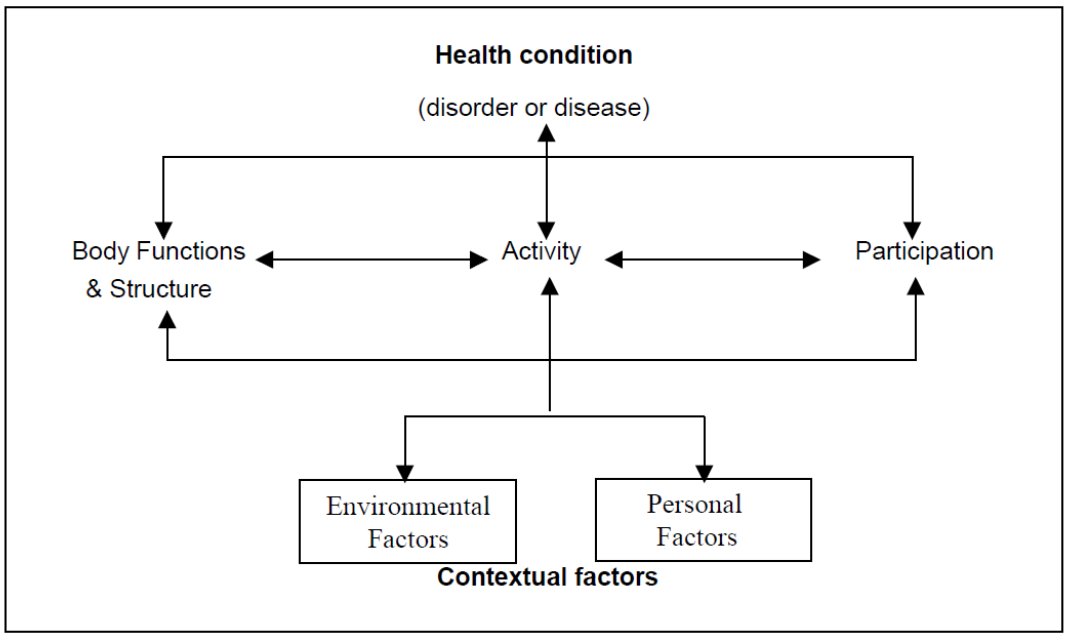


Figure 5. ICF, WHO 2001 (49)

5 AIMS

Overall aim

Few total population studies of congenital upper limb anomalies have previously been carried out and thus the incidence rates of different types of congenital upper limb anomalies are uncertain. The lack of generalizable incidence rates is further compounded by the fact that the internationally accepted classification scheme of congenital upper limb anomalies, the IFSSH classification, has inconsistencies. Furthermore, the IFSSH classification is not based on an up-to-date understanding of limb development. A new classification scheme, the OMT classification, was recently proposed, but it has not been fully evaluated and there are no available incidence figures based on it.

Another area of research to which this thesis seeks to contribute is perceived disability and patient related outcome measures in children and adults with radial longitudinal deficiency, about which little is known. The long-term results of surgical wrist correction are discouraging and evident improvements in individuals´ activity level have been difficult to verify.

To address these gaps in knowledge, this thesis sought to describe the epidemiology of congenital upper limb anomalies in a total population, evaluate a newly proposed classification system for congenital upper limb anomalies, and to investigate how certain physical parameters of the deformity in radial longitudinal deficiency correlate with *activity* and *participation* in afflicted children and adults.

Specific aims

Against this background, the specific aims of this thesis were to:

1. investigate the incidence of the different congenital upper limb anomalies in the total population of Stockholm County, Sweden.

2. apply the newly proposed OMT classification of congenital upper limb anomalies on the population studied in paper I and to evaluate this system.

3. examine what aspect(s) of the complex anomaly in radial longitudinal deficiency is the primary determinant for *activity* and *participation* in children.

4. examine what aspect(s) of the complex anomaly in radial longitudinal deficiency is the primary determinant for *activity* and *participation* in adults.

6 PATIENTS AND METHODS

The methods used in each study are briefly presented below. Full accounts of the methods used are given in the respective papers.

6.1 OVERVIEW OF THE FOUR PAPERS

Table 6.

Paper	Scope	Research Questions	Data sources	Study Design
I	Epidemiology of Congenital Upper Limb Anomalies (CULA)	What is the incidence of the different CULA in the population of Stockholm County?	Study period: Jan 1997 - Dec 2007. Medical registries, SMBR, SHDR, SRMC, Statistics Sweden, Swedish Tax Agency.	Retrospective epidemiologic total population study
II	Epidemiology of Congenital Upper Limb anomalies (CULA): Application of the OMT classification	Does the newly proposed OMT classification scheme account for all CULA in a total population, and can it be used to accurately establish incidence rates?	Study period: Jan 1997 - Dec 2007. Medical registries, SMBR, SHDR, SRMC, Statistics Sweden, Swedish Tax Agency.	Retrospective epidemiologic total population study
III	Hand Function in individuals with radial longitudinal deficiency (RLD). Relation between measurements of *body structure & function* and *activity* and *participation* according to the ICF framework.	What aspect(s) of the complex anomaly in RLD is the primary determinant for *activity* and *participation* in children?	Swedish multi-center study. Medical registries. Examination of 20 individuals with RLD, Bayne II-IV, age 4-17 years. ICF-CY framework.	Therapeutic study Case series
IV		What aspect(s) of the complex anomaly in RLD is the primary determinant for *activity* and *participation* in adults?	Swedish multi-center study. Medical registries. Examination of 20 individuals with RLD, Bayne II-V, age > 18 years. ICF framework.	Therapeutic study Case series

6.2 EPIDEMIOLOGIC STUDIES (PAPERS I-II)

6.2.1 Data collection and methods

The two epidemiologic studies of the incidence of CULA in Stockholm County are based on data from medical registries at all the hospitals in the region that treat children with congenital anomalies, as well as from the three registries held by the National Board of Health and Welfare (NBHW): the Swedish Medical Birth Register (SMBR), the Swedish Hospital Discharge Register (SHDR) and the Swedish Register on Congenital Malformations (SRCM).

During the study period, January 1, 1997 to December 31, 2007, there were 261 914 live births in the Stockholm region, consisting of 134 528 males (51.4%) and 127 386 females (48.6%). At the end of this period the total population consisted of 1 949 516 inhabitants according to Statistics Sweden and the Swedish Tax Agency. Information on place of birth was obtained from the Swedish Tax Agency.

All children born in the Stockholm region during the period January 1, 1997 to December 31, 2007, with an ICD-10 diagnosis coding corresponding to a congenital condition affecting the upper limb, i.e. Q68.1 to Q87.4, were included in studies I and II.

From medical records and, if available, radiographs all cases were analyzed. Diagnoses that were impossible or difficult to identify due to late presentation, large span of clinical presentation and sometimes lacking upper extremity involvement, as well as extremely rare conditions were excluded (Table 7).

Table 7.

Excluded Diagnoses (Paper II and II)	
1	Congenital radial head dislocation
2	Congenital tumorous conditions
3	Epidermiolysis bullosa
4	Ichtyosis
5	Marfan´s syndrome
6	Madelung´s deformity
7	Arthrogryposis multiplex congenita

In total, 562 children with CULA were included in the study. Medical records were available in all cases and radiographs prior to surgery in 53% of the cases. All cases were analyzed with regards to gender, laterality, associated non-hand anomalies, occurrence among relatives, syndromes, and previous surgery.

6.2.2 IFSSH Classification (paper I)

The main congenital anomaly of each limb was classified according to the modified version of the IFSSH classification system (22). When individuals had a bilateral anomaly belonging to the same IFSSH category it was counted as one main anomaly.

In 23 individuals, the right and the left side anomaly belonged to different categories and these were therefore counted as two anomalies. Thus, the material consisted of 585 anomalies in 562 individuals.

6.2.3 OMT Classification (paper II)

In paper II all 562 individuals who were included in paper I were reclassified according to the refined and extended version of the OMT classification (8) initially proposed by Oberg, Feenstra, Manske and Tonkin in 2010 (7). As in the first study, individuals with a bilateral anomaly belonging to the same OMT category were counted as one main anomaly. In 15 individuals, the right and the left side anomalies belonged to different OMT categories and they were therefore counted as two anomalies. Thus, the material in paper II consisted of 577 anomalies in 562 individuals. The discrepancy with the figures in paper I is due to the fact that the IFSSH classification system is more detailed in its descriptions of syndactyly, radial and ulnar deficiency, clinodactyly and brachydactyly. Therefore, in paper I eight additional individuals had bilateral anomalies counted as two.

6.2.4 Statistical analyses

IBM SPSS Statistics 17.0 (paper I) and IBM SPSS Statistics 21 (paper II) were used for the descriptive statistical analyses. Incidence (number of new cases per live births per year) rather than prevalence (number of existing cases at a specific time) was chosen. To calculate incidence the number of anomalies was divided by the total number of live births during the period and multiplied by 10,000. In paper II, confidence intervals for the incidence rate of each category were calculated with Open Epi (www.openepi.com) using Fischer´s exact test.

6.3 STUDIES OF HAND FUNCTION (PAPERS III - IV)

6.3.1 Study design in accordance with ICF/ICF-CY

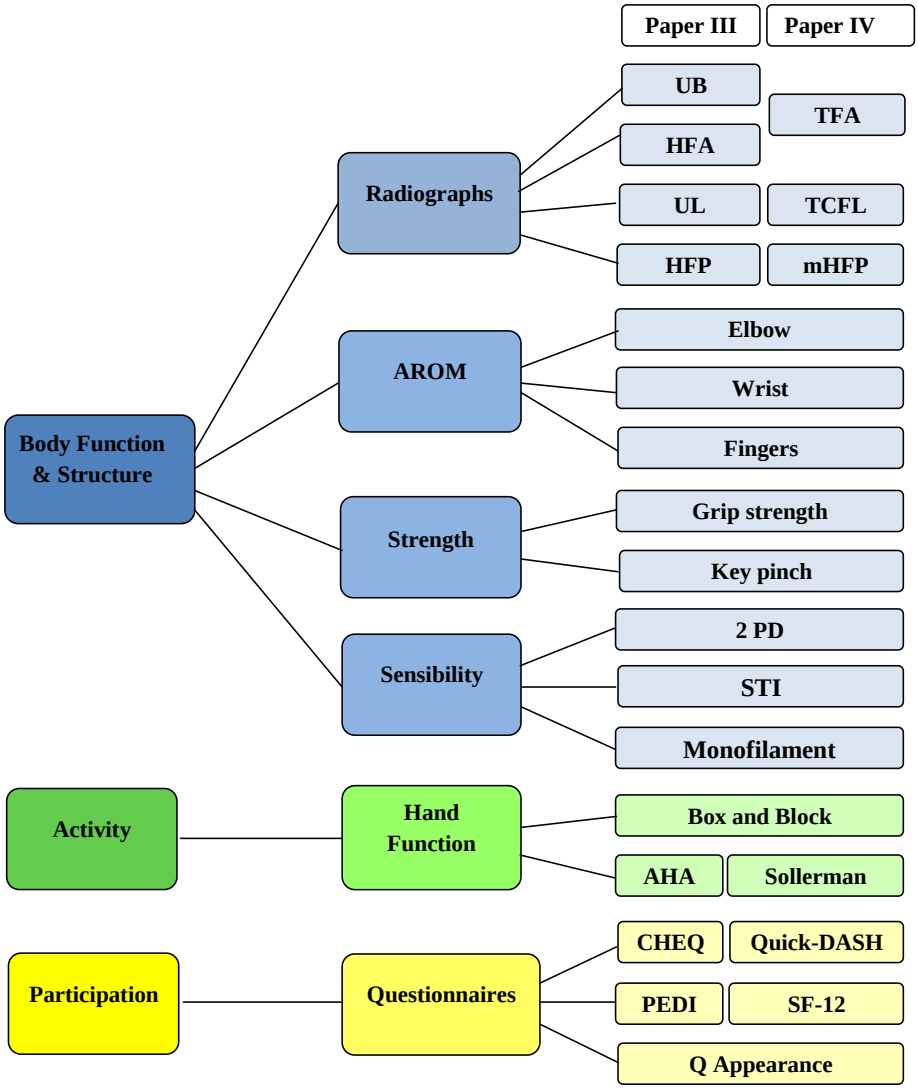


Figure 6. Study Design ICF Framework (Paper III-IV)

6.3.2 Participants

The two multicenter studies of hand function in individuals with RLD were conducted at four Swedish regional departments of Hand Surgery: the Department of Hand Surgery at Uppsala Academic Hospital; the Department of Hand Surgery at Södersjukhuset in Stockholm; the Department of Plastic Surgery, Hand Surgery and Burns in Linköping; and the Department of Hand Surgery at Skåne University Hospital.

In paper III, inclusion criteria were children age 4 to 17 years with a unilateral or bilateral RLD Bayne type II-IV (51, 52). Thirty-one children in the medical registries fulfilled the inclusion criteria. Twenty families gave their signed informed consent for participation and thus twenty children were included in the study.

In paper IV, inclusion criteria were individuals age over 18 years with a unilateral or bilateral RLD Bayne type II-V (51-53). Twenty-seven individuals in the medical registries fulfilled the inclusion criteria and were asked to enroll in the study. Twenty individuals gave their signed informed consent and participated in the study.

6.3.3 ICF

Studies III and IV were designed based on the ICF (International Classification of Functioning and Health (WHO 2001)) (49), focusing on three different aspects of disability: *body function and structure* (i.e. changes in body function and structure), *activity* (i.e. execution of activities of daily life) and *participation* (i.e. involvement in various life situations) (Figure 6).

In paper III, the International Classification of Functioning, Disability and Health, version for Children and Youth, (ICF-CY), WHO 2007, (106) was used. In paper IV, the original version, the International Classification of Functioning, Disability and Health (ICF), WHO 2001, (49), was used.

6.3.4 Measures of body function & structure

Active range of motion

Active ranges of motion (AROM) were measured with a handheld goniometer for shoulder, elbow, wrist, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), distal phalangeal joints (DIP) and thumb interphalangeal joints bilaterally. Total active ranges of motion were calculated for each presented parameter. Total active motion of digits was defined as the sum of AROM for MCP, PIP and IP/DIP joints. The measurements of AROM were transformed to the Vilkki Severity Grading for RLD (Hand, Wrist, Other; HWO) (78). We also used a modification of the Vilkki Severity Grading for RLD (modified Hand; mH), only including the mobility of fingers and thumb and assessment of thumb function. In paper IV the active least radial deviation of the wrist was measured with a goniometer (Wrist Radial Deviation, WRD).

Strength

Grip strength and key pinch were measured in kilograms (kg) with an electronic Jamar dynamometer and Pinchmeter (E-Link®, Biometrics).

Sensibility

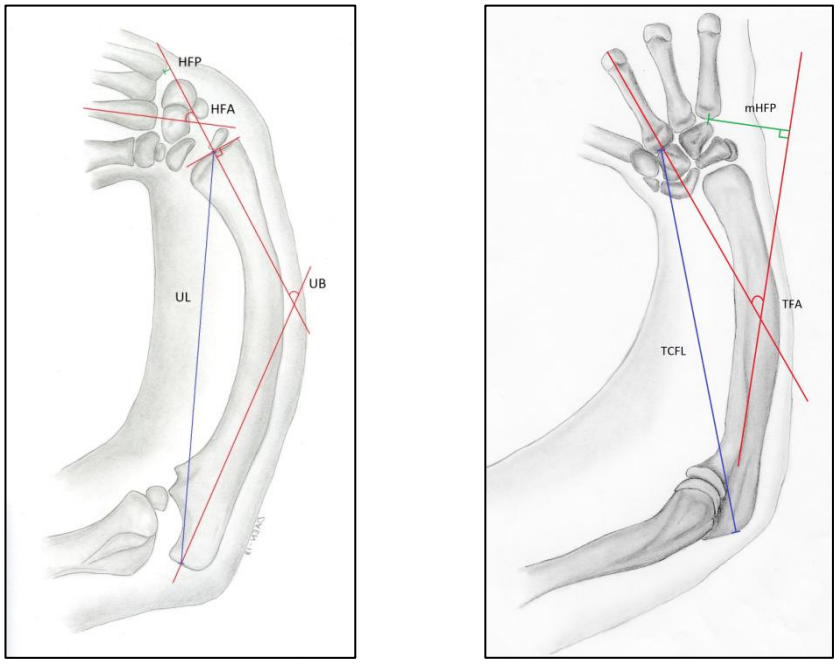
Sensibility of the fingers was evaluated by the two-point discrimination test (2-PD) (107), Shape-Texture-Identification test (STI) (108) and Semmes-Weinstein monofilament test (109).

Radiographic measurements

Standard postero-anterior (PA) and lateral radiographs of arm, forearm, wrist and hand were taken bilaterally. In paper III, the radiographic measurements proposed by Manske et al. (82) : Hand Forearm angle (HFA), Hand Forearm position (HFP), Ulnar Bow (UB) and Ulnar length (UL) were used (Figure 7). In younger children, measurements were made between the epiphyseal plates, and in older children the

measurements included the epiphyses. To get a comparable measure of forearm length, UL in relation to BL was calculated as UL as a percent of total BL (UL/BL%).

These standardized measurements were not measurable in several adults due to prior centralization of the wrist resulting in an indistinguishable distal ulna. In paper IV we therefore used three other measurements: Total Carpal Forearm length (TCFL), Total Forearm Angle (TFA) and modified Hand Forearm position (mHFP) (Figure 7).
To get a comparable measure of forearm length, TCFL in relation to BL was calculated as TCFL as a percent of total BL (TCFL/BL%).



Child **Adult**

Figure 7. Radiographic measurements of children (Paper III) and adults (Paper IV).

6.3.5 Assessments of activity

Box and Block test

The Box and Block Test of Manual Dexterity is a tool for testing manual dexterity that has shown good validity and reliability. Normative data is available for children ages 6-19 years as well as for adults (110, 111). The individual is instructed to transfer as many wooden cubes as possible from one compartment to another in one minute. The score for each hand is equal to the number of transferred cubes. The Box and Block test was used both in paper III and paper IV.

Assisting Hand Assessment – prosthesis, amputation, deficiency (AHA-PAD) (paper III)

The AHA hand function test (112-115) was initially developed for children with unilateral upper limb dysfunction from cerebral palsy or brachial plexus birth palsy. A new version, adjusted for individuals with reduction deficiencies of the upper limb, called the AHA-PAD, is currently undergoing validation (personal communication L. Krumlinde-Sundholm 2012). In the AHA, the child is given toys to play with, that require the use of two hands, and a video recording of the session is then used to score

the efficiency of the affected hand in spontaneous use in bimanual activity. The maximal scaled score is 100. The version AHA-PAD was used on the children in paper III. Since the AHA-PAD is a test designed for unilateral disorders, only the 15 children with unilateral RLD were included in the statistical analyses.

Sollerman Hand Function test (paper IV)

The Sollerman Hand Function test (116) is a reliable and validated test based on variations of the basic seven hand grips: pulp pinch, key pinch, tripod pinch, five-finger pinch, diagonal volar grip, transverse volar grip and spherical volar grip. The test consists of 20 activities of daily living and each task is scored from four to zero points. Individuals with normal hand function achieve 80 points with the dominant hand and 77-79 points with the non-dominant hand. The Sollerman Hand Function test was used on the adults in paper IV.

6.3.6 Assessments of participation

Children´s Hand-use Experience Questionnaire (CHEQ) (paper III)

The Children´s Hand-use Experience Questionnaire (CHEQ; www. cheq.se, Swedish version) (117), is a newly developed, web-based, validated questionnaire for evaluation of children´s experience of their performance with the disabled hand while doing bimanual tasks. The questionnaire includes 29 different activities, each rated on three scales covering different aspects of bimanual hand use: efficiency of the grasp, the time it takes to perform the task and whether the child feels bothered while doing it. The maximal scaled score is 100. In paper III, all children answered the CHEQ, either by themselves or assisted by a parent. Bilaterally affected children were told to answer the questionnaire with regard to their most severely affected hand, and that score was used for both arms.

Pediatric Evaluation of Disability Inventory (PEDI) (paper III)

The Pediatric Evaluation of Disability Inventory (PEDI) (118, 119) is a validated questionnaire for children with functional disabilities and is designed to evaluate the child´s performance and participation in activities of daily living. For paper III, all children´s parents answered questions in the domain Functional skills in PEDI. PEDI is validated for children aged 2.0-6.9 years as well as for older children, if their level of function is below that of a non-disabled 7.5-year-old. Since this study includes children up to age 17 years, only analyses of the specific tasks in PEDI were undertaken.

Short version of Disabilities of the Arm, Shoulder and Hand Outcome Measure (Quick DASH) (paper IV)

The Quick DASH evaluates an individual´s own perspective on their upper extremity disabilities and has shown good reliability and validity (120). The instrument includes two optional sections aimed at measuring participation in Sports/Music and Work activities. Higher scores indicate increased disability. Normative data for the full DASH is available for the general US and German populations (121, 122) . The Swedish version of the Quick DASH (123) was used in paper IV.

Medical Outcomes 12-item Short-Form Health Survey (SF-12) (paper IV)

The Medical Outcomes Study 12-item Short-Form Health Survey (SF-12) (124, 125) is a reliable and validated health status questionnaire that produces both a physical component summary score (PCS-12) and a mental component summary score (MCS-12). Normative data for the general US population is available (124). Higher scores reflect a better health.

Questionnaire about Appearance

All children and adults in paper III and IV answered a short questionnaire about the appearance of their anomalous arm(s) on a scale ranging from 1-5. To facilitate comparison with other measures the score was transformed to a score out of 100 by subtracting with one and multiplying by 25 (equivalent to scoring the Quick DASH). A lower score reflects a greater satisfaction with the appearance of the arm(s). This questionnaire was used both in paper III and paper IV.

6.3.7 Statistical analyses

Paper III

Descriptive statistics were presented for age, gender, CHEQ and appearance (n=20, each individual), AHA (n=15, unilateral cases only) and of affected side, grip strength, HFA, HFP, UL/BL%, UB, TAM Wrist ext-flex and TAM Digits (n=25, each affected limb). Linear regression, adjusting for age, gender, side, uni-or bilateral affection and normal other side, was performed to test for associations between Box and Block Test as well as the CHEQ questionnaire and the other variables. Linear regression, adjusting for age, gender, side and normal other side, was performed to test for associations between the AHA and the other variables. The standardized regression coefficients are presented. The sandwich estimator was applied to Box and Block Test and to the CHEQ variables to correct for possible correlations due to the fact that five bilateral children were included twice. The normality assumption was assessed for the multiple linear regressions with QQ-plots and the Shapiro-Wilk test and no violations were detected for Box and Block Test, CHEQ *Grasp Efficiency* and CHEQ *Bother*. However, CHEQ *Time* showed signs of not following a normal distribution, but was for comparative reasons still analyzed with parametric methods. Thus, the result should be interpreted with some care. All analyses were performed in R v 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria) (regressions), IBM SPSS Statistics 20 (descriptive statistics) and Microsoft Office Excel 2007 (plots). The level of significance was set to 0.05 (two-sided).

Paper IV

Descriptive statistics were presented for age, gender, SF-12, Quick DASH and appearance (n=20, each individual) and of affected side, TAM Elbow, TAM Wrist ext-flex, TAM Digits, TFA, TCFL, TCFL/BL%, mHFP, WRD, Vilkki HWO, Vilkki mH, grip strength, key pinch, Box and Block Test and Sollerman Test (n=29, each affected limb). Linear regression, adjusting for age, gender, side and uni- or bilateral, was performed to test for associations between the two functional tests, i.e. Box and Block Test and Sollerman Hand Function Test as well as the questionnaires SF-12 and Quick DASH and the outcome variables grip strength, key pinch, HWO, mH, TFA, TCFL, TCFL/BL%, TAM Elbow, TAM Wrist, TAM Digits and WRD. The standardized

regression coefficients are presented. The Huber-White estimator was applied to correct for possible correlations due to the fact that nine bilateral individuals were included twice. The normality assumption was assessed for the multiple linear regressions with QQ-plots and the Shapiro-Wilk test and no violations were detected. All analyses were performed in IBM SPSS Statistics 21 and Microsoft Office Excel 2007 (plots). The level of significance was set to 0.05 (two-sided).

7 ETHICS

All studies were conducted according to the principles of the WMA Declaration of Helsinki – Ethical Principles for Medical research Involving Human Subjects (WMA 2008).

All studies in the thesis were approved by the Regional Ethics Review Board at Karolinska Institutet in Stockholm, Sweden. (Study I and Study II: 2008/1893-31/4. Study III: 2010/1125-31/3, 2011/626-32. Study IV: 2010/1126-31/3, 2011/627-32.

In Studies I and II informed consent was not mandatory.
In Studies III and IV informed consent was obtained from the participants or from the parents of the children.

8 RESULTS

8.1 OVERVIEW OF THE FOUR PAPERS

Table 8.

Paper	Research Question	Study Design	Results	Conclusion
I	What is the incidence of CULA in the population of Stockholm County?	Retrospective epidemiologic total population study based on the IFSSH classification of CULA.	The incidence rate of CULA in children born in Stockholm between 1997 and 2007 was 21.5 per 10,000 live births. Incidence rates and relative frequencies for the different types of CULA were presented.	The incidence of CULA in Stockholm County was similar to the only comparable total population study. The results can be used as a reference for CULA in a total population.
II	Does the newly proposed OMT classification scheme account for all CULA in a total population, and can it be used to accurately establish incidence rates?	Retrospective epidemiologic total population study based on the OMT classification of CULA. Evaluation of the OMT classification and comparison with the IFSSH classification.	All CULA were classifiable in the OMT classification system. The distribution of the anomalies was as follows: *Malformation*s 74%, *Deformations* 22%, *Dysplasias* 2% and *Syndromes* 2%. A comparison between the IFSSH and OMT classification systems was presented.	The OMT classification is useful and accurate and with further refinements can serve as an appropriate replacement of the IFSSH classification. The results can be used as a reference for CULA in a total population.
III	What aspect(s) of the complex anomaly in RLD is the primary determinant for *activity* and *participation* in children?	Therapeutic study. Case series. The ICF-CY framework was used to examine the relations between *body function & structure* on the one hand and *activity* and *participation* on the other.	The AHA had significant relation with total range of motion of digits. Self-experienced time of performance had significant relationship to total active motion of wrist. Radial angulation of the wrist did not show any significant relations with measurements of *activity* and *participation*.	In children with RLD, total range of motion of digits and wrist may be of more cardinal importance to *activity* and *participation* than the radial angulation of the wrist.
IV	What aspect(s) of the complex anomaly in RLD is the primary determinant for *activity* and *participation* in adults?	Therapeutic study. Case series. The ICF framework was used to examine the relations between *body function & structure* on the one hand and *activity* and *participation* on the other.	Significant relations between measurements of *activity* and *participation* were found for strength in grip and pinch, total active motion of digits and elbow as well as for forearm length. Radial angulation of the wrist did not show any significant relationship to *activity* and *participation*.	In adults with RLD, grip strength, key pinch, forearm length and elbow and digital motion may be more important to the individual´s *activity* and *participation* than the radial angulation of the wrist.

8.2 EPIDEMIOLOGY OF CULA IN STOCKHOLM COUNTY (PAPERS I-II)

8.2.1 Incidence and relative frequency of CULA

The total incidence of children born with a CULA was 21.5 per 10,000 live births in Stockholm County between 1997 and 2007 (Figure 8).

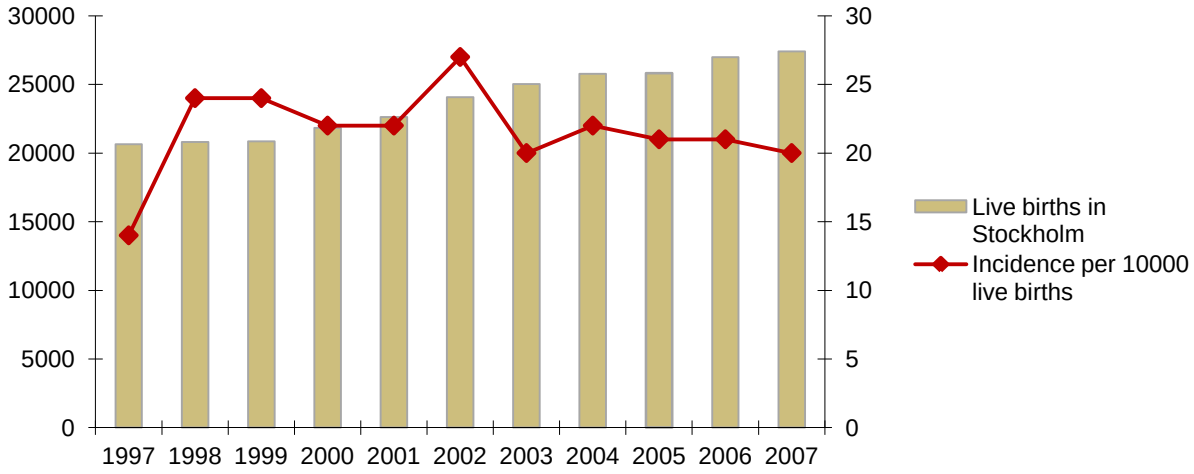


Figure 8. Incidence of CULA per 10,000 live births and Live births in Stockholm region between1997 and 2007. Adapted from Ekblom et al. (23) with permission from the publisher.

8.2.2 Distribution of CULA in the IFSSH and OMT Classifications

As previously explained, the discrepancy between paper I and paper II regarding the number of anomalies is due to the fact that the IFSSH classification system is more detailed in its descriptions of the specific anomalies than the OMT classification.

IFSSH Classification (paper I)

When 585 CULA in the 562 children were classified according to the IFSSH classification (paper I) the category *Failure of differentiation* was the largest category (276 cases), followed by *Duplications* (155 cases) and *Failure of Formation* (103 cases). The categories *Overgrowth* (10 cases), *Undergrowth* (18), *Constriction ring syndrome* (9 cases) and *Generalized abnormalities and syndromes* (14 cases) were much less frequent (Figure 9).

In Appendix 1, the IFSSH classification and incidence of CULA per 10,000 live births, relative frequency, gender distribution, affected side, associated non-hand anomalies and occurrence among relatives for 585 CULA in 562 children are presented.

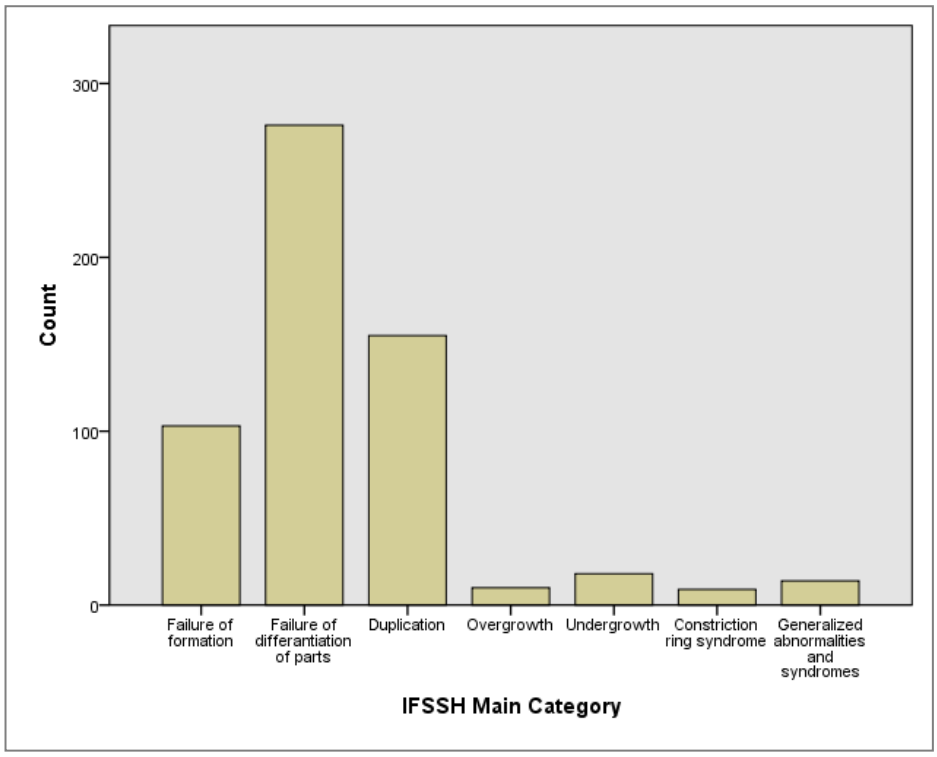


Figure 9. Distribution of CULA among the IFSSH main categories

OMT Classification (paper II)

When 577 CULA in the same 562 children were classified according to the OMT classification (paper II) the *Malformations* category was by far the largest (429 cases). The second largest category was *Deformations* (124 cases) followed by *Syndromes* (14 cases) and *Dysplasias* (10 cases). In the OMT classification the main category *Dysplasias* consists of both *Hypertrophy* and *Tumorous conditions*. Since tumorous conditions were excluded in paper II, all the 10 cases in *Dysplasias* belonged to the subcategory *Hypertrophy* (Figure 10).

In Appendix 2, the OMT classification and incidence of CULA per 10,000 live births, relative frequency, gender distribution, affected side, associated non-hand anomalies and occurrence among relatives for 577 CULA in 562 children are presented.

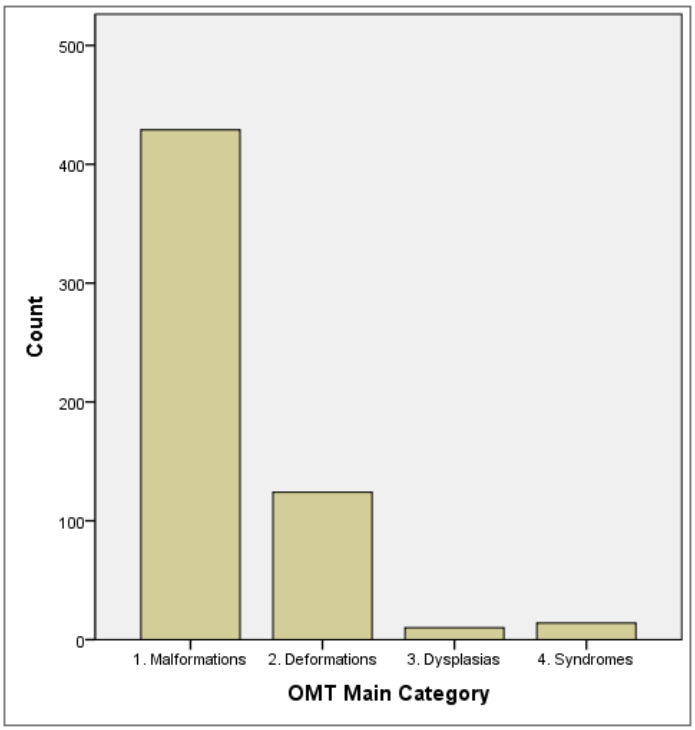


Figure 10. Distribution among the OMT main categories

8.2.3 Differences in distribution of gender, affected side, associated non-hand anomalies and occurrence among relatives (paper II)

Since the OMT classification is based on the current understanding of limb development the differences in gender, affected side, associated non-hand anomalies and occurrence among relatives are better described from that perspective.

The *Malformations* category (429 cases), (Figure 11), is subdivided into conditions affecting the entire limb (1A) and conditions affecting the hand plate only (1B).

In subgroup 1A. *Failure of axis formation/differentiation – entire upper limb* (73 cases), there was a predominance of males (64%). This male predominance was even more pronounced among the radial - ulnar malformations (77%), especially ulnar sided (100%). The left side (49%) was more often affected than the right side (36%). Associated non-hand anomalies (32%) were common but occurrence among relatives (3%) rare.

In subgroup 1B. *Failure of axis formation/differentiation - hand plate* (356 cases), there was only a slight predominance of males (56%). Also in this subgroup there was a male predominance among the radial - ulnar malformations. However, the radial deficiencies affecting the carpus only were more common in females. The right and left sides were equally affected. Associated non-hand anomalies (25%) and occurrence among relatives (27%) were common.

Among the *Deformations* category (124 cases) there was a slight predominance of females (58%) and associated non-hand anomalies and occurrence among relatives were uncommon.

In the *Dysplasias* category (10 cases) gender distribution was even, 30% had an associated non-hand anomaly and there was no occurrence among relatives.

For children in the *Syndromes* category (14 cases) the gender distribution was even, all individuals had a bilateral affliction, associated non-hand anomalies were common and there was no occurrence among relatives.

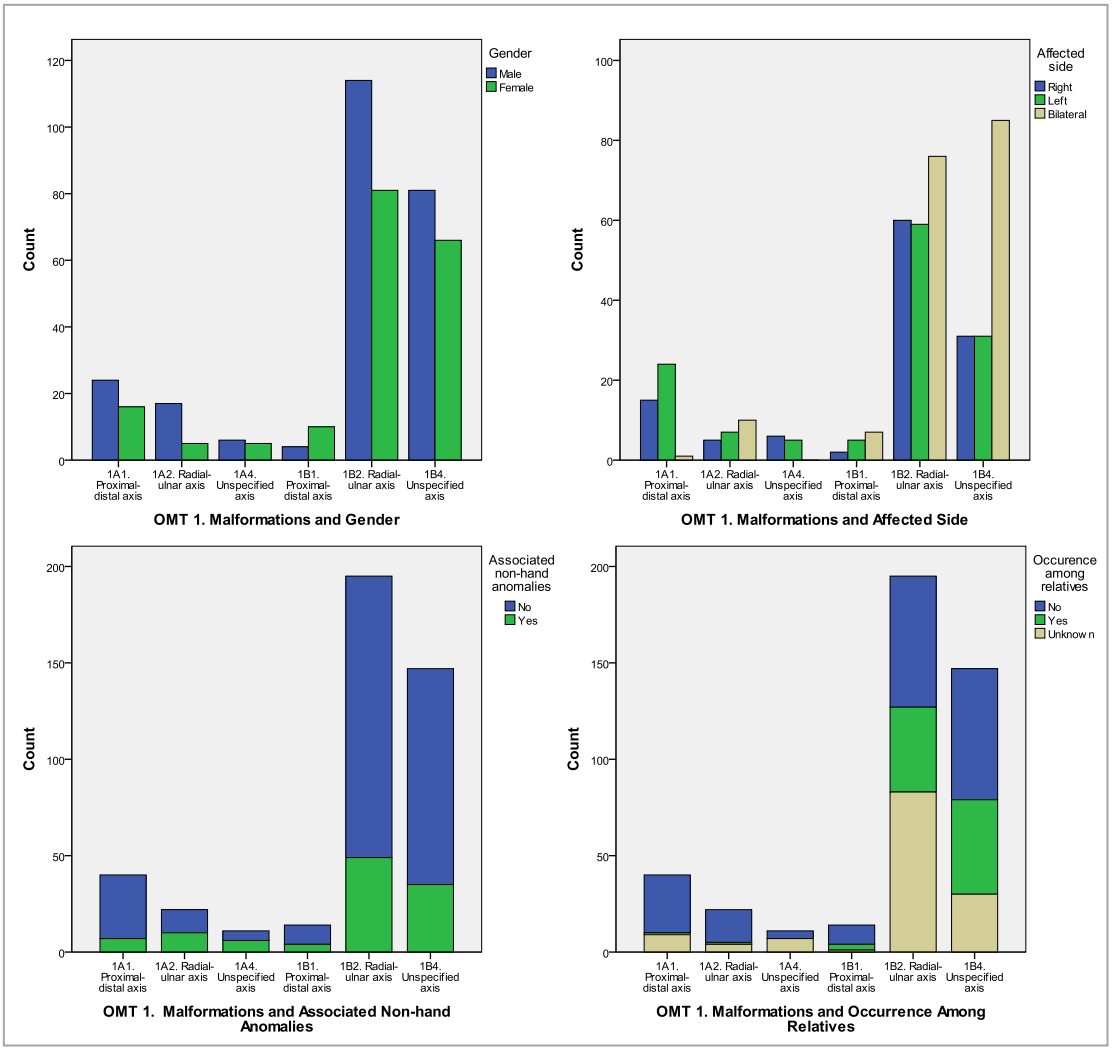


Figure 11.OMT Malformations category: Distribution of gender, affected side, associated non-hand anomalies and occurrence among relatives.

8.2.4 Associated non-hand anomalies (paper I)

Associated non-hand anomalies were present in 130 of 562 children. Association with lower limb anomalies was most common. The distribution of the associated non-hand anomalies order of frequency is presented in Table 9.

Table 9.

Distribution of Associated Non-hand Anomalies in 562 Children in order of frequency			
Associated anomaly	*Number of children*	*Percent of 562 children*	*Percent of 252 Associated non-hand anomalies*
Lower limb	54	9.6	21.5
Syndromes	38	7.1	14.7
Circulatory system	30	5.3	11.9
Head and neck	26	4.6	10.4
Urogenital	25	4.4	10.0
Digestive system	25	4.4	10.0
Central nervous system	19	3.4	7.6
Vertebral column	12	2.1	4.8
Respiratory system	10	1.8	4.0
Body wall	9	1.6	3.6
Skin	4	0.7	1.6
Total number of children with associated non-hand anomalies	130	23.1	100.1*

*The sum of percentages exceeds 100 owing to rounding.

Adapted from Ekblom et al. (23) with permission from the publisher.

8.2.5 "Top Ten" diagnoses (paper I)

The most commonly seen CULA among the 562 affected children in Stockholm County was Trigger digits (115 cases) followed by ulnar polydactyly (92 cases), radial polydactyly (59 cases), camptodactyly (40 cases), syndactyly (36 cases), radial longitudinal deficiency (33 cases), clinodactyly (31 cases), ulnar longitudinal deficiency (25 cases), central ray deficiency, i.e. symbrachydactyly and cleft hand, (23 cases) and complex syndactyly with synostosis of phalanges (13 cases). The ten most common diagnoses and their incidence are presented in Figure 12.

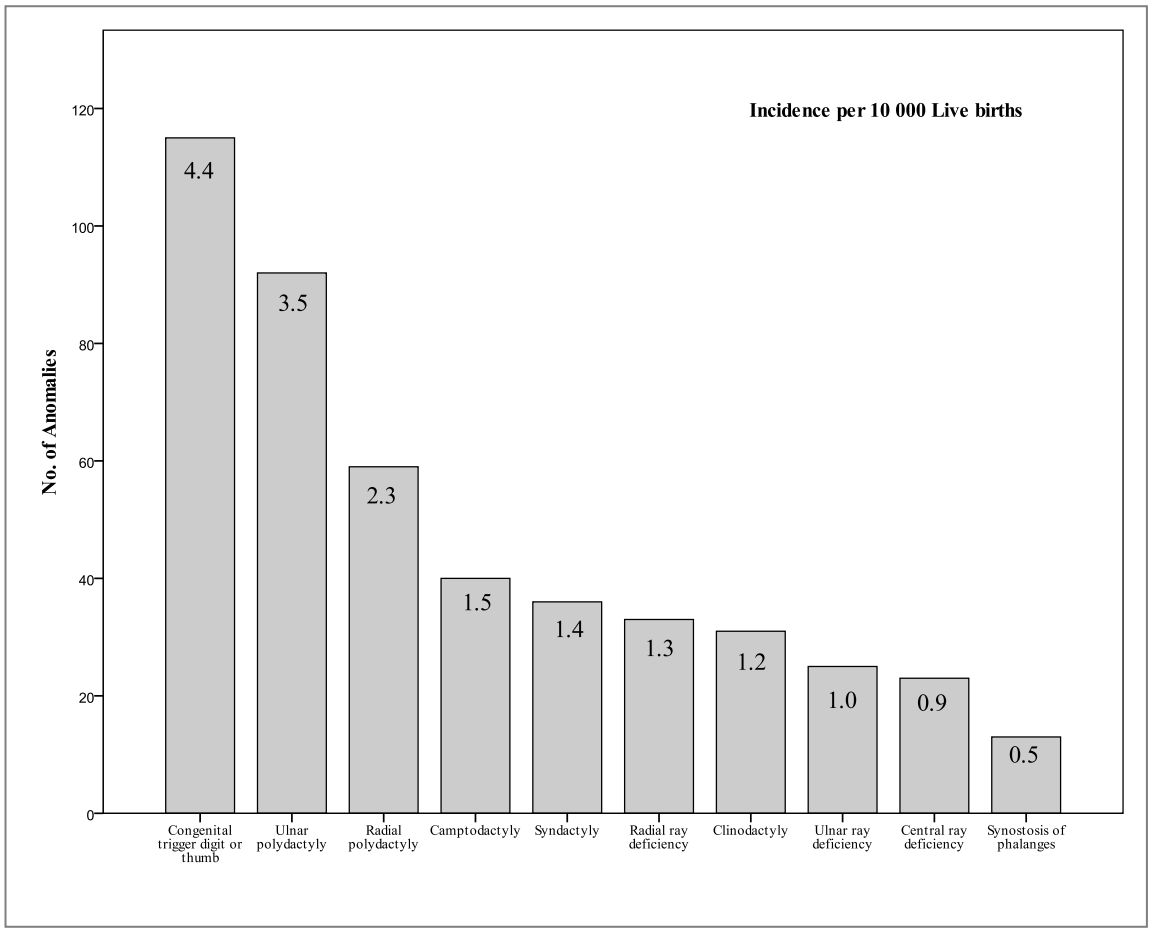


Figure 12. Ten most common CULA in 562 children in order of frequency and incidence per 10,000 live births. From Ekblom et al. (23) with permission from the publisher.

8.2.6 Relation between the IFSSH and the OMT Classifications (paper II)

The OMT main category *Malformations* incorporates most cases in the IFSSH classification Group I (*Failure of formation*), II (*Failure of differentiation*), III (*Duplications*) and V (*Undergrowth*). The second main OMT category, *Deformations*, incorporates IFSSH Group VI (*Constriction ring syndrome*) and *Trigger digits*, which belongs to IFSSH Group II. The third main OMT category *Dysplasias* corresponds to *Congenital Tumorous* conditions in IFSSH Group II together with IFSSH Group IV (*Overgrowth*). However, tumorous conditions were excluded in paper II and therefore here *Dysplasias* includes only cases of overgrowth. The fourth main OMT category, *Syndromes*, is equivalent to IFSSH Group VII (*Generalized Abnormalities and Syndromes*) (Figure 13).

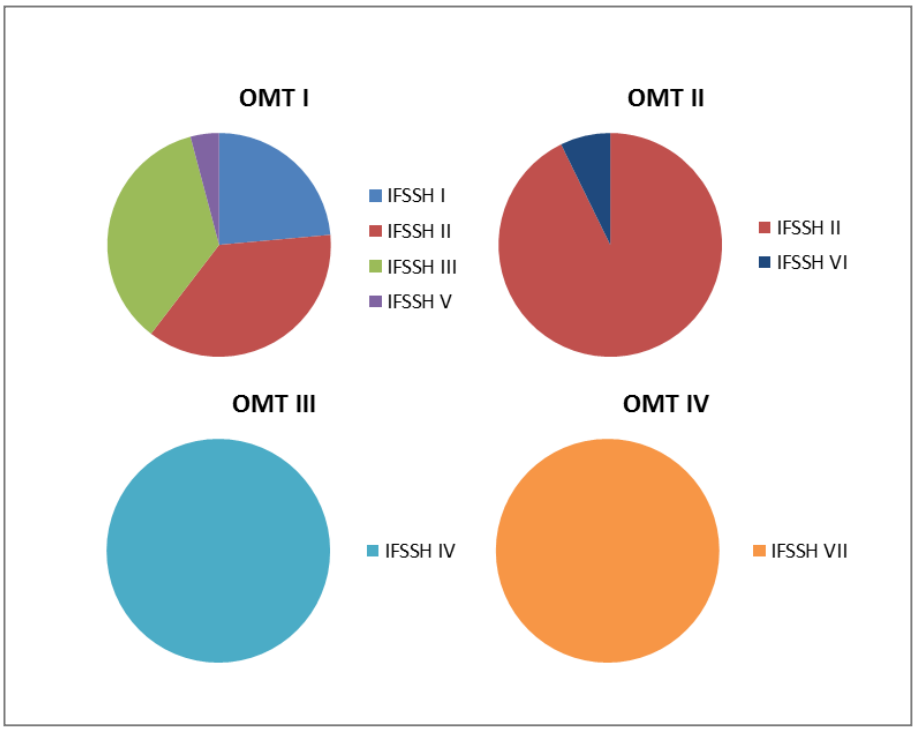


Figure 13. Relation between the IFSSH and OMT Classifications

8.3 HAND FUNCTION IN INDIVIDUALS WITH RLD (PAPERS III-IV)

8.3.1 Demographics

Paper III

Twelve boys and eight girls with RLD were examined for paper III.
Seven of 20 children had a known general syndrome, including four VATER associations, two Goldenhar syndromes, and one TAR syndrome. Additionally nine children had an associated non-hand anomaly that was not part of a known syndrome.

Five children had a bilateral RLD where both arms fulfilled the inclusion criteria. Hence, paper III included 25 limbs with RLD Bayne type II-IV.

Eight children had less pronounced radial deficiency (Bayne 0 to I) on the **not** included side and seven children had a completely normal other side. There was preponderance of RLD on the left side (15/25 limbs). Bayne IV was the most common category (16/25) followed by Bayne II (5/25), and Bayne III was found in 4/25 limbs.
In 18/25 limbs, surgical wrist correction had been performed. Of these, 13 had been treated with prior soft tissue distraction. Twelve of 25 limbs had been operated on by radialization procedure, six by a non-notched centralization procedure and three had undergone ulnar lengthening by callus distraction. Eleven of 25 hands had been pollicized. Six limbs in five children were not surgically treated.

Demographic data for paper III are presented in Appendix 3.

Paper IV

Twelve men and eight females with RLD, Bayne II-V, were examined for paper IV. Nine of these adults had a known syndrome, including four with VATER association, three TAR syndromes and two Holt-Oram syndromes. Additionally five individuals had an associated non-hand anomaly that was not part of a known syndrome.

Nine individuals had a bilateral RLD where both arms fulfilled the inclusion criteria, thus paper IV includes 29 limbs with RLD Bayne II-V.

Distribution of affected side was even, with 14 limbs right side anomalies and 15 limbs left side anomalies. Bayne IV was most common (19/29), followed by Bayne III (6/29), Bayne V (3/29) and Bayne II (1/29). Nine of the unilateral cases had a less pronounced radial deficiency (Bayne 0-1) on the **not** included side and two individuals had a completely normal other side.

Seventeen of 29 limbs had been treated with centralization procedure, including two with a prior soft tissue distraction and two with additional callus distraction of the ulna. Three of 29 limbs had been treated with radialization procedure, one with a vascularized fibular bone graft and one with primary arthrodesis of the wrist. Eighteen hands were treated with pollicization. Six limbs in three individuals were not surgically treated.

Demographic data for paper IV are presented in Appendix 4.

Descriptive statistics for paper III and paper IV are presented in Table 10.

Table 10.

RLD Descriptive Statistics				
	RLD Children (paper III)		RLD Adults (paper IV)	
	Mean	SD	Mean	SD
Age (years)	10.5	3.9	27	10
TAM Elbow (°)	78	47	90	33
TAM Wrist ext-flex (°)	50	34	43	33
TAM Digits (°)	447	263	377	212
HFA (°)	34	31	-	-
UL (mm)	13	3	-	-
UL/BL%	9	2	-	-
UB (°)	37	26	-	-
HFP (mm)	5	9	-	-
Wrist radial deviation (°)	43	38	31	28
TFA (°)	-	-	59	27
TCFL (mm)	-	-	143	50
TCFL/BL%	-	-	9	2
mHFP (mm)	-	-	-39	32
Grip strength (kg)	2.7	1.8	4.0	2.9
Key pinch (kg)	1.1	1.2	1.4	1.7
AHA-PAD	56	6	-	-
Box and Block test	34	14	55	14
Sollerman test	-	-	56	11
CHEQ *Grasp efficiency*	69	16	-	-
CHEQ *Time*	63	20	-	-
CHEQ *Feeling bothered*	71	18	-	-
QDASH *Disability*	-	-	18	18
QDASH *Sport/Music*	-	-	15	21
QDASH *Work*	-	-	11	18
SF-12 *Physical health*	-	-	51	8
SF-12 *Mental health*	-	-	53	9
Q Appearance	26	26	41	30

8.3.2 Radiographic assessments

Paper III

In paper III the radiographic measurements proposed by Manske et al. (82) were used. UL was markedly shorter, ranging from 40 to 80% to age-related norms (126) and UL in proportion of age related norms (mean 62%) were equal in surgically and non-surgically treated limbs. UL in relation to BL (UL/BL%) decreased with age, which is the opposite to what occurs in normally developed children, where UL increases in relation to BL (UL/BL%) during growth (Table 10).

Paper IV

Due to the complex three-dimensional deformity and in some cases ankylosis of the ulnocarpal joint after centralization, in several adult limbs it was impossible to obtain the appropriate radiological measurement previously used in paper III. Instead the other measurements previously described were used (Figure 7, Table 10).

8.3.3 Functional outcomes

Paper III

One child with bilateral RLD was not able to participate in the examination of grip strength, key pinch and sensibility. In the remaining 23 limbs grip strength was considerably lower compared to norms (127.) In three limbs the dynamometer was grasped in an atypical fashion. Key pinch was also markedly lower than norms (Figure 14). In six hands key pinch was not measurable and in these cases the strongest pinch, i.e., the interdigital grip between the ulnarmost digits, instead was measured. Neither grip strength nor key pinch increased with age as they do in normally developed children. In twelve limbs, the pinching-pattern was between the two ulnarmost digits and in four of these hands the pattern was present despite former pollicization.

Sensibility, as tested with two-point discrimination test and Semmes-Weinstein monofilament test, was normal (107) or close to normal. The STI-scores were normal or close to normal (108) in 19 of 23 hands and subnormal in 4 of 23 measured hands. The results in the Box and Block test for the children with RLD were considerably lower than norms (111).

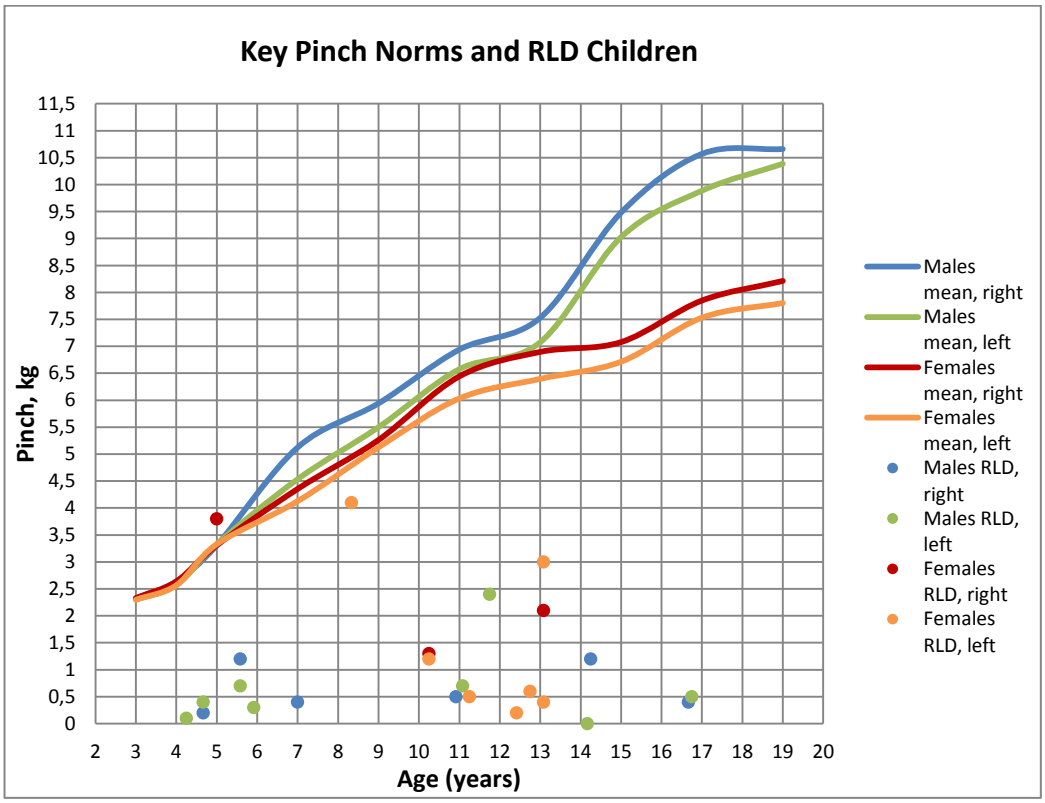


Figure 14. Key pinch Norms and RLD Children

Paper IV

In the examined adults with RLD, grip strength and key pinch were considerably lower than norms (128). For three limbs the power grip was considered atypical. In six hands key pinch was not measurable and in these cases, the interdigital grip between the two ulnarmost fingers was measured. The six limbs in three individuals with TAR syndrome had a better key pinch (mean 3.8 kg) and a better grip (7.8 kg) than the 23 limbs on the other adults in the study (key pinch mean 0.7 kg and grip mean 3.0 kg). In spite of former pollicization, in eight out of 18 pollicized hands the interdigital grip between the two ulnarmost fingers was still preferred.

In the Sollerman test none of the examined 28 limbs had normal values (116). The tasks that were most difficult to perform were undoing buttons, putting a key into a lock and turning it 90°, handling coins, screwing a nut on a bolt, unscrewing jar lids, opening and closing zippers, and turning a screw with a screwdriver.

In the Box and Block test the number of transferred cubes per minute was lower than age related norms (110).

Sensibility as tested with the two-point discrimination test, STI and Semmes-Weinstein monofilament was normal or close to normal in all hands.

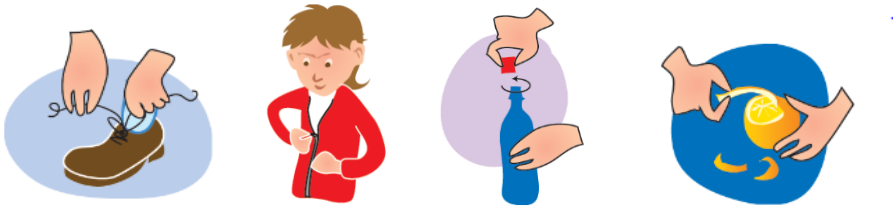
8.3.4 Patient related outcomes

Paper III

The results from the CHEQ questionnaire indicate that children with RLD judge their grasp efficiency as high, do not regard the performance as more time consuming than for their mates, and do not feel especially bothered while doing the different tasks. The tasks that the children most frequently considered difficult were opening up a carton of milk or juice, cutting meat on a plate, fastening a necklace, tying shoelaces, peeling an orange, unscrewing the cap of an unopened soft drink bottle, fastening a helmet and opening a bag (of e.g. crisps).

The results in self-care domain of the PEDI Functional skills questionnaire indicated that the most difficult tasks were manipulation of fasteners and zippers in clothing, wiping self thoroughly after bowel movements, and tying shoelaces.

Despite of deformity, the children with RLD regarded the appearance of the anomalous arm/s fairly high.



From www.CHEQ.s with permission .

Paper IV

Among the adults with RLD the upper extremity outcome measure (Quick-DASH) indicated that they perceived themselves as having only a mild disability. Regarding recreational activities, i.e. sports and music, the scores were in line with the general population (121, 122). Despite the activity limitations, the individuals' physical and mental health scores (SF-12) were equivalent to norms (124).

Nine out of 20 individuals where either married or lived with a partner and six had children. Fourteen of 20 individuals had a driver's license. Five individuals were university students, 14 were employed and one was unemployed. Out of the 14 employed individuals, two were teachers, one was a nurse, two were shop assistants, one was a car rental worker, one was a truck driver, one was a journalist, five were office workers and one was self-employed in a web shop business.

The adults with RLD rated the appearance of their disabled arm/s, on average, as moderately positive.

8.3.5 Relationship between body function & structure, and activity and participation

Paper III

For the children with RLD the AHA showed significant relationships with the Vilkki HWO score as well as with total active motion of digits (TAM Digits). CHEQ *Time* significantly correlated to the total arc of wrist extension to flexion (TAM Wrist ext-flex). In children with RLD, the radial angulation of the wrist (HFA) did not significantly correlate to *activity* (AHA, Box and Blocks test) or *participation* (CHEQ).

The statistical correlations for paper III are provided in Table 11.

Table 11.

RLD Children Statistical Correlation (paper III)										
	Box and Blocks		AHA		CHEQ *Grasp efficiency*		CHEQ *Time*		CHEQ *Feeling bothered*	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Grip strength	0.22	0.211	0.57	0.146	0.08	0.735	-0.01	0.949	-0.13	0.408
HFA	-0.15	0.393	-0.94	0.055	-0.29	0.228	-0.37	0.140	-0.09	0.574
HWO	-0.21	0.210	-0.81	0.018	-0.15	0.531	-0.08	0.682	0.03	0.849
mH	-0.24	0.112	-0.57	0.091	-0.16	0.455	-0.07	0.705	0.03	0.887
UL/BL %	0.19	0.242	0.70	0.182	0.26	0.357	0.16	0.426	-0.03	0.893
UB	-0.15	0.314	-0.31	0.431	-0.22	0.269	-0.08	0.636	-0.03	0.842
TAM Elbow	0.08	0.604	0.46	0.201	-0.32	0.081	-0.22	0.138	-0.03	0.852
TAM Wrist ext-flex	-0.01	0.962	0.48	0.240	0.31	0.116	0.39	0.043	0.13	0.335
TAM Digits	0.27	0.137	0.78	0.042	0.24	0.207	0.18	0.244	-0.10	0.565

p=p-value, r = standardized regression coefficient.

Multiple linear regression, adjusted for age, gender, side, uni-/bilateral and normal other side.

AHA not adjusted for uni./bilateral.

From Ekblom et al. (129), BMC Musculoskeletal Disorders, Open Access.

Paper IV

For the adults with RLD significant relationships were found between Box and Block test and grip strength, key pinch and total active motion of digits (TAM Digits). The Sollerman test showed significant relationship with total active motion of elbow (TAM Elbow) and digits (TAM Digits). The Quick-DASH and SF-12 showed significant relationships with forearm length (TCFL), total active motion of elbow (TAM Elbow), and total active range of motion of digits (TAM Digits). SF-12 Physical health score, in addition to these, had significant relationship with grip strength. Radial deviation of the wrist (WRD and TFA) did not show any significant correlations with Box and Block, Sollerman, Quick-DASH or SF-12 Physical component score. However, the SF-12 Mental component score showed a significant relationship with WRD.

The statistical correlations for paper IV are provided in Table 12.

Table 12.

RLD Adults Statistical Correlations (paper IV)										
	Box and Blocks		Sollerman		Q-DASH		SF-12 *PSC*		SF-12 *MSC*	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Grip strength	0.42	0.012	0.31	0.154	-0.33	0.083	0.45	0.016	-0.09	0.630
Key pinch	0.45	<0.001	0.19	0.317	-0.11	0.521	0.20	0.284	-0.30	0.128
HWO	-0.27	0.062	-0.61	<0.001	0.60	<0.001	-0.63	<0.001	-0.41	0.005
mH	-0.51	0.003	-0.43	0.011	0.53	<0.001	-0.53	<0.001	-0.17	0.490
TFA	0.16	0.244	-0.06	0.775	0.23	0.156	-0.25	0.107	-0.31	0.129
TFCL	0.17	0.198	0.18	0.151	-0.43	<0.001	0.50	<0.001	0.34	0.081
TFCL/BL %	0.21	0.295	0.30	0.102	-0.34	0.093	0.28	0.144	0.48	0.007
TAM Elbow	0.09	0.654	0.58	<0.001	-0.41	0.001	0.59	<0.001	0.24	0.098
TAM Wrist ext-flex	-0.15	0.181	0.14	0.389	<0.01	0.971	0.01	0.913	0.22	0.161
TAM Digits	0.60	<0.001	0.66	<0.001	-0.47	<0.001	0.45	<0.001	0.18	0.233
WRD	0.03	0.870	-0.18	0.229	-0.01	0.968	-0.03	0.889	-0.23	0.019

p=p-value, r = standardized regression coefficient.

Multiple linear regression, adjusted for age, gender, side and uni-/bilateral.

9 DISCUSSION

The overall aims of this thesis were to describe the epidemiology of congenital upper limb anomalies in a total population (paper I), to evaluate a newly proposed classification of congenital upper limb anomalies (paper II) and to investigate the relationship between the physical parameters of radial longitudinal deficiency and the ability of affected children and adults to carry out activities in daily life and to participate various life situations (paper III and IV).

9.1 EPIDEMIOLOGY OF CULA (PAPERS I-II)

The accuracy of epidemiological studies is dependent on the possibility of collecting correct data. Sweden provides a unique opportunity for carrying out epidemiological total population studies because of its well-developed national registration of inhabitants in combination with registries held at the National Board of Health and Welfare (NBHW) and national quality registries. Incidence figures based on the kind of total population studies that these registries allow are in principle more accurate than incidence figures from specialized centers that rely only on treated patients.

The more accurate incidence figures obtainable from total population studies are important for enabling comparisons between regions and over time. Measured changes in incidence rates can act as an alarm-bell and can stimulate studies of underlying cause. In the case of congenital upper limb anomalies information about gender distribution, laterality, associated anomalies and occurrence among relatives is important information and may shed new light on causative mechanisms. To enable comparison between different studies it is crucial to have a common descriptive framework that facilitates unambiguous communication. A uniformly accepted and accurate classification system can provide such a framework.

9.1.1 Methodological considerations

9.1.1.1 Data collection and Disparity between registries

In papers I and II, data was obtained from Statistics Sweden, the Swedish Medical Birth Register, the Swedish Hospital Discharge Register and the Swedish Register of Congenital Malformations as well as from the hospital-based registries in Stockholm County. Although unquestionable valuable, all register studies are inevitably influenced by measurement errors (i.e. classification errors) and selection bias, as was illustrated in a previous study of upper and lower limb anomalies based on the Edinburgh Register of the Newborn (36). When we cross-checked data from the various Swedish registries, we found some disparities between them (Figure 15). One disparity was that many of the cases identified in the hospital-based registries were not found in the registries held by NBHW. Furthermore, in a majority of the cases identified in the NBHW registries, a congenital upper limb anomaly could not be confirmed. This discrepancy could be due to the fact that some conditions are not detectable at birth, others are difficult to separate from traumatic conditions and some might not have been diagnosed properly. Since the aim in papers I and II was to present confirmable data only, we included only

cases verified in medical records. This may, however, have resulted in the incidence of some conditions, especially ulnar polydactyly and syndactyly, being underestimated.

We decided to exclude conditions with late debut, those with a large span of clinical presentation sometimes lacking upper extremity involvement, disorders difficult to differentiate from traumatic conditions and extremely rare conditions. This led to the exclusion of some important groups of congenital hand anomalies, e.g. arthrogryposis and tumorous conditions. Although the decision to exclude these few conditions affected calculations of the relative frequency of each CULA category, it did not influence overall incidence rates of each category since the figures are based on a total population.

The exclusions of stillbirths in papers I and II is also a limitation of the studies but seemed warranted since the possibility of identification and correct classification of congenital upper limb anomalies among these cases is considerably limited.

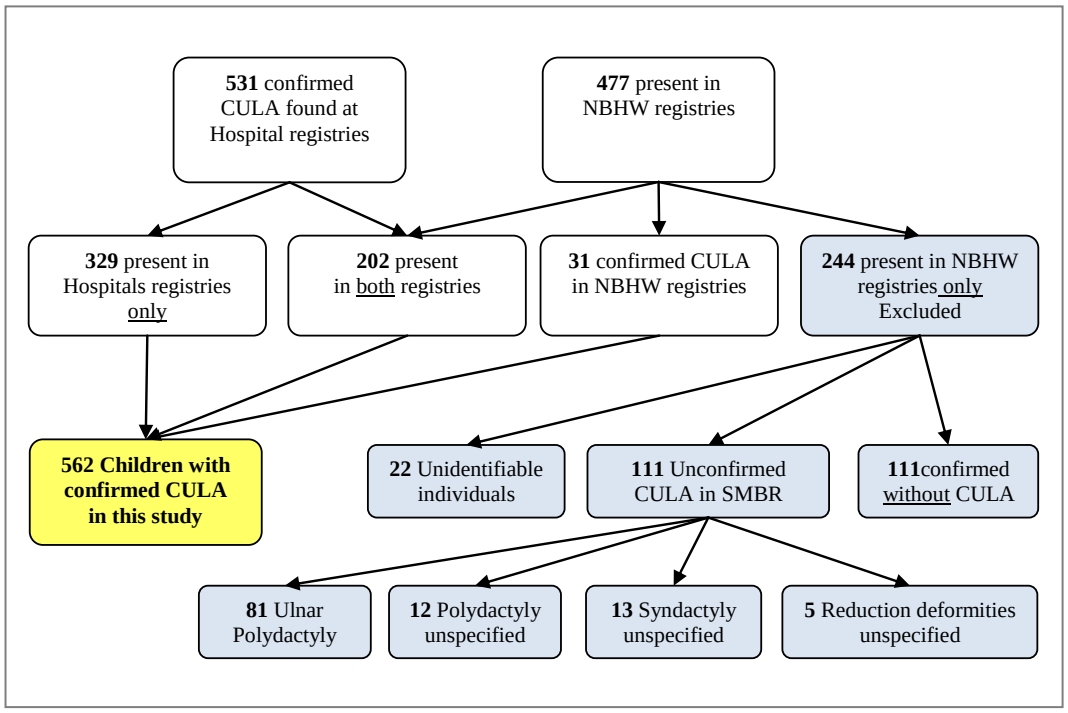


Figure 15. Disparity between registries

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9.1.1.2 Inconsistencies with the IFSSH classification

While classifying CULA according to the IFSSH classification in paper I it became obvious that the classification scheme itself has some inconsistencies.

One of these is that the clinical entity syndactyly includes both cutaneous syndactyly and complex syndactyly with synostoses of the distal phalanges. In the IFSSH classification these clinically related conditions are stratified into two different subcategories: *Failure of differentiation, soft tissue involvement* and *Failure of*

differentiation, skeletal involvement. Moreover, complex syndactyly with central polydactyly is stratified to *Duplications*. Embryological studies, however, indicate a common etiology for central polydactyly, syndactyly and cleft hand (130-132), suggesting that the disparate classification of them in the IFSSH scheme may be misguided. A suggested solution has been to add the category "*Abnormal induction of digital rays*" to the IFSSH classification (26), but this would still not incorporate the radial and ulnar polydactylies.

The classification of the absence of digits is also troublesome and has previously been debated (22, 25, 27, 28). The distinction between symbrachydactyly, brachysyndactyly and transverse arrest is not clearly defined and the dividing line is drawn differently in different studies, making comparisons difficult.

The category *Undergrowth* is also problematic since it incorporates various types of underdevelopment with different etiologies. In the total population study from Australia by Giele et al. (37), thumb hypoplasia was classified as *Undergrowth*, but in paper I these conditions were classified as *Failure of formation, longitudinal arrest, radial ray*, which is in line with the developmental background (52). These differences also make comparisons difficult.

Poland´s syndrome, with absence or hypoplasia of the pectoral muscles and a coexisting hand anomaly, is also difficult to classify within the IFSSH classification. Should the hand anomaly or the shoulder anomaly be regarded as the main anomaly? In papers I and II these cases were classified according to the hand anomaly.

Within the IFSSH classification important information may be lost for children with multiple anomalies. Certain anomalies may therefore be underrated. A non-classifying recording method has been proposed by Luijsterburg et al. (133), but the system is time- consuming to use and the evaluation of the severity of aberrations is difficult.

9.1.1.3 Difficulties with the OMT classification

When reclassifying the anomalies included in paper I to the OMT classification we found it difficult to accurately classify general hypoplasia of the upper limb, complex abnormalities of the cervical spine and shoulder, brachydactyly, windblown hand, synostosis of phalanges/symphalangism, and complex syndactyly with synostosis of phalanges.

On the one hand, proponents of the OMT classification suggest that symbrachydactyly and transverse deficiency should be regarded as conditions affecting the entire upper limb. On the other hand, however, radial and ulnar longitudinal deficiencies without obvious proximal involvement are classified by the OMT system as conditions affecting the hand plate only. In paper II, all 15 symbrachydactylies had a predominant hand involvement and six out of 22 of the transverse deficiencies were at the carpal level or more distal. Cases of symbrachydactyly and transverse deficiency with no obvious proximal involvement might therefore better be classified as conditions affecting the hand plate only.

The problem with coexisting anomalies remains with the OMT classification (e.g. Poland´s syndrome and coexisting hand anomaly).

To facilitate comparison between studies in spite of divergent classification strategies it is important to clearly report which strategy was chosen for the specific study, which we were careful to do both in papers I and II.

9.1.2 Comparison between regions and over time (paper I)

The incidence of CULA found in paper I was higher than those found in previously published series of incidence of CULA (Table 13). Some of the previous studies (15, 36, 134) were not based on the IFSSH classification and the figures presented in Table 13 are based on our attempt to reclassify the original data. The lower incidences cited in the older studies may be explained by the fact that these studies were hospital-based and some of the minor anomalies may not have been seen at these clinics at all. Furthermore, the somewhat higher incidence of CULA in paper I compared to the older studies is most likely due to our meticulous search for cases. My opinion is therefore that our findings do not represent a true increase in the incidence of CULA in the population over time.

Table 13.

Comparison of Published Series of Population Incidence per 10,000 Births of each IFSSH category of CULA

	Birch-Jensen* (15)	Conway and Bowe (33)	Rogala* (36)	Lamb (34)	Wynne-Davies* (134)	Giele (37)	Ekblom (23)
Failure of formation	1.55		8.4	6.1	8.4		3.9
Failure of differentiation			5.0	2.9			10.5
Duplication			9.5	7.1	13.1		5.9
Overgrowth			0.2	0.2			0.4
Undergrowth			2.0	1.3			0.7
Constriction ring			0.6	0.4	0.6		0.3
Generalized syndromes and abnormalities							0.5
Total CULA		16		18		19.7	21.5
No. of Individuals	625	164	156	1095	387	509	562

*The authors reclassified the original data according to the IFSSH classification

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When compared to previously published series of the distribution of different types of CULA, our results mainly correspond well (Table 14). That hospital-based studies from highly specialized centers (34, 58, 133, 135-138) present slightly different distributions of categories of CULA undoubtedly reflect the type of patients treated at their departments. Some differences can also, once again, be explained by divergence in classification strategies (37). Our high frequency of anomalies in the categories *Failure*

of differentiation and *Duplication* is probably explained by the large number of identified cases of congenital trigger digits or thumb and the high report frequency of ulnar polydactyly from the delivery wards.

Table 14.

Comparison of Published Series of Relative Frequency (%) of each IFSSH category of CULA									
	Ogino (135)	Leung (138)	Flatt* (58)	Cheng (136)	de Smet (26)	Luijsterburg (133)	Lamb (34)	Giele (37)	Ekblom (23)
Failure of formation	11	11	20.5	12.2	19.8	40.9	16.6	15	17.6
Failure of differentiation	52	30	39.3	31.3	55.4	36.1	39.5	32	47.2
Duplication	19	40	14.8	35.9	15.4	18.5	22.9	38	26.5
Overgrowth	0.5	0.5	0.9	0.5	0.7	0.9	1	0.8	1.7
Undergrowth	9	2	5.3	4.3	8.3	2.4	15	8	3.1
Constriction ring	5	4.5	2.2	6.5	6.4	1.2	5	3	1.5
Generalized abnormalities and syndromes	3	12	4.4	9.3	3.1	0	-	3	2.4
Unclassified	0.5	-	9.5				-	-	
Summary	100	100	100	100	109.1	100	100	98.8	100
No. children	943	326	1476	578	650	231	1095	509	562

*The authors reclassified the original data to the IFSSH classification

Adapted from Ekblom et al. (23) with permission from the publisher.

9.1.3 Differences in distribution of gender, laterality, associated non-hand anomalies and occurrence among relatives (paper II)

The distribution of types of CULA according to gender, laterality, associated non-hand anomalies and occurrence among relatives raises interesting questions for future research.

Males were more frequently affected with malformations affecting the entire upper limb, especially those affecting the radial-ulnar axis. In contrast, radial deficiencies restricted to the hand were more common among females. This gender difference could indicate a variation in vulnerability to different insults in male and female foetuses.

CULA occurred equally often, overall, on the left and right sides. We found in paper II, however, that the left side was more frequently affected in malformations affecting the entire limb, whereas the right and left side were equally affected in hand plate related conditions. The reason for this difference remains unexplained. By contrast, transverse deficiency, symbrachydactyly and Sprengel´s deformity were all more frequently found on the left side. The theory that these conditions might be caused by interruption of the blood supply in the subclavian artery (139), combined with the anatomic side

differences for the subclavian artery, could be a possible explanation for the left side predominance.

Associated non-hand anomalies were much more common with radial ray deficiencies than with ulnar ray deficiencies, which could indicate a difference in the underlying cause.

Occurrence among relatives was more frequent among *Malformations* than among *Deformations,* which supports the theory that deformations are caused by an external insult after normal development.

9.1.4 Limb development and classification of CULA

9.1.4.1 Comparison between the IFSSH and the OMT classifications

Increasing knowledge of developmental biology has made the drawbacks of the IFSSH classification more obvious. The IFSSH main categories *Failure of formation* and *Failure of differentiation* emanate from theories of embryology, but the other main categories - *Duplication*, *Overgrowth*, *Undergrowth* and *Constriction ring syndrome* - are mainly based on morphology. *Generalized abnormalities and syndromes* incorporate the syndromic cases, but as the genetic causes of more and more syndromes are revealed they might better be classified according to the limb anomaly with the classification of the syndrome added. Furthermore, complex cases are difficult to classify within the IFSSH classification, especially those within the spectrum of cleft hand and symbrachydactyly.

In contrast to the IFSSH classification, the OMT system derives its classifications solely from the current understanding of limb development and consequently divides CULA into the main categories *Malformations, Deformations, Dysplasias* and *Syndromes.* The further subdivision of *Malformations* is based on theories of the molecular pathways that organize the three axes of the developing limb. This way of stratifying cases can elucidate the linkage between a congenital upper limb anomaly and the underlying cause.

The OMT classification can incorporate all conditions in the IFSSH classification as demonstrated in paper II, where all CULA previously classified within the IFSSH classification in paper I could be classified according to the OMT classification system. Compared to the IFSSH classification system the classification of triphalangeal thumb, thumb hypoplasia, humero-radial synostosis, as well as the embryologically related, cleft hand, polydactyly, and syndactyly is improved with the OMT classification. The problem of which of two coexisting anomalies should be regarded as the main anomaly persists, but the proponents of the OMT classification scheme (8) suggest separate classifications in case of multiple anomalies. The troublesome distinction between brachysyndactyly and symbrachydactyly has previously been debated (22, 25, 27, 28, 140), but reflects primarily the incomplete knowledge of the underlying cause of these conditions. Paper II revealed that even though the OMT classification is an improvement over the IFSSH, some problems remain in the classification of some conditions. In light of this, we proposed some additions to the OMT classifications in paper II.

9.1.5 Future perspectives

The incidence of CULA appears to vary only slightly among regions and over time. Sudden changes of incidence are therefore an important signal that the possibility of altered or new exposures to environmental factors should be investigated. For this reason, repeated epidemiologic studies of CULA should be performed.

Classification schemes provide a common framework for communication about a disorder and are thereby important for studies of epidemiology, etiology, treatment and prognosis. A system of classification must be logical and easy to use, but still be sufficiently accurate. The balance between being too brief or too detailed is difficult and there is an ongoing struggle between "lumpers and splitters". Moreover, a classification scheme should be able to adapt to increasing knowledge. The OMT classification has been shown to be useful and accurate, but not without flaws. With further refinements through consensus building within the community of pediatric hand surgeons and geneticists, the OMT classification system can, we believe, provide a useful new framework for communication about congenital upper limb anomalies.

9.2 HAND FUNCTION IN INDIVIDUALS WITH RLD (PAPERS III-IV)

Children and adults with RLD have considerable deficiencies with regards to *body function and structure* caused by varying degrees of malformation of the radial side of the hand and forearm. The aim of surgical wrist correction is to try to "normalize" appearance and to improve function by correcting the radial angulation of the wrist and increasing the functional length of the arm. Another aim of surgery is to improve wrist position for later pollicization. Unfortunately, several previous studies have verified high rates of late deformity recurrence and significant impairment of ulnar growth after corrective surgery in RLD (43-45, 84).

Since the long-term results of surgery are discouraging, it is important to elucidate which component of the deformity in fact is the most essential for the individual's *activity* and *participation* in daily life. Yet few studies have evaluated activity limitations in individuals with RLD (46-48, 68) and purported improvements in activity have been difficult to verify. Furthermore, the aspects of RLD we can and do easily measure (e.g. range of motion, strength, and radiographic measurements) might not be the aspects of the anomaly that are most significant to the individual.

When evaluating the full impact of a functional disorder on an individual, it is important not to focus on the functional impairments alone. Disability can be regarded as the interaction between an individual with a functional impairment and attitudinal and environmental barriers that restrict participation in society on an equal basis with others (105). The ICF/ICF-CY (49, 106) provides a useful framework for description of disability. To give a broader picture of individuals with RLD this framework was adopted in paper III and IV.

9.2.1 Hand function, activity and participation in RLD

Compared to norms (110, 111, 116, 127, 128, 141, 142), the children and adults with RLD who were examined in papers III and IV had severely limited motion in elbow, wrist and digits; impaired grip strength and key pinch; and difficulties in manipulation tasks.

In spite of this, the children with RLD performed well in spontaneous bimanual activities, their level of self-perceived disability was low, and they rated the appearance of their arm positively. Surprisingly, in the adults with RLD, the upper extremity outcome measure (Quick-DASH) indicated that they perceived only a mild disability. Regarding their ability to partake in recreational activities, i.e. sports and music, their scores were in line with the general population (121, 122). Furthermore, despite the obvious activity limitations, the adults' physical and mental health scores (SF-12) were equivalent to norms (124).

Even though the severe deformity in both children and adults with RLD leads to obvious activity limitations, our studies strongly suggest that these limitations do not significantly restrict individuals´ ability to participate in daily life and to live full lives in society. Having said this, we should note that the demands on individuals and restrictions on their participation in daily life may vary widely among different socio-cultural environments though.

Previous studies of individuals with RLD use different hand function tests and outcome instruments (46-48, 51, 143), which makes comparisons difficult. However, like our studies, they all found that individuals with RLD experienced only moderate limitations in activity, and that adults with RLD did not perceive their disability to restrict their participation in work or social life significantly (46, 48).

Two of the previous studies (47, 48) did not evaluate radial angulation of the wrist and the radiographic measurements in the other two studies (46, 143), are not comparable with the measurements used on the adults in paper IV.

One of the previous two studies of children with RLD (47) included the same number of children as our study did , but differed from ours with regards to included Bayne types and the proportion of surgically treated individuals. The other study by Kotwal et al. (143) included a large number of individuals, but in contrast to other studies, their study focused on comparing surgically and non-surgically treated children and only included the more severe Bayne types III and IV. None of the two previous studies of children with RLD evaluated *participation*.

Although the previous studies of adults with RLD (46, 48) also differ with regards to the included Bayne types and the proportion of surgically treated individuals, the study populations are similar to paper IV regarding number of participants and age as well as the severely impaired range of motion and strength.

9.2.1.1 Body structure and function

Measurements of *body structure and function* demonstrate a considerable impairment in both children and adults with RLD. Compared to adults in Goldfarb et al.´s study (46), who had an average radiographic measure HFA of 25º, the children in our study had a higher measure of 34 º(paper III). This is most likely due to the fact that all limbs in Goldfarb et al.´s study were surgically treated by centralization, whereas only 18/25 limbs in our study were surgically treated. The resting angle of the wrist in Goldfarb et al.´s study (46), however, was similar to the comparable WRD we measured in adults in paper IV (36° vs. 31°in our study). The proportion of surgically treated limbs in the adults paper IV (23/29), however, was higher than of the children in paper III. Two of the previous studies (47, 48) did not evaluate radial angulation of the wrist and the radiographic measurements in the other two relevant studies (46, 143), are not comparable with the measurements used in paper IV.

The range of digital motion in the examined individuals in papers III and IV was impaired and, to an extent, comparable to that found in previous studies (46, 47, 143). The arc of wrist extension- flexion, however, varies considerably between these earlier studies and papers III and IV. This might be due to the use of different techniques to measure range of motion as well as to different distributions of included Bayne types and surgical procedures in the earlier studies.

The individuals with RLD in papers III and IV had lower grip strength (children 2.7 kg, adults 4 kg) compared to that reported in previous studies of children (3.5 kg) (47) and adults (5kg) (46). This may be explained by a difference in patient characteristics between the studies (mean age and included Bayne types).

It is interesting that ulnar interdigital grip was preferred in spite of former pollicization in as many as four of the twelve pollicized hands in children and in eight of the eighteen pollicized hands in adult with RLD. Many of these individuals chose the pollicized thumb for grasping or stabilizing larger objects, but used the ulnar interdigital pinch in manipulation of smaller objects

The fact that sensibility was normal or close to normal in all hands and did not differ between treated and not treated individuals is valuable information.

9.2.1.2 Activity

The hand function tests of both children and adults with RLD revealed a considerable activity limitation. The AHA score for the children with RLD (paper III) was lower than in the study of Buffart et al. (47). However, in contrast to the present thesis, in that study they used the original version of the AHA, which is not validated for children with reduction deformities. They also included bilaterally affected children, which is not in line with the AHA instructions. This may be an explanation for the divergent results.

The Box and Block test and Sollerman hand function test scores were considerably lower than norms, but have not previously been used in the evaluation of individuals with RLD.

9.2.1.3 Participation

The self-perceived outcome measures indicated only a mild disability among individuals with RLD.

The self-perceived disability in the adults with RLD, measured with Quick-DASH, had a surprising concordance with the study by Goldfarb et al. (46),where DASH was used (18 points in both studies). Also, Holtslag et al. (48), did not find great restrictions in participation among adults with RLD, as evaluated by the Impact on Participation and Autonomy questionnaire (IPA).

The SF-12 and CHEQ have not been used previously for evaluation of individuals with RLD, but the adults' physical and mental health scores (SF-12) were in line with the general population (124).

Adults´ evaluations of appearance of their disabled arm indicated a moderate degree of satisfaction. This is in line with the results of both previous studies of adults with RLD (46, 48). The significant relationship between SF-12 mental health scores and radial deviation of the wrist also points in that direction. The children in paper III were more content with the appearance of their arm than were the adults both in paper IV and in previous studies of adults with RLD (46, 48). The children rated their appearance similarly to the ratings by surgically treated children in the study by Kotwal et al. (143), but higher than the non-surgically treated children in the same study. Here too, it should be kept in mind that how individuals rate the appearance of an anomalous limb may vary widely across sociocultural contexts.

9.2.2 Relationship between deformity and activity and participation

The results in paper III and IV indicate that the radial angulation of the wrist may not be the primary determinant for activity and self-perceived disability in individuals with RLD. The measurements of radial angulation (i.e. HFA, TFA, and WRD) did not show any significant relationship with measures of *activity* and *participation* in children or adults with RLD. The one exception is the SF-12 mental health score, which had a significant relationship with WRD in the adults. In contrast, grip strength, key pinch, carpal-forearm length and active range of motion of elbow and digits all had a significant relationship with measures of *activity* and *participation* in the adults with RLD. In children active range of motion of digits had a significant relationship with activity and active range of motion of wrist with self-perceived disability.

Few studies, two in children (47, 143) and two in adults (46, 48), have previously evaluated the relationship between *body function and structure* and *activity* in individuals with RLD. Only two previous studies (46, 48) have evaluated this relationship with *participation*.

In children (paper III), we did not find any significant relationship between the Box and Blocks hand function test and any measure of *body function and structure*, but the AHA-PAD hand function test had a significant relationship with active range of digital motion. Likewise, Buffart et al. (47) found significant correlations between the AHA

hand function test and digital motion, as well as with strength in grip and pinch and motion of wrist. However, Buffart et al. did not use the AHA version validated for reduction deformities and also included bilaterally affected children.

The children´s perception of the time required to perform different tasks (CHEQ *Time*) and arc of wrist extension to flexion (TAM Wrist ext-flex) showed a significant correlation. This could indicate that wrist mobility is important for activity performance in children, which is in line with previous studies (47, 143).

The significant relationship between range of motion of digits and *activity* among adults with RLD (paper IV) has been observed earlier (47, 48, 143), but the relationship between the range of elbow motion and *activity* is novel. Strength in grip and key pinch also had significant relationship with *activity* among the adults with RLD (paper IV), which is similar to the results in the previous studies of children with RLD (47, 143). However, in contrast to the present children in and the studies by Buffart et al. and Kotwal et al. (47, 143) , we did not find any relationship between the range of motion of the wrist and the *activity* among adults with RLD (paper IV).

In two previous studies of adults (46, 48), the extent of impairments in *body function and structure* did not significantly correlate with *participation*. This is in contrast to the results of paper IV that indicated that *participation* is related to grip strength, forearm length and elbow and finger motion in adults with RLD. Furthermore, in adults the SF-12 mental health score was related to radial deviation of the wrist.

Buffart et al. and Holtslag et al. (47, 48) did not investigate the relationship between measurements of radial angulation and *activity* or *participation*.
In children, Kotwal et al. (143) found a significant correlation between hand forearm angle (HFA) and self-esteemed activity (Prosthetic Upper extremity Functional Index (PUFI)). In contrast, Goldfarb et al. (46) could not verify any significant correlation with radial angulation (HFA) and upper-extremity function (Jebsen-Taylor) or self-perceived disability (DASH) in adults. This is concordant with our data, where no significant relationship between radiographic measurement of radial angulation (TFA) and *activity* or *participation* was found.

9.2.3 Methodological considerations

9.2.3.1 Measurements of body function & structure, activity and participation

Radial longitudinal deficiency is a very rare condition and in spite of a multicenter approach the number of examined individuals in paper III and IV is small. Interpretations should therefore be made with caution. Furthermore, the individuals are heterogenous with respect to severity, prior surgical treatment and laterality. The included limbs had a large span of involvement and varying forms of treatment, including pollicization. However, the purpose was not to compare different surgical treatments or to correlate severity grade with outcome. The focus was instead to investigate the relationship between the different components of the deformity and *activity* and *participation*, regardless of severity and prior surgical treatment. The heterogeneity of clinical presentation facilitated this investigation.

We used standardized methods in measurements of range of motion and strength as well as standardized and validated hand function tests. Although the hand function tests are not specifically designed for reduction deficiencies, they are commonly used to evaluate manual dexterity and overall hand function.
Likewise, the outcome measures are also frequently used in assessment of upper extremity disorders, but are not especially adapted for these individuals.

The radiographic measurements proposed by Manske et al. (82) were used in the RLD children. However, in the adults, due to ankylosis of the wrist and the severe deformity, in many cases it was impossible to correctly use these standardized measurements. This problem has previously not been described. Instead, we used a modification of Manske´s measurements (paper IV), which unfortunately makes comparison with previous studies difficult.

The questionnaire of self-rated appearance is not validated. The transformation of the 1-5 scale to a score out of 100 is not really a valid approach. The transformation was made to facilitate comparison with other measures on a 0-100 scale, but can reduce the sensitivity of the score.

The Vilkki Severity Grading of RLD (87) is an attempt to create a measure of the complex anomaly in RLD. The Vilkki score is, to our knowledge, not psychometrically evaluated, but it gives a good impression of the extent of the deformity.

9.2.4 Future implications for treatment strategies

The considerable deformity in RLD precludes functioning in a standard manner, but despite this individuals with RLD find ways to function well in a world designed for those without a hand difference. Our finding that, that the activity limitations caused by the functional impairments in RLD do not considerably restrict participation in daily life for children or for adults, is valuable information for these individuals and their parents.

Our results also indicate that radial angulation of the wrist does not seem to be the primary determinant for activity and self-perceived disability in individuals with RLD. Rather, strength in grip and pinch; range of motion in elbow, wrist and digits; and carpal-forearm length are more important factors. This suggests that surgical wrist correction does not address the component of the deformity in RLD that influences *activity* or *participation* the most. Since long term results of surgical wrist correction are disappointing and, furthermore, can have negative consequences changes in treatment regime should be considered.

Today's surgical options are mainly limited to correcting the radial deviation of the wrist and improving grasp by pollicization. Increasing strength in grip and pinch as well as digital range of motion is not yet possible by surgical means.

The results of the this thesis suggest that in many individuals with RLD non-surgical treatment with a focus on maintaining digital motion and improving strength might be a better treatment strategy. If surgery has to be performed, the method that has the least

impact on ulnar growth and wrist motion should be chosen. Thus, the notched centralization procedure should be avoided. Distraction lengthening of the radius and/or ulna could be considered. In a severely radially angulated wrist a pollicized thumb will have a very non-functional position. Therefore, in these cases pollicization is probably not a good choice.

Our knowledge of how the complex malformation in RLD influences life for affected individuals is still sparse and the relationship between the deformity and *activity* and *participation* should be further investigated. Knowledge about how pollicization relates to these parameters is also meager. The cortical representation of the anomalous hand is another area that would benefit from further research.

10 CONCLUSIONS AND CLINICAL IMPLICATIONS

- The incidence rate of congenital upper limb anomalies in Stockholm, Sweden, between 1997 and 2007 was 21.5/10,000 live births. The present total population study of congenital upper limb anomalies, based on the IFSSH classification (paper I), confirms the incidence rate in the only comparable total population study in this field (37).

- Congenital upper limb anomalies are rare and represent a minority of birth defects. The incidence of congenital upper limb anomalies does not seem to change over time. In the present and previous epidemiologic studies of congenital upper limb anomalies there is a slight variation in the distribution of different types of anomalies. This variation is probably due primarily to differences in classification strategies and divergent selection of included individuals. Genetic variations between populations and environmental differences among regions may also contribute to the diversity. Sudden changes of incidence are an important signal to search for altered or new exposures to environmental factors. For this reason, recurrent epidemiologic studies of CULA should be performed.

- Congenital upper limb anomalies are frequently associated with non-hand anomalies, often in a relatively predictable pattern. Knowing the type of hand anomaly can thereby help pediatricians to focus further investigations in the right direction. Examination of heart, internal organs, spine and upper and lower limbs as well as blood samples and genetic counseling could be appropriate. Familial occurrence of congenital upper limb anomalies is common and patterns of inheritance are important to map out.

- The OMT classification is useful and accurate, but not without flaws. With further refinements, the OMT classification can provide a new useful framework for the communication of congenital upper limb anomalies. This thesis presents the first total population study of congenital upper limb anomalies based on the OMT classification (paper II) and the result can be used as a reference of congenital upper limb anomalies in a total population.

- Classifications provide a common framework for communication about a disorder and are thereby important for studies of epidemiology, etiology, treatment and prognosis. The IFSSH classification of congenital upper limb anomalies (21, 22) has inconsistencies and is not adapted to today´s knowledge of limb development. The OMT classification (7, 8) is based on the current understanding of limb development and thereby differences between subcategories can help elucidate the linkages between congenital upper limb anomalies and their underlying cause.

- The incidence of RLD (paper II) was 1.1/10,000 live births. The more severe types of RLD (0.4/10,000 live births) were more common in males, but radial deficiency restricted to the hand was more common among females. Associated non-hand anomalies were frequent in individuals with RLD.

- Compared to normally developed individuals, children and adults with RLD have considerable shortening of the forearm, angulation of the wrist and stiffness in the fingers as well as severely limited strength in grip and pinch and low scores in manipulation tasks. In spite of this, the individuals with RLD in our studies perceived their disability as mild. Thus, although the deformity in RLD leads to seemingly considerable activity limitations, these do not seem to significantly restrict participation in various areas of life (papers III and IV).

- The present thesis indicates that radial angulation of the wrist is of lesser importance for *activity* and *participation* than strength in grip and pinch; forearm length; and active motion of elbow, wrist and digits (paper III and IV).

- Previous studies have verified a high rate of late deformity recurrence and significant impairment of ulnar growth after surgical wrist correction in RLD and evident improvements in activity due to the procedures have been difficult to verify. The lack of relationship between radial wrist angulation and *activity* and *participation* casts doubts on the current principles for surgical wrist correction. Future treatment regimes should focus on retaining joint motion and improving manual strength, even if this may be difficult to achieve.

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APPENDICES

APPENDIX 1. 585 CONGENITAL UPPER LIMB ANOMALIES IN 562 CHILDREN IN STOCKHOLM, SWEDEN 1997-2007. IFSSH CLASSIFICATION (PAPER I)

Incidence, Relative frequency, Gender, Affected side, Associated non-hand anomalies and Ocurrence among relatives in 585 CULA in 562 Children born in Stockholm, Sweden 1997-2007. IFSSH Classification.

Congenital Upper Limb Anomaly, IFSSH Classification	Number of anomalies	Incidence per 10 000 live births	Relative frequency (%)	Gender					Affected side						Associated anomalies		Ocurrence among relatives	
				Male No	Male %	Female No	Female %		Right No	Right %	Left No	Left %	Bilateral No	Bilateral %	No	%	No	%
I. Failure of formation	**103**	**3,9**	**17,6**	**69**	**67,0**	**34**	**33,0**		**36**	**35,0**	**42**	**40,8**	**25**	**24,3**	**30**	**29,1**	**10**	**9,7**
A. Transverse arrest	22	0,8	3,8	13	59,1	9	40,9		9	40,9	13	59,1	0	0,0	6	27,3	0	0,0
B. Longitudinal arrest	81	3,1	13,8	56	69,1	25	30,9		27	33,3	29	35,8	25	30,9	24	29,6	10	12,3
Radial ray deficiency	33	1,3	5,6	17	51,5	16	48,5		9	27,3	7	21,2	17	51,5	20	60,6	2	6,1
Thumb deficiency	20	0,8	3,4	8	40,0	12	60,0		6	30,0	3	15,0	11	55,0	9	45,0	2	10,0
Radius hypolastic/abscent	13	0,5	2,2	9	69,2	4	30,8		3	23,1	4	30,8	6	46,2	11	84,6	0	0,0
Ulnar ray deficiency	25	1,0	4,3	21	84,0	4	16,0		10	40,0	9	36,0	6	24,0	2	8,0	4	16,0
Central ray deficiency	23	0,9	3,9	18	78,3	5	21,7		8	34,8	13	56,5	2	8,7	2	8,7	4	17,4
Cleft hand	8	0,3	1,4	7	87,5	1	12,5		4	50,0	3	37,5	1	12,5	2	25,0	3	37,5
Symbrachydactyly	15	0,6	2,6	11	73,3	4	26,7		4	26,7	10	66,7	1	6,7	1	6,7	1	6,7
Intersegmental arrest	0	0,0																
II. Failure of differentiation	**276**	**10,5**	**47,2**	**137**	**49,6**	**139**	**50,4**		**78**	**28,3**	**83**	**30,1**	**115**	**41,7**	**47**	**17,0**	**52**	**18,8**
A. Soft tissue involvement	216	8,2	36,9	111	51,4	105	48,6		63	29,2	77	35,6	76	35,2	38	17,6	34	15,7
Sprengel deformity	5	0,2	0,9	2	40,0	3	60,0		1	20,0	4	80,0	0	0,0	4	80,0	0	0,0
Poland syndrome	4	0,2	0,7	4	100,0	0	0,0		3	75,0	1	25,0	0	0,0	1	25,0	0	0,0
Cutaneous syndactyly	36	1,4	6,2	21	58,3	15	41,7		5	13,9	6	16,7	25	69,4	16	44,4	19	52,8
Camptodactyly	40	1,5	6,8	23	57,5	17	42,5		9	22,5	13	32,5	18	45,0	8	20,0	8	20,0
Thumb in palm deformity	7	0,3	1,2	5	71,4	2	28,6		0	0,0	1	14,3	6	85,7	1	14,2	1	14,3
Deviated finger without bony deformity	4	0,2	0,7	2	50,0	2	50,0		2	50,0	1	25,0	1	25,0	0	0,0	1	25,0
Wind-blown hand	5	0,2	0,9	4	80,0	1	20,0		0	0,0	0	0,0	5	100,0	1	20,0	2	40,0
Congenital trigger digit or thumb	115	4,4	19,7	50	43,5	65	56,5		43	37,4	51	44,3	21	18,3	7	6,0	3	2,6
B. Skeletal involvement	60	2,3	10,3	26	43,3	34	56,7		15	25,0	6	10,0	39	65,0	9	15,0	18	30,0
Shoulder level, other	2	0,1	0,3	0	0,0	2	100,0		2	100,0	0	0,0	0	0,0	1	50,0	0	0,0
Proximal radio-ulnar synostosis	3	0,1	0,5	2	66,7	1	33,3		1	33,3	0	0,0	2	66,7	0	0,0	1	33,3
Synostosis of phalanges (complex syndactyly)	13	0,5	2,2	8	61,5	5	38,5		3	23,1	1	7,7	9	69,2	5	38,5	5	38,5
Symphalangia	1	0,0	0,2	1	100,0	0	0,0		0	0,0	0	0,0	1	100,0	0	0,0	1	100,0
Clinodactyly	31	1,2	5,3	10	32,3	21	67,7		7	22,6	4	12,9	20	64,5	2	6,5	8	25,8
Triphalangeal thumb	10	0,4	1,7	5	50,0	5	50,0		2	20,0	1	10,0	7	70,0	1	10,0	3	30,0
III. Duplication	**155**	**5,9**	**26,5**	**91**	**58,7**	**64**	**41,3**		**45**	**29,0**	**50**	**32,3**	**60**	**38,7**	**40**	**25,8**	**39**	**25,2**
Digit	155	5,9	26,5	91	58,7	64	41,3		45	29,0	50	32,3	60	38,7	40	25,8	39	25,2
Radial polydactyly	59	2,3	10,1	34	57,6	25	42,4		33	55,9	17	28,8	9	15,3	13	22,0	14	23,7
Central polydactyly	4	0,2	0,7	2	50,0	2	50,0		2	50,0	1	25,0	1	25,0	0	0,0	3	75,0
Ulnar polydactyly	92	3,5	15,7	55	59,8	37	40,2		10	10,9	32	34,8	50	54,3	27	29,3	22	23,9
IV. Overgrowth	**10**	**0,4**	**1,7**	**5**	**50,0**	**5**	**50,0**		**5**	**50,0**	**3**	**30,0**	**2**	**20,0**	**3**	**30,0**	**0**	**0,0**
Hemihypertrophy	7	0,3	1,2	4	57,1	3	42,9		4	57,1	3	42,9	0	0,0	2	28,6	0	0,0
Macrodactyly	3	0,1	0,5	1	33,3	2	66,7		1	33,3	0	0,0	2	66,7	1	33,3	0	0,0
V. Undergrowth	**18**	**0,7**	**3,1**	**5**	**27,8**	**13**	**72,2**		**4**	**22,2**	**6**	**33,3**	**8**	**44,4**	**5**	**27,8**	**3**	**16,7**
Whole limb	2	0,1	0,3	0	0,0	2	100,0		1	50,0	1	50,0	0	0,0	0	0,0	0	0,0
Brachymetacarpia	3	0,1	0,5	0	0,0	3	100,0		0	0,0	1	33,3	2	66,7	1	33,3	0	0,0
Brachysyndactyly	2	0,1	0,3	0	0,0	2	100,0		1	50,0	1	50,0	0	0,0	1	50,0	0	0,0
Brachydactyly	11	0,4	1,9	5	45,5	6	54,5		2	18,2	3	27,3	6	54,5	3	27,3	3	27,3
VI. Constriction ring syndrome	**9**	**0,3**	**1,5**	**2**	**22,2**	**7**	**77,8**		**1**	**11,1**	**2**	**22,2**	**6**	**66,7**	**4**	**44,4**	**0**	**0,0**
VII. Generalized abnormalities and syndromes	**14**	**0,5**	**2,4**	**7**	**50,0**	**7**	**50,0**		**0**	**0,0**	**0**	**0,0**	**14**	**100,0**	**11**	**78,6**	**0**	**0,0**
Total No. of Anomalies	**585**	**22,3**	**100**	**316**	**54,0**	**269**	**46,0**		**169**	**28,9**	**186**	**31,8**	**230**	**39,3**	**141**	**24,1**	**104**	**17,8**
Total No. of Children	**562**	**21,5**	**-**	**304**	**54,1**	**258**	**45,9**		**169**	**30,1**	**186**	**33,1**	**207**	**36,8**	**130**	**23,1**	**99**	**17,6**

APPENDIX 2. 577 CONGENITAL UPPER LIMB ANOMALIES IN 562 CHILDREN IN STOCKHOLM, SWEDEN 1997-2007. OMT CLASSIFICATION (PAPER II)

Incidence, Relative Frequency, Gender, Affected Side, Associated Non-hand Anomalies and Ocurrence Among Relatives in 577 CULA in 562 Children born in Stockholm, Sweden, 1997-2007. OMT Classification.

Congenital Upper Limb Anomaly, OMT Classification	Number of Anomalies	Incidence/10 000 Live births	Incidence/10 000 Confidence Interval	Relative frequency (%)	Gender				Affected side						Associated anomalies		Occurrence among relatives	
					Male No	Male %	Female No	Female %	Right No	Right %	Left No	Left %	Bilateral No	Bilateral %	No	%	No	%
1. Malformations	**429**	**16.4**	**14.87-18.01**	**74.4**	**246**	**57.3**	**183**	**42.7**	**119**	**27.7**	**131**	**30.5**	**179**	**41.7**	**111**	**25.9**	**98**	**22.8**
A. Failure of axis formation/differentiation - entire upper limb	**73**	**2.8**	**2.18-3.50**	**12.7**	**47**	**64.4**	**26**	**35.6**	**26**	**35.6**	**36**	**49.3**	**11**	**15.1**	**23**	**31.5**	**2**	**2.7**
1. Proximal- distal axis	40	1.5	1.09-2.08	6.9	24	60.0	16	40.0	15	37.5	24	60.0	1	2.5	7	17.5	1	2.5
i. Brachymelia with brachydactyly	3	0.1	0.02-0.33	0.5	0	0.0	3	100.0	2	66.7	1	33.3	0	0.0	1	33.3	0	0.0
ii. Symbrachydactyly	15	0.6	0.32-0.94	2.6	11	73.3	4	26.7	4	26.7	10	66.7	1	6.7	0	0.0	1	6.7
iii. Transverse deficiency	22	0.8	0.53-1.27	3.8	13	59.1	9	40.9	9	40.9	13	59.1	0	0.0	6	27.3	0	0.0
iv. Intersegmental deficiency	0	0.0		0.0														
2. Radio-ulnar (anteroposterior axis)	22	0.8	0.53-1.27	3.8	17	77.3	5	22.7	5	22.7	7	31.8	10	45.5	10	45.5	1	4.5
i. Radial longitudinal deficiency	11	0.4	0.21-0.75	1.9	8	72.7	3	27.3	3	27.3	4	36.4	4	36.4	9	81.8	0	0.0
ii. Ulnar longitudinal deficiency	4	0.2	0.04-0.39	0.7	4	100.0	0	0.0	1	25.0	1	25.0	2	50.0	1	25.0	0	0.0
iii. Ulnar dimelia	0	0.0		0.0														
iv. Radio-ulnar synostosis	3	0.1	0.02-0.33	0.5	2	66.7	1	33.3	1	33.3	0	0.0	2	66.7	0	0.0	1	33.3
v. Humero-radial synostosis	4	0.2	0.04-0.39	0.7	3	75.0	1	25.0	0	0.0	2	50.0	2	50.0	0	0.0	0	0.0
3. Dorsal - ventral axis	0	0.0		0.0														
4. Unspecified axis	11	0.4	0.21-0.75	1.9	6	54.5	5	45.5	6	54.5	5	45.5	0	0.0	6	54.5	0	0.0
i. Undescended shoulder (Sprengel)	7	0.3	0.11-0.55	1.2	2	28.6	5	71.4	4	42.9	4	57.1	0	0.0	5	71.4	0	0.0
ii. Abnormal shoulder muscles	4	0.2	0.04-0.39	0.7	4	100.0	0	0.0	3	75.0	1	25.0	0	0.0	1	25.0	0	0.0
B. Failure of axis formation/differentiation - handplate	**356**	**13.6**	**12.22-15.08**	**61.7**	**199**	**55.9**	**157**	**44.1**	**93**	**26.1**	**95**	**26.7**	**168**	**47.2**	**88**	**24.7**	**96**	**27.0**
1. Proximal - distal axis	14	0.5	0.29-0.90	2.4	4	28.6	10	71.4	2	14.3	5	35.7	7	50.0	4	28.6	3	21.4
i. Brachydactyly	14	0.5	0.29-0.90	2.4	4	28.6	10	71.4	2	14.3	5	35.7	7	50.0	4	28.6	3	21.4
2. Radial-ulnar axis (anteroposterior axis)	195	7.4	6.44-8.57	33.8	114	58.5	81	41.5	60	30.8	59	30.3	76	39.0	49	25.1	44	22.6
i. Radial (thumb) deficiency (no radius involvement)	18	0.7	0.41-1.09	3.1	7	38.9	11	61.1	6	33.3	3	16.7	9	50.0	7	38.9	2	11.1
ii. Ulnar deficiency (no ulna involvement)	16	0.6	0.35-0.99	2.8	13	81.3	3	18.8	9	56.3	6	37.5	1	6.3	1	6.3	3	18.8
iii. Radial polydactyly	59	2.3	1.71-2.91	10.2	34	57.6	25	42.4	33	55.9	17	28.8	9	15.3	13	22.0	14	23.7
iv. Triphalangeal thumb	10	0.4	0.18-0.70	1.7	5	50.0	5	50.0	2	20.0	1	10.0	7	70.0	1	10.0	3	30.0
v. Ulnar polydactyly	92	3.5	2.83-4.31	15.9	55	59.8	37	40.2	10	10.9	32	34.8	50	54.3	27	29.3	22	23.9
3. Dorsal - ventral axis	0	0.0		0.0														
4. Unspecified axis	147	5.6	4.74-6.60	25.5	81	55.1	66	44.9	31	21.1	31	21.1	85	57.8	35	23.8	49	33.3
a. Soft tissue	91	3.5	2.80-4.27	15.8	54	59.3	37	40.7	16	17.6	21	23.1	54	59.3	26	28.6	30	33.0
i. Syndactyly	35	1.3	0.93-1.86	6.1	20	57.1	15	42.9	5	14.3	6	17.1	24	68.6	16	45.7	18	51.4
ii. Camptodactyly	40	1.5	1.09-2.08	6.9	23	57.5	17	42.5	9	22.5	13	32.5	18	45.0	8	20.0	8	20.0
iii. Thumb in palm deformity	7	0.3	0.11-0.55	1.2	5	71.4	2	28.6	0	0.0	1	14.3	6	85.7	1	14.3	1	14.3
iv. Dewated finger without bony deformity	9	0.3	0.16-0.65	1.6	6	66.7	3	33.3	2	22.2	1	11.1	6	66.7	1	11.1	3	33.3
b. Skeletal deficiency	31	1.2	0.80-1.68	5.4	10	32.3	21	67.7	6	19.4	5	16.1	20	64.5	2	6.5	8	25.8
i. Clinodactyly	30	1.1	0.77-1.64	5.2	9	30.0	21	70.0	6	20.0	5	16.7	19	63.3	2	6.7	7	23.3
ii. Kirner's deformity	0	0.0		0.0														
iii. Metacarpal and carpal synostosis	1	0.0	0.001-0.21	0.2	1	100.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	100.0
c. Complex	25	1.0	0.62-1.41	4.3	17	68.0	8	32.0	9	36.0	5	20.0	11	44.0	7	28.0	11	44.0
i. Cleft hand	8	0.3	0.13-0.60	1.4	7	87.5	1	12.5	4	50.0	3	37.5	1	12.5	2	25.0	3	37.5
ii. Synpolydactyly - central	16	0.6	0.35-0.99	2.8	10	62.5	6	37.5	5	31.5	2	12.5	9	56.3	4	25.0	8	50.0
iii. Apert hand	1	0.0	0.001-0.21	0.2	0	0.0	1	100.0	0	0.0	0	0.0	1	100.0	1	100.0	0	0.0
2. Deformations	**124**	**4.7**	**3.94-5.64**	**21.5**	**52**	**41.9**	**72**	**58.1**	**44**	**35.5**	**53**	**42.7**	**27**	**21.8**	**11**	**8.9**	**3**	**2.4**
A. Constriction ring sequence	9	0.3	0.16-0.65	1.6	2	22.2	7	77.8	1	11.1	2	22.2	6	66.7	4	44.4	0	0.0
B. Trigger digits	115	4.4	3.63-5.27	19.9	50	43.5	65	56.5	43	37.4	51	44.3	21	18.3	7	6.1	3	2.6
C. Not otherwise specified	0	0.0		0.0														
3. Dysplasias	**10**	**0.4**	**0.18-0.70**	**1.7**	**5**	**50.0**	**5**	**50.0**	**5**	**50.0**	**3**	**30.0**	**2**	**20.0**	**3**	**30.0**	**0**	**0.0**
A. Hypertrophy	10	0.4	0.18-0.70	1.7	5	50.0	5	50.0	5	50.0	3	30.0	2	20.0	3	30.0	0	0.0
1. Whole limb	7	0.3	0.11-0.55	1.2	4	57.1	3	42.9	4	57.1	3	42.9	0	0.0	2	28.6	0	0.0
i. Hemihypertrophy	7	0.3	0.11-0.55	1.2	4	57.1	3	42.9	4	57.1	3	42.9	0	0.0	2	28.6	0	0.0
2. Partial Limb	3	0.1	0.02-0.33	0.5	1	33.3	2	66.7	1	33.3	0	0.0	2	66.7	1	33.3	0	0.0
i. Macrodactyly	3	0.1	0.02-0.33	0.5	1	33.3	2	66.7	1	33.3	0	0.0	2	66.7	1	33.3	0	0.0
4. Syndromes	**14**	**0.5**	**0.29-0.90**	**2.4**	**7**	**50.0**	**7**	**50.0**	**0**	**0.0**	**0**	**0.0**	**14**	**100.0**	**11**	**78.6**	**0**	**0.0**
Total No. of Anomalies	**577**	**22.0**	**20.3-23.9**	**100.0**	**310**	**53.7**	**267**	**46.3**	**168**	**29.1**	**187**	**32.4**	**222**	**38.5**	**136**	**23.6**	**101**	**17.5**
Total No. of Children	**562**	**21.5**	**19.72-23.31**		**304**	**54.1**	**258**	**45.9**	**168**	**29.9**	**187**	**33.3**	**207**	**36.8**	**129**	**23.0**	**99**	**17.6**

APPENDIX 3. RLD CHILDREN DEMOGRAPHICS (PAPER III)

RLD Children Demographics

					Classification		Vilkki Severity Grading		Range of Motion		Radiographs					Treatment					Opposite hand if not included	
Child No	Gender	Age (yr)	Syndrome	Side	Bayne	Blauth	HWO	mH	Wrist ext-flex(°)	Digits TAM(°)	HFA(°)	UL(mm)	HFP(mm)	UB(°)	BL(cm)	R/C	SD	CD	P/O/S/Rot	Non-surgically	Bayne	Blauth
1	F	5,0	Goldenhar	R	III	V	10	8	35	375	5	84	9.4	93	105.5	R	SD		P		None	None
2	F	8,3		L	III	IIIA	8	7	20	470	45.5	124	0	12	132.5	R	SD	CD	OS		None	None
3	M	5,9		L	IV	V	12	8	0	205	98	90	-18	6.5	97.5					NS	None	None
4	F	11,3		L	II	V	1	0	75	725	15.5	157	-8.5	4.5	135	R	SD		P		I	II
5	M	10,9	VATER	R	IV	IV	11	8	40	175	90.5	117	-11.5	37	135	R	SD		P		0	V
6	M	11,8		L	II	IIIA	4	3	85	730	20.5	158	-11	3	142.5			CD			0	II
7R	F	13,1		R	IV	V	13	9	0	70	24	96	8	52	143	C			P			
7L	F			L	IV	V	9	5	95	145	65	123	-26	73	143					NS		
8	M	16,7		R	IV	V	12	8	20	145	*	108	*	61	179.5	C					None	None
9	F	12,8	VATER	L	IV	V	7	6	120	610	1	150	1.5	36	146	R	SD		P		I	II
10	M	14,3		R	III	V	8	5	55	290	-2	165	4	27	174	C					None	None
11	M	4,3		L	IV	V	12	6	60	315	79	86	-15	33	102.5					NS	None	None
12R	F	13,1	TAR	R	IV	I	5	3	65	555	35	107	6.5	90	149.7	R	SD					
12L	F			L	IV	I	6	2	15	730	33	117	5.5	53	149.7	R						
13	F	12,4		L	III	V	11	8	55	475	17	175	3.5	45	159	R	SD		P		0	III
14R	M	5,6	VATER	R	IV	IV	12	8	30	125	42	104	-6.5	11	108	C	SD					
14L	M			L	IV	V	12	8	75	285	76	99	-18	20	108					NS		
15	M	11,1	VATER	L	IV	V	9	7	40	310	63	137	-7.5	14	145	C	SD		Rot MCII		0	II
16	M	14,2		L	IV	V	11	6	0	355	29	147	0	71	171	R	SD	CD	P		None	None
17	M	7,0		R	IV	IV	8	6	35	710	50	112	-5	60	128	R	SD		P		0	II
18	M	16,8	Goldenhar	L	IV	V	3	2	100	650	12	215	13.5	23	188.5	R			P		0	V
19R	F	10,3		R	II	II	3	1	60	850	0	121	-5	30	132					NS		
19L	F			L	II	II	-1	-1	95	1095	3	148	0	13	132					NS		
20R	M	4,7		R	II	IV	3	2	10	495	-7	111	6	25	94	C	SD		P			
20L	M			L	IV	V	7	7	55	280	18	97	8	41	94	R	SD		P			

* =not measurable P=pollicization Rot=rotational osteotomi MC I NS=non-surgical treatment
R=radialization O=oppensplasty SD=soft tissue distraction None=normal
C=centralization S=stabilization CD=callus distraction

APPENDIX 4. RLD ADULTS DEMOGRAPHICS (PAPER IV)

RLD Adults Demographics

					Classification		Vilkki Severity Grading					Range of Motion					Treatment					Opposite hand if not included	
Adult No	Gender	Age (yr)	Syndrome/ *Anomalies*	Side	Bayne	Blauth	HWO	mH	TFA (°)	TCFL(mm)	mHFP(mm)	WRD (°)	TAM Elbow(°)	Wrist ext -flex(°)	TAM Digits(°)	BL(cm)	R/C/V/A/O	SD	CD	P/OP	Non-surgically	Bayne	Blauth
1R	M	19	VATER	R	IV	V	4	4	30	196	-24	0	120	25	505	175,5	C			P			
1L				L	IV	III	6	4	47	193	-65	40	110	20	665		C		CD	P			
2R	F	21	TAR	R	IV	II	8	5	70	124	-9	45	115	70	175	162	C						
2L				L	IV	II	8	5	47	98	15	35	100	40	0		C						
3L	M	19		L	IV	IV	8	7	40	120	*	10	50	60	155	168,5	C/O			P		0	I
4R	F	18	*skeletal dysplasia*	R	IV	IV	6	5	80	73	-76	20	110	20	65	148	R/O			P			
4L				L	IV	IV	9	7	85	92	-80	20	110	45	175		R/O			P			
5L	F	19	VATER	L	IV	V	10	9	64	154	-81	-15	65	50	195	168	C			P		None	None
6R	M	21		R	III	V	10	7	*	*	-29	10	40	5	415	159,5	C/O/A	SD		P			
6L				L	III	V	8	5	52	207	-25	10	50	90	510		C			P/OP			
7R	F	21	TAR	R	IV	I	4	2	60	156	-53	25	95	20	740	164	C						
7L				L	IV	I	4	2	97	144	-83	40	120	50	685		C						
8L	M	23	*VSD*	L	IV	IV	8	6	80	199	-50	50	120	90	225	175,5	C			P		I	II
9R	M	24	*esophagal atresia*	R	IV	IV	11	8	*	*	*	80	140	40	165	172	C			P		0	I
10L	M	24	*scolioís*	L	III	IV	10	8	78	116	0	40	90	35	235	172	F			P		0	None
11R	M	24		R	III	II	3	3	-2	181	-15	-20	120	85	540	177	R			P		0	II
12L	M	35		L	III	III	6	6	70	137	-60	0	135	30	560	163	C/A			P		I	III
13R	M	24	TAR	R	IV	III	4	-1	*	*	*	75	85	45	490	167,5					NS		
13L				L	IV	III	6	1	*	*	*	70	85	25	460						NS		
14R	M	22	VATER	R	IV	IV	10	8	40	152	6	40	100	5	110	169	C	SD	CD	P		0	IV
15R	F	44	VATER	R	III	V	6	4	69	151	-63	35	115	0	655	168	C			P			
15L				L	II	IV	2	2	11	242	-13	-5	145	125	790					P			
16R	M	33	*vertebra + ear*	R	IV	V	10	7	45	110	-7	50	55	65	360	160	C			P		0	V
17R	F	60	Holt-Oram	R	V	V	7	2	84	182	-61	40	40	65	390	172					NS		
17L				L	V	V	*	6	*	*	*	*	30	*	355						NS, prosthesis		
18R	F	32		R	IV	V	11	7	89	109	-30	90	60	0	260	167,5	C			P		0	IV
19R	M	23	Holt-Oram	R	IV	V	11	8	91	214	-86	45	75	0	380	183,5					NS		
19L				L	V	V	10	6	*	*	*	10	70	90	335						NS		
20L	F	30		L	IV	unappropr	8	5	23	130	-3	20	50	0	350	170	A					None	None

* = not measurable
R=radialization
C=centralization
F= vascularized free fibula

A= arthrodesis of the wrist
O=osteotomi
P=pollicization
OP= opponensplasty

SD=soft tissue distraction
CD= callus distraction
NS=non surgical treatment

None=normal

PAPERS I-IV