The ichthyoses are a family of genetic skin disorders characterized by dry, thickened, scaling skin. There are over twenty types that differ by their underlying genetic cause, outward appearance and/or mode of inheritance. Some are primarily limited to the skin, e.g., Ichthyosis Vulgaris (IV), X-linked Ichthyosis (XLI), Lamellar Ichthyosis/Congenital Ichthyosiform Erythroderma (LI/CIE), Epidermolytic Hyperkeratosis (EHK), and Netherton Syndrome, although the consequences of the skin condition may affect the individual in many ways, both physical and social/psychological (see below). In others the genetic effects may be more generalized and affect other parts of the body, e.g., Neutral lipid storage disease, Sjögren-Larsson Syndrome, Keratitis-Ichthyosis-Deafness (KID) Syndrome and several others. In the ichthyoses, most of the body surface is involved in the process. But in other genetic disorders included under the FIRST umbrella, the rough, scaling, thickened skin may be more limited in distribution, and seen only in patches, or on certain parts of the body. Some of these conditions include Darier Disease, Pachyonychia Congenita, the palmoplantar keratodermas (of which there are many genetic forms), and several others. A more complete list of the FIRST family of disorders is included at the end of this brochure.

1 There are some acquired [nongenetic] forms of ichthyosis. They occur in a variety of conditions, including cancer, endocrine diseases, and severe nutritional deficiencies. These forms of ichthyosis do not have their onset in infancy or early childhood as the genetic forms do.

2 “Mode of Inheritance”: (e.g., whether inherited as a dominant or recessive trait). The inheritance patterns of the FIRST family of disorders are discussed in more detail in another FIRST publication, “A Genetic Primer for the Ichthyosis Family of Disorders.”
Most of the FIRST family of disorders are quite uncommon to rare and affect only one person in several tens of thousands, but there are exceptions. Ichthyosis Vulgaris (IV), ("vulgar" means "common" in Latin), may affect as many as one person in every 250. It is often rather mild in severity and therefore likely that some people with IV are undiagnosed and may think they simply have "dry skin". X-linked Ichthyosis (XLI) is somewhat less common, usually more severe than IV, and occurs only in males. Estimates of its frequency range between one in every two-to-six thousand male babies. Lamellar Ichthyosis/Congenital Ichthyosiform Erythroderma (LI/CIE) itself is a family of disorders, with at least 6 causative genes; but collectively this group is quite uncommon, occurring in perhaps fewer than one in 100,000 births. Epidermolytic Hyperkeratosis (EHK) is similarly uncommon and it too is a family of disorders, with at least 3 causative genes. There is a range of severity in LI/CIE and EHK, with some patients having quite severe involvement, while others may have more limited disease (EHK) or be only mildly to moderately affected. These differences are due largely to the effects of the individual’s underlying genetic cause (i.e., the specific mutation).
NORMAL SKIN STRUCTURE AND FUNCTION AND WHAT GOES WRONG IN THE ICHTHYOSES

In order to understand what causes ichthyoses, it is necessary to understand how normal skin functions and how it is renewed. The skin's primary function is to protect the body – to keep the outside out and the inside in. This barrier function itself has many components, which include a barrier to excessive loss of body fluids or uptake of noxious chemicals in contact with the skin (the permeability barrier), as well as to provide a chemical and mechanical shield against invasion by microorganisms (viruses, bacteria, fungi, etc.), and protection against mechanical injury and injury from ultraviolet light, oxidative injury and many other stressors. While the skin is made up of several layers, it is the outermost layer, the stratum corneum, that is largely responsible for these protective functions. Because the diverse members of the FIRST family of disorders have in common problems with the function of the stratum corneum, problems that result in visible roughness and scaling, a more detailed look at the stratum corneum is required for understanding these conditions.

The stratum corneum is made up of many thin layers of flattened, dead cells called squames (or corneocytes) that contain keratin fibers, a tough, threadlike protein. The corneocytes are surrounded by a resilient shell of proteins knitted together, called the cornified cell envelope. Together, these protein structures give the stratum corneum its mechanical strength and flexibility. Outside the corneocytes are sheets (lamellar membranes) composed of fatty substances (lipids) that wrap around the corneocytes in multiple layers and fill the spaces between the
cells. These membranes are composed of specific types of lipids, cholesterol, free fatty acids and ceramides, that repel water (i.e., are very hydrophobic); thus these membranes are responsible for waterproofing the skin (i.e., for permeability barrier function). Because our body is mostly composed of water, yet we live surrounded by a dry atmosphere, formation of a competent barrier to prevent water loss, and, conversely, to prevent a flood of water coming inside when we bathe or swim, is perhaps the most critical function of the stratum corneum. This function is impaired to some degree in virtually all of the ichthyoses.

The corneocytes are connected by protein bridges (corneodesmosomes) that hold the corneocytes together. These bridges are gradually dissolved through the action of enzymes that digest proteins (proteases) as corneocytes are pushed outward toward the skin surface. By the time the squames reach the skin surface, these connectors are weakened sufficiently to allow them to separate from one another and be swept away by frictional forces, individually and invisibly. This process of normal shedding (desquamation) is also abnormal in all of the FIRST family of diseases.

Within the corneocytes are also found small molecules derived from the breakdown of cellular proteins, especially filaggrin, as the cells die. These small molecules help to attract water into the corneocytes, thereby hydrating the skin. Also in the corneocytes are signaling molecules, that, in case of injury or loss of permeability barrier function, can initiate repair (homeostatic) responses in the underlying living cell layers. Also present in the spaces between the corneocytes (intercellular domains) are proteins and lipids that have anti-microbial activity; i.e., they protect against invasion by bacteria and other microbes.

Genetic defects in many of these stratum corneum components have been found among the causes of the FIRST family of diseases. For example, defects in keratins cause EHK and defects in corneocyte envelope formation are the cause of LI/CIE in some patients, while deficiency of filaggrin is the cause of IV. Defects
resulting in the wrong lipids forming the lamellar membranes, or deficiency of lamellar membranes underlie a number of disorders, including XLI, Neutral lipid storage disease, and Harlequin Ichthyosis.

The underlying layers of the skin can be thought of as providing the supporting structures and materials, including new cells and chemical and protein building blocks needed to generate a normal stratum corneum. The direct suppliers of the stratum corneum are cells (keratinocytes) of the underlying, living epidermis. Keratinocytes have nuclei and are active synthetic factories, making keratin, filaggrin and other corneocyte proteins, including enzymes, as well as the lipids that will form the lamellar membranes. The dividing or renewing cells (basal cells) reside in the inner or bottom layer of the epidermis. As the skin constantly renews itself, new cells formed by cell division move upward through the epidermis, synthesizing proteins and lipids, and eventually “dying”, i.e., turning into corneocytes. Within the cytoplasm of the keratinocytes, the newly synthesized lipids, along with antimicrobial proteins and certain enzymes, including proteases and the protease inhibitors that keep their activities in check, are packaged into membrane-bound organelles (lamellar bodies). These organelles are expelled or secreted into the spaces between the cells (intercellular domain) of the stratum corneum, where their contents are in a position to form the lamellar membranes and to perform their other functions. Failure to form lamellar bodies underlies Harlequin Ichthyosis; while in other disorders (e.g., EHK), there is failure of secretion.

The entire process from formation of a new cell to migration to the inner surface of stratum corneum normally takes about 2 weeks; to migrate through the stratum corneum and desquamate at the skin surface takes another 2 weeks. As long as the corneocytes are shed from the surface at the same rate that new

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3. Below the epidermis is another, larger layer called the dermis, which contains supporting structures, including collagen and elastic fibers, blood vessels and nerves. And below the dermis is the subcutaneous fat layer.
cells are created in the basal layer of the epidermis, the skin is in a normal state of equilibrium, or "steady state." In some of the ichthyoses the entire process is accelerated, with more basal cells dividing and new cells reaching the stratum corneum within only 4 to 5 days (e.g., EHK, CIE); while in others, rates of cell regeneration and maturation are essentially normal, but desquamation is delayed (e.g., IV, XLI). Ichthyosis can be visualized as a traffic jam of corneocytes, similar to the traffic jam that results if an inordinate number of cars enter the highway - rush hour, for instance - or if the normal number of cars cannot exit —because of an accident or other obstruction in the road. In the ichthyoses, a "traffic jam" of corneocytes can occur for either of these reasons: because the production of cells is too rapid or because the natural shedding process is slowed or inhibited, or both.

For squames to be shed invisibly, they must be released from the connections that hold them to one another. This process of release is gradually accomplished as the corneocytes move outward through the stratum corneum through the action of proteases. The proteases in turn are switched on and off by activators and inhibitors. In some ichthyoses (e.g., EHK and Harlequin Ichthyosis), this protease activity is deficient because of a failure to deliver them to the right location while in others, their activity is switched off because of too much inhibitor (e.g., XLI). What we see as thickened, rough, scaly skin in the ichthyoses is the consequence of a thickened stratum corneum. Moreover, these ichthyotic cells are often shed in large clumps. The shedding of these easily visible scales is often a source of considerable annoyance and embarrassment to the person with ichthyosis.

The thick stratum corneum in most of the ichthyoses can be viewed as a quantitative response to a qualitative defect. To

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4. In contrast, in Netherton Syndrome, there is deficiency of a protease inhibitor, with the result that proteases are too active, digesting the corneodesmosomes too soon and resulting in a thin, incompetent stratum corneum. 5. As noted above, with the exception of Netherton Syndrome.
varying degrees, its permeability barrier function is impaired, resulting in increased rates of loss of water from the skin. This results in repair signals (“Make and deliver more lipid!” “Make more cells!”) that result in increased metabolic activity (hypermetabolism) in the epidermis and increased rates of new cell production (hyperplasia). In normal skin, once repair is completed, these signals are switched off and the normal steady-state resumes. In the ichthyoses, because the underlying cause (genetic defect) persists, the repair signals are not terminated and hypermetabolism and hyperplasia persist. Perhaps it is helpful to add to the visual analogy of a traffic jam what would happen in one composed of broken, barely operative vehicles, fenders missing, running on only a few cylinders; because in the hyperproliferative ichthyoses in the rush to provide corneocytes to the stratum corneum, maturation may be incomplete and all the components of a well-functioning stratum corneum not completely assembled. Thus in the ichthyoses there is “too much of a bad thing”: the stratum corneum is thicker than normal, but it is not capable of performing its duties normally.
Because of the multiplicity of genes involved in the ichthyoses, it is not surprising that there are differences in outward appearance. Sometimes the entire body surface is involved (e.g., LI/CIE), while in others (IV, XLI) the face and folds of the body may not be involved. The scales tend to be dark and coarse in some (e.g., LI), while in others (e.g., CIE, IV) they may be finer and lighter in color. In EHK the scales often have a ridged or even spiny character, and this can be especially apparent in body folds or over joints. Skin fragility and formation of blisters can also occur in EHK. Sometimes the skin under the scales is very red (erythrodermic); this is especially common in Harlequin Ichthyosis and CIE, but may also be seen in EHK and Netherton Syndrome, and others. The correlations between genetic causes and clinical results (genotype-phenotype correlations) are still being worked out for several of the ichthyosis families, especially LI/CIE.

The appearance of the skin in a newborn infant with ichthyosis is often quite different from how the child will look later on. This is because the fetus is immersed in amniotic fluid, an environment that imposes different demands on the stratum corneum from those following exposure to a dry atmosphere at birth. Some infants are encased in very thick, constrictive scales (e.g., Harlequin Ichthyosis), while others have a taut, shiny, “shellaced”

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6. **Genotype** is the term that refers to the specific genetic composition or mutation. **Phenotype** refers to the effect of that genotype on the individual, for example, the appearance of the skin in a person with ichthyosis.
appearance, the so-called “collodion baby”. In both instances the tight skin may pull the eyelids open (ectropion) and the lips outward (eclabion). During the first weeks of life these thickened scales or “membranes” are shed, and the mature pattern gradually develops. Many types of ichthyosis may begin as a collodion baby, but LI/CIE is most common. Other types of ichthyosis may begin with generalized erythroderma (e.g., Netherton Syndrome), or with exaggerated peeling or desquamation shortly after birth (e.g., XLI, Sjögren-Larsson Syndrome). IV typically is not present until later in infancy or childhood. In contrast to all of these, in EHK the newborn often presents with widespread blistering and denuded skin, rather than scaling.
THE IMPLICATIONS OF ICHTHYOSIS

Because most of the ichthyoses are uncommon to rare, it is not atypical for someone with one of these conditions to go through his/her entire life never meeting another with the same disorder. The public is also usually not familiar with these conditions. This can result in curiosity and, at times, in unpleasant behaviors such as staring, rude questioning or the giving of unsolicited advice. Ichthyosis can be a disfiguring disorder and as such has numerous social and psychological repercussions. Children are especially vulnerable to its social and psychological side effects. Even if they are spared blatant ridicule they may find themselves ostracized, ignored and isolated. In addition, the attentions of over-protective parents and other adults can also impair their development. Adolescence is a time of self-consciousness, self-doubt and exaggerated concern with appearance and physical attractiveness for even the healthiest and best-looking youngsters. It can be an especially painful experience for teenagers with ichthyosis. Yet despite these problems to confront, most people with ichthyosis go on to lead full, rich and productive lives. Adjusting to having a child with ichthyosis is challenging for families. Words are inadequate to express the shock new parents may feel when first confronted by the unusual and sometimes even frightening appearance of their newborn’s skin. Delivery room and nursery personnel often have little to no experience with these rare disorders and their lack of expertise contributes to parental dismay. Later on, parents may feel guilty, blaming themselves for their child’s condition. Siblings may be resentful of the time given to the “sick” child, or
may be thrust into an over-protective role when others taunt their brother or sister; they may even feel guilty about their own healthy skin. Children and adults with ichthyosis and their family members benefit greatly from meeting and talking with other people who share their situations. FIRST offers opportunities for these interactions; through its newsletter, website and other publications, peer counseling activities, its biennial family conferences, and regional conferences.

Ichthyotic skin is often dry, tight and inelastic. This rigidity may produce discomfort through formation of painful cracks in the skin and open areas. Extreme thickening of the skin on the soles of the feet can make walking difficult for many patients, and cracks and fissures on the fingers can make even simple tasks difficult or painful. Tight skin can interfere with joint mobility, and over time, lead to decreased joint mobility. In some types of ichthyosis (e.g., EHK) the skin is very fragile and will rub off from even a slight abrasion. Cracks and abrasions then leave the skin open to infections. Indeed, recurrent skin infections are a problem for many patients with ichthyosis.

Thick scales can obstruct the outflow of sweat ducts. This inability to sweat can make some patients with ichthyosis quite vulnerable to overheating in a hot environment or following vigorous exercise. Severe scaling on the scalp may also interfere with hair growth. Patients with some forms of ichthyosis (e.g., LI/CIE, Harlequin Ichthyosis) may be unable to close their eyes completely (ectropion) because of the tightness of the skin around the eyes and eyelids and may seem to "sleep with their

7. For example, people with ichthyosis are frequently asked if it is contagious. Because these are genetic conditions and are not due to infection with bacteria, viruses, or other microorganisms, the answer is, of course, “No”. 8. The Foundation offers many types of support to individuals and families dealing with ichthyosis, informational brochures, peer counseling, access to expert advice, etc. For more information on psychosocial adjustment in children, the Foundation has a video (VHS) “Butterflies: The Children of Ichthyosis” and a brochure “Ichthyosis: A Guide for Teachers”. It also offers a DVD “Living with Ichthyosis. A Teenage Perspective”. 9. Although these are genetic disorders, in many if not most instances there are no other known affected family members; and the appearance of ichthyosis in the family comes as a shocking surprise.
eyes open." For this reason, ophthalmologic care is an important part of treating ichthyosis for some patients.

As discussed above, the abnormal stratum corneum in ichthyosis results in an impaired permeability barrier with increased water loss from the skin surface.\textsuperscript{10} As water evaporates, it carries along with it energy loss as heat of evaporation. Infants and children with severe forms of ichthyosis may lose sufficient energy (calories) in this manner to inhibit growth. The demands of a hypermetabolic epidermis may add to this caloric deficiency. Provision of sufficient calories in the diet to support growth as well as extra fluid to replace skin losses can be difficult. In some cases, special measures, such as tube feedings, may be required.

\textsuperscript{10} This type of water loss (\textbf{transepidermal water loss}) is different from sweating, which is a secretion of water to the skin surface by sweat glands as part of regulation of body temperature (\textbf{thermoregulation}). Transepidermal water loss is the loss of body water by diffusion. Its rate is dependent upon external humidity and the competency of the permeability barrier to obstruct water movement.
Because of the multiplicity of genetic disorders included under the umbrella term ichthyosis and its related skin disorders, making the correct diagnosis can be a challenge, even for experts. General practitioners and even dermatologists may have little to no experience with these disorders. FIRST can help patients find physicians who are interested and knowledgeable in these disorders. It also offers two web-based training modules for physicians that can assist the general provider in the initial approach to the diagnosis of these disorders. The diagnosis of ichthyosis relies on features of the patient’s history (e.g., appearance at birth, family history) and physical findings (e.g., quality of the scale, pattern of involvement, presence of blisters or the presence of signs of involvement of other organ systems). A skin biopsy may be needed for routine histopathology or for other studies such as fibroblast cultures or electron microscopy. Occasionally blood tests may be needed. Once the diagnosis is narrowed to a specific form of ichthyosis, confirmation by genetic testing may be possible. Genetic testing offers several benefits, including certainty of diagnosis and early detection of future pregnancies (prenatal diagnosis).

11. www.firstskinfoundation.org “Types of Ichthyosis & Making the Correct Diagnosis” and “Management of Ichthyosis in the Neonate”. 12. Genetic testing and counseling are discussed in more detail in another FIRST publication, “Ichthyosis: The Genetics of It’s Inheritance”.

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Because the disorders included in the FIRST family are genetic diseases, at present there are treatments but no permanent cures. Treatments are focused on increasing skin comfort and preventing or treating complications, such as restrictive movements and skin infections. Therapies may either be topical (e.g., applied directly to the skin) or systemic (e.g., taken by mouth). Often a combination of therapies is used. Because of their unremitting, genetic basis, treatments for these disorders must be daily and ongoing.

There are two basic goals in topical therapies: 1) to reduce the thickness of the scales; and 2) to moisturize the skin. If these goals are achieved, the skin becomes more flexible and less susceptible to painful cracking and tightness. Of course, removal of visible scales also improves appearance; this is an important motivation for older children and adults.

Keratolytics are substances that weaken the connections between corneocytes, and thereby loosen scale. Commonly used keratolytics include salicylic acid, urea, and alpha-hydroxy acids such as lactic and glycolic acids; these are contained in many over the counter and prescription lotions, creams and ointments. Some keratolytics such as salicylic acid can be absorbed through the skin with potentially harmful side effects on the body, and should only be used under the guidance of a physician. Most of

13. FIRST is dedicated to finding cures for its family of disorders through providing support for research into their causes and treatments.
these agents are irritating and may sting if there are open areas of skin or fissures. This side effect, in addition to some concerns about potential toxicity, limits their usefulness in infants and preschool children. Physician guidance is recommended for this age group. Bland creams and ointments (emollients) help to trap water in (moisturize) the skin. Common ingredients in these (mostly) over-the-counter preparations include glycerin, petrolatum, lanolin, and other lipids (fats and oils). Newer products may contain lipids more natural (physiologic) to the stratum corneum (e.g., sterols, ceramides and fatty acids). These formulations tend to be more expensive and may be available only by prescription. Often trial and error efforts are required for an individual to find the formulation that works best for him/her. These emollients are typically applied after soaking in the bathtub to retain the moisture that has been absorbed into the skin, and may need to be reapplied several times throughout the day. Because these treatments are usually not reimbursed by insurance carriers, they result in significant out-of-pocket expenses for families.

Some patients find that occluding all or parts of the body overnight with occlusion suits or plastic food wrap allows water to soak into the skin and soften it well enough for it to slough off with minimal scrubbing the next morning. Using a propylene glycol and water mixture inside the suit may hasten the process. Because this maneuver can increase absorption of topical therapies, these treatments should be under physician guidance.

Many patients find that long baths are helpful in reducing the overall amount of scale on the body. Additives such as baking soda and salt can assist in the process of removing scale. Applying emollients directly after bathing can help to hold in moisture which is added to the skin during a bath. For those with thickening of the palms and soles, there are many mechanical methods which can be used to carefully remove thickened skin; these include using sanding wheels and mechanical paring instruments (Ped-Egg®). Some patients prefer to use these after a bath, while others use them on dry skin.
Retinoids are a class of drugs that are synthetic derivatives of Vitamin A. Both topical and systemic retinoids are used in the treatment of ichthyosis and related skin disorders, although they have not been approved by the FDA for these conditions.\textsuperscript{14} Retinoids are particularly effective in producing a thinner stratum corneum. Topical therapy is limited by the irritation that these agents can produce and by their expense. Nonetheless, topical retinoids can be very useful for management of localized and specific problems. Patients with more severe forms of ichthyosis and related conditions may benefit from systemic retinoids treatment. The two agents currently used are isotretinoin (e.g., Sotret®) and acitretin (Soriatane®). Although very effective in removing scale, these drugs have associated side effects. Some of the potential side effects include elevated blood fats (triglycerides), which may lead to an increased risk of coronary artery disease, and calcification of tendons and ligaments. Children may be at risk for premature closure of bone growth centers, which could result in stunted or asymmetrical bone growth. Most importantly, these drugs cause severe birth defects when taken by pregnant women. The decision to treat with systemic retinoids requires consultation with a physician experienced in their use for these conditions.

Special diets have been advocated for a few of the rarer syndromes (e.g., Refsum Disease), but in general, dietary changes have little or no effect on the ichthyoses. Although retinoids are used to treat ichthyosis, taking Vitamin A in excess of normal daily requirements is not recommended. Excess Vitamin A is toxic and can result in cerebral edema (swelling of the brain) and damage to the liver. Children can be particularly sensitive to toxic amounts of Vitamin A.

\textsuperscript{14} Off label use (i.e., use of a drug approved for a different condition than the one in question) is a common medical practice. For rare, “orphan” disease like ichthyosis, this may become a necessity, since there may be few or no approved drugs to use as alternatives.
FIRST, The Foundation for Ichthyosis and Related Skin Types, Inc.™ (formerly The National Ichthyosis Foundation, Inc.), is a non-profit organization dedicated to providing support to individuals and families affected by ichthyosis and related skin disorders. FIRST supports education and self-help through a national newsletter and its website, informational brochures, fact sheets, and videos; a biennial national family conference, and its network of regional representatives and Medical Advisory Board. Members receive up-to-date information about ichthyosis and a chance to meet or correspond with others in the ichthyosis community, to give and receive information and support. FIRST is also dedicated to finding cures for its family of disorders offering support for research into their causes and treatments.
THE FIRST FAMILY OF DISORDERS: A Partial List

Generalized Scaling; Involvement Exclusively Or Primarily Limited To The Skin:
- Ichthyosis Vulgaris (IV)
- X-linked Ichthyosis (XLI)
- Lamellar Ichthyosis/ Congenital Ichthyosiform Erythroderma (LI/CIE)
- Epidermolytic Hyperkeratosis (EHK)(Bullous CIE; Ichthyosis Bullosa of Siemens; Ichthyosis Hystrix of Curth-Macklin)
- Harlequin Ichthyosis
- Netherton Syndrome
  Loricrin Keratoderma (Vohwinkel Syndrome (Camissa type))

General Scaling; With Involvement Of Other Organ Systems
- Contiguous Gene Syndromes With XLI
- Sjögren-Larsson Syndrome
- Neutral Lipid Storage Disease (Chanarin-Dorfman Syndrome)
- Refsum Disease Adult Type
- Gaucher Syndrome (Type 2)
- Multiple Sulfatase Deficiency
- Keratitis Ichthyosis Deafness (KID) Syndrome
- Trichothiodystrophy (Tay Syndrome: IBIDS)
- Neu-Laxova Syndrome

More Localized Scaling; Involvement Exclusively Or Primarily Limited To Skin
- Darier Disease (Keratosis Follicularis)
- Pachyonychia Congenita
- Hailey Hailey Disease
- Erythrokeratodermia Variabilis
• Erythrokeratodermia Progressive Symmetrica
• Vorner-Unna Palmoplantar Keratoderma (PPK)
• Striate PPK
• Mal De Meleda

More Localized Scaling; With Involvement Of Other Organ Systems
• Ichthyosis Follicularis With Atrichia And Photophobia (IFAP) Syndrome
• Cardiofaciocutaneous (CFC) Syndrome
• Zurich Neuroectodermal Syndrome (Zurich-Kaye, CHIME Syndrome)
• Conradi-Hünemer-Happle syndrome (X-linked chondrodysplasia punctata)
• CHILD Syndrome
• Vohwinkel Syndrome (Classic Type)
• Papillon Lefevre Syndrome
• PPK With Cardiomyopathy Syndrome
• Howel Evans Syndrome (Tylosis with Esophageal Cancer)