The Uppsala Genodermatosis Centre and the European GENESKIN Project

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Table I. *Coworkers at Uppsala Genodermatosis Centre*

Departments of Medical Science (Dermatology)

Marie Virtanen, Agneta Gånemo, Carl Swartling, Hans Törmä, Inger Pihl-Lundin, Elizabeth Pavez-Lorie, Jean Christopher Chamcheu

Departments of Clinical Genetics and Pathology

Niklas Dahl, Maritta Hellström-Pigg, Johanna Dahlqvist, Malin Melin, Per Westermark

Over the last decade a burst of research on inherited diseases has resulted not only in the elucidation of the etiology of many genodermatoses, but also in new ideas about how to improve therapy. As a consequence, many patients expect that the health care system should be able to provide DNA-based diagnosis, improved genetic counselling, and up-to-date information about the pathogenesis and treatment of all these rare diseases. One way of meeting these demands is to organize special competence centres and to work on a national as well as international level to create networks of scientists, clinical experts and patient organizations who are devoted to genodermatoses.

To this end, a national centre was established in Uppsala 8 years ago. The centre relies principally on a collaboration between the departments of Dermatology and Clinical Genetics at Uppsala University Hospital (Table I). It also interacts with various national and international bodies, such as the Swedish patient organisations for ichthyosis (Iktyosföreningen), epidermolysis bullosa (EB; DEBRA föreningen) and Ehlers-Danlos syndrome (EDS föreningen), as well as Nordic DEBRA and many individual research groups in- and outside Scandinavia.

The Uppsala Genodermatosis Centre

The genodermatosis project actually started as a national survey of congenital ichthyosis in Sweden, which was initiated both by the discovery of transglutatminase 1 gene (TGM1) mutations in lamellar ichthyosis (1) and by our longstanding interest in retinoid therapy of keratinisation disorders.

The survey took place in 1997, when Specialist Nurse Agneta Gånemo, Chairman of Iktyosföreningen, and I together visited several dermatology departments in Sweden and examined over 40 patients with congenital ichthyosis. Blood samples, skin biopsies and detailed clinical data were collected. A subsequent laboratory work-up revealed TGM1 mutations in approximately half of the patients (2) and numerous other biochemical and ultrastructural defects were also identified (3, 4). Inspired by these results we started a Genodermatosis Clinic, which nowadays focuses not only on keratinization disorders,

Fig. 1: The team at work (*from left to right*): Maritta Hellström-Pigg (Geneticist), the patient, a resident, the author, Marie Virtanen (Dermatologist), and Agneta Gånemo (Specialist Nurse). Photo by Dr Flemming Brandrup, Odense.

Table II. *The setting of a Genodermatosis Clinic*

- One clinic every month, maximum 4–6 patients per clinic
- 2 specially equipped rooms (incl. nursing table and a skin model)
- Team consisting of 1–2 dermatologists, 1 geneticist, 1 specially trained nurse, and (optional) a paediatrician and a dietician
- Staff at the research laboratory to collect and analyze samples
- Follow-up (via telephone or mail) when required
- On call/on mail service for consultations regarding newborn babies with suspected genodermatoses

Table IV. *Routine examinations*

Blood tests
Histopathology
Immunohistochemistry
Electron microscopy
Hair microscopy
DNA analysis (see text for details)
Standardized protocols (incl. score) for clinical examination
Photography

but also on skin fragility syndromes, like EB and EDS. Fig. 1 and Table II describe the setting of the clinic. The clinic attracts between 50–100 referrals per year, mostly from Sweden. By "outsourcing" some of our research to Tartu (Dr Terje Kukk) and Odense (Drs Flemming Brandrup and Anette Bygum), and by working in close alliance especially with the late Dr Tobias Gedde-Dahl at Rikshospitalet in Oslo, we have successfully broadened the geographic representation of the patient material. So far about 350 patients have been characterized as part of the activity. The most prevalent diagnoses are congenital ichthyosis (in all its forms, bullous as well as non-bullous), keratodermas, pachonychia congenita (PC), Darier's disease, EB in all its forms, and EDS. Only the latter patients are routinely admitted to the hospital for 2–3 days, enabling them to see up to 10 specialists from different departments (Table III). Coordinated via the Genodermatosis Centre, all these specialists contribute to put a correct diagnosis and to give the patient the best available information about prophylaxis and treatment of EDS.

Table III. *Specialists involved in the investigation of Ehlers-Danlos syndrome*

Dermatologist
Physiotherapist
Pain specialist
Social worker
Vascular surgeon
Dentist
Geneticist
Occupational therapist
Rheumatologist
Cardiologist
Gynecologist
Orthopedic surgeon

Most other genodermatosis patients only come once to the out-patient clinic; further contacts are usually indirect via the referring physician or direct via mail/phone to the patient (or the parents). However, patients receiving a complicated therapy, e.g. investigational retinoid regimens or plantar injections of botulinum toxin to prevent sweat-induced foot blisters in EB and PC (5), may require re-visits.

How do we work?

Besides a thorough clinical examination, the work-up of a genodermatosis patient usually includes a series of laboratory tests and skin biopsies (Table IV). This enables us to examine e.g. keratin genes involved in bullous ichthyosis (epidermolytic hyperkeratosis) and PC, or genetic deficiencies in the lipoxygenase pathway, which, together with TGM1 mutations, underlie non-bullous ichthyosis/ichthyosiform erythroderma (Fig. 2 and 3). Other gene products of interest are the connexins involved in various keratodermas (6), fatty aldehyde

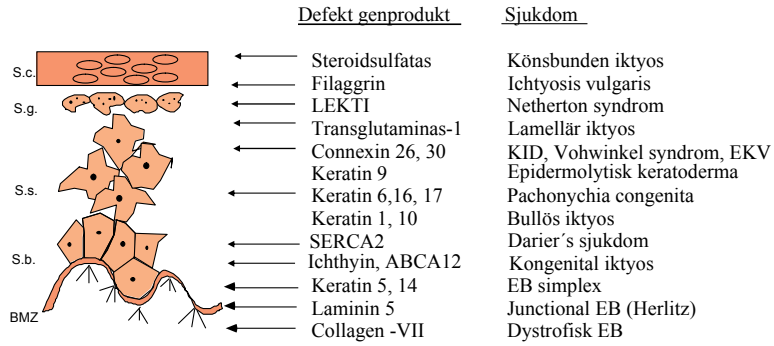

Fig. 2. Examples of mutated genes in epidermis causing specific genodermatoses

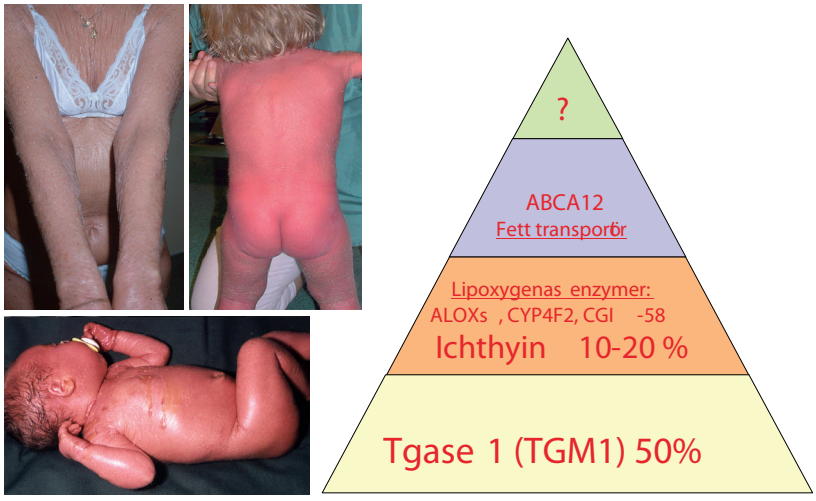

Fig. 3: Current knowledge about mutated genes causing non-bullous, non-syndromic congenital ichthyosis/ichtyosiform erythroderma.

dehydrogenase in Sjögren-Larsson syndrome (SLS), Lekti in Netherton syndrome and steroid sulphatase in x-linked ichthyosis. The complexity of the ichthyosis etiology is nicely reviewed in a recent article (7).

In the EB group of diseases, a suspected case of junctional (Herlitz) EB should be first screened for hot spot mutations in the LAMB gene, whereas other EB subtypes are usually diagnosed faster by immunostaining of blistering skin, a service provided by the EB diagnostic laboratory in Freiburg, Germany. Only occasionally is electron microscopy indicated any longer.

Although laboratory sampling is becoming increasingly important in the diagnosis of genodermatoses, a thorough clinical examination by an experienced team is crucial and in some cases sufficient to make a correct diagnosis. Regardless of whether or not sampling is required, these appointments always take a long time! Many patients have previously received an incorrect diagnosis or obsolete information, which take time to rectify. Furthermore, severe psychological reactions may occur, for instance, when parents learn about the poor prognosis of their child diagnosed with lethal EB, SLS or other severe forms of genodermatosis. Thus, after the initial investigation, we usually offer additional consultations to be given in a separate room where one of the team can sit down and talk at length with the family/patient. This can be very challenging, especially when communication has to take place via an interpreter, since many of our patients are immigrants coming from the middle-east or other foreign countries where recessive disorders tend to cluster.

The European GENESKIN Project

A close collaboration with other international centres devoted to genodermatoses is crucial to our ambition to offer optimal services to the patients. This is facilitated by an EU-sponsored project, GENESKIN, recently initiated by Professor Gianna Zambruno in Rome; 30 centres have

Fig. 4: The GENESKIN projects involves over 30 centres around Europe. Uppsala is the only one in northern Europe.

now been invited to participate in this activity (Fig. 4). The purpose is to establish a network of doctors, nurses and scientists interested in different types of genodermatoses and to train junior colleagues in this speciality by organising courses and facilitating visits to other centres. Another important mission is to create a website where information about the various diseases and the diagnostic services is collected so that both the medical profession and interested patients can be easily updated. The first version of the website has recently been opened (www.geneskin.org).

Although the GeneSkin project is not primarily research-driven, numerous international research collaborations have ensued. Our own research is focused on congenital ichthyosis; examples of theses produced on this theme in Uppsala are shown in Table V. A recent publication identifies a founder mutation for the ichthyosis prematurity syndrome (8), which clusters in the Trondheim-Östersund area as originally detected by Gedde-Dahl.

In conclusion, organisation of national competence centres and special teams for helping patients with rare diseases, such as genodermatoses, is probably a good way of promoting health care and clinical research in the interest of patients, affected families and society.

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Table V. *Doctorial theses produced in relatation to the Genodermatosis project*

Maritta Pigg: Molecular Genetic Studies on Three Autosomal Recessive Disorders. Sjögren-Larsson Syndrome, Glutathione Synthetase Deficiency and Congenital Ichthyosis.(2000).

Marie Virtanen: On Keratin Mutations in Epidermolytic Hyperkeratosis and the Regulation of Keratin Expression by Retinoids. (2001).

Agneta Gånemo: Hereditary Ichthyosis. Causes, Skin Manifestations, Treatments and Quality of Life. (2002).

Carl Swartling: Botulinum Toxin in the Treatment of Focal Hyperhidros and Dyshidrotic Hand Dermatitis. (2002).

Joakim Klar: Positional Cloning of Disease Causing Genes. A Genetic Study of Obesity, Ichthyosis Prematurity Syndrome and Meniere's Disease. (2005).