TAG 2007 335

6th Genodermatoses in Mediterranean working session
1st TAG meeting

May 22 - May 25, 2009, Greece

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State of art in Italy

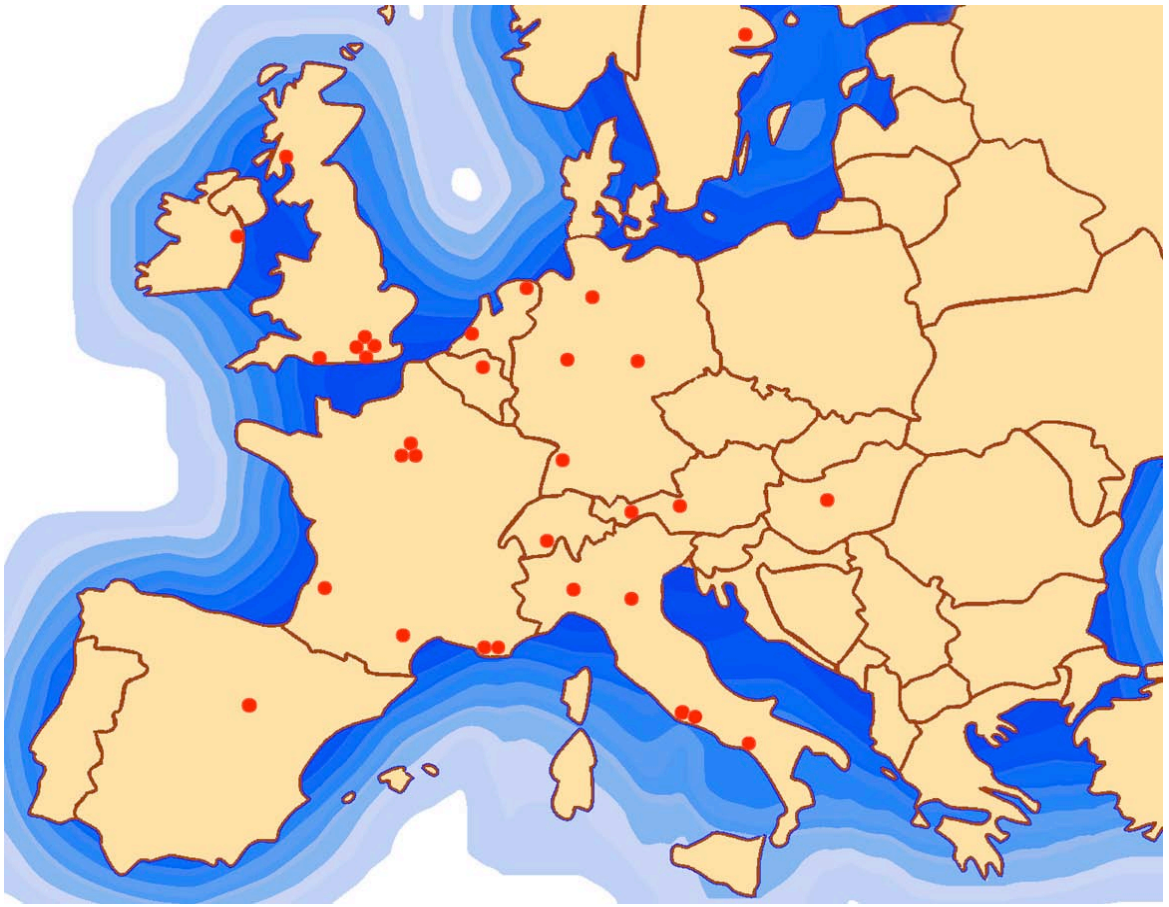
- **Development of collaborations at the European level**
- *The progress towards the development of centres of expertise for the 6 groups of diseases*
- *The progress in the assessment of needs of the patients and the costs of the diseases for the patients for the 6 groups of diseases*
- *The progress in the assessment of associations of patients and development of collaborative links*
- *The development of a national network*
- *The epidemiological data for the 6 groups of diseases*
- *The review of the strategies of the management of genodermatoses*

Development of collaborations
at the European level

Taking advantage of the GENESKIN
experience and network

GENESKIN project

- Title: Rare genetic skin diseases: advancing diagnosis, management and awareness through a European network
- Type: European Union-funded, **coordination** action
- Duration: **36 months** (01/07/2005 – 30/06/2008)



GENESKIN participants

32 clinical and research centres, and patients' associations (27 legal entities) from 12 European countries

1A Dr. Giovanna Zambruno, Rome, Italy

1B Dr. Giandomenico Russo, Rome, Italy

2A Dr. Miria Stefanini, Pavia, Italy

2B Dr. Michele D'Urso, Naples, Italy

3 Prof. Ivonne Ronchetti, Modena, Italy

4 Prof. Leena Bruckner-Tuderman, Freiburg, Germany

5 Prof. Heiko Traupe, Münster, Germany

6 Prof. Hans C. Hennies, Cologne, Germany

7 Prof. Karl-Heinz Grzeschik, Marburg, Germany

8 Prof. John A. McGrath, London, UK

9A Prof. Irene M. Leigh, Dundee, UK

9B Prof. David P. Kelsell, London, UK

10 Prof. Alan Lehmann, Brighton, UK

11 Dr. Malcolm B. Hodgins, Glasgow, UK

12 *Mr. John R.W. Dart, DebRA, Crowthorne, UK*

13 Dr. Alan D. Irvine, Dublin, Ireland

14A Dr. Guerrino Meneguzzi, Nice, France

14B Prof. Alain Hovnanian, Toulouse, France

14C Prof. Alain Taieb, Bordeaux, France

15 Prof. Jean-Paul Ortonne, Nice, France

16 Dr. Alain Sarasin, Villejuif, France

17 Prof. C. Bodemer, Paris, France

18 Dr. Judith Fischer, Evry, France

19 Prof. Daniel Hohl, Lausanne, Switzerland

20 Prof. Anne De Paepe, Gent, Belgium

21 Prof. J.H.J. Hoeijmakers, Rotterdam, Netherlands

22 Prof. Marcel F. Jonkman, Groningen, Netherlands

23 Dr. Antonio Bernad, AEBE, Madrid, Spain

24 Prof. Robert Strohal, Feldkirch, Austria

25 Prof. Johann W. Bauer, Salzburg, Austria

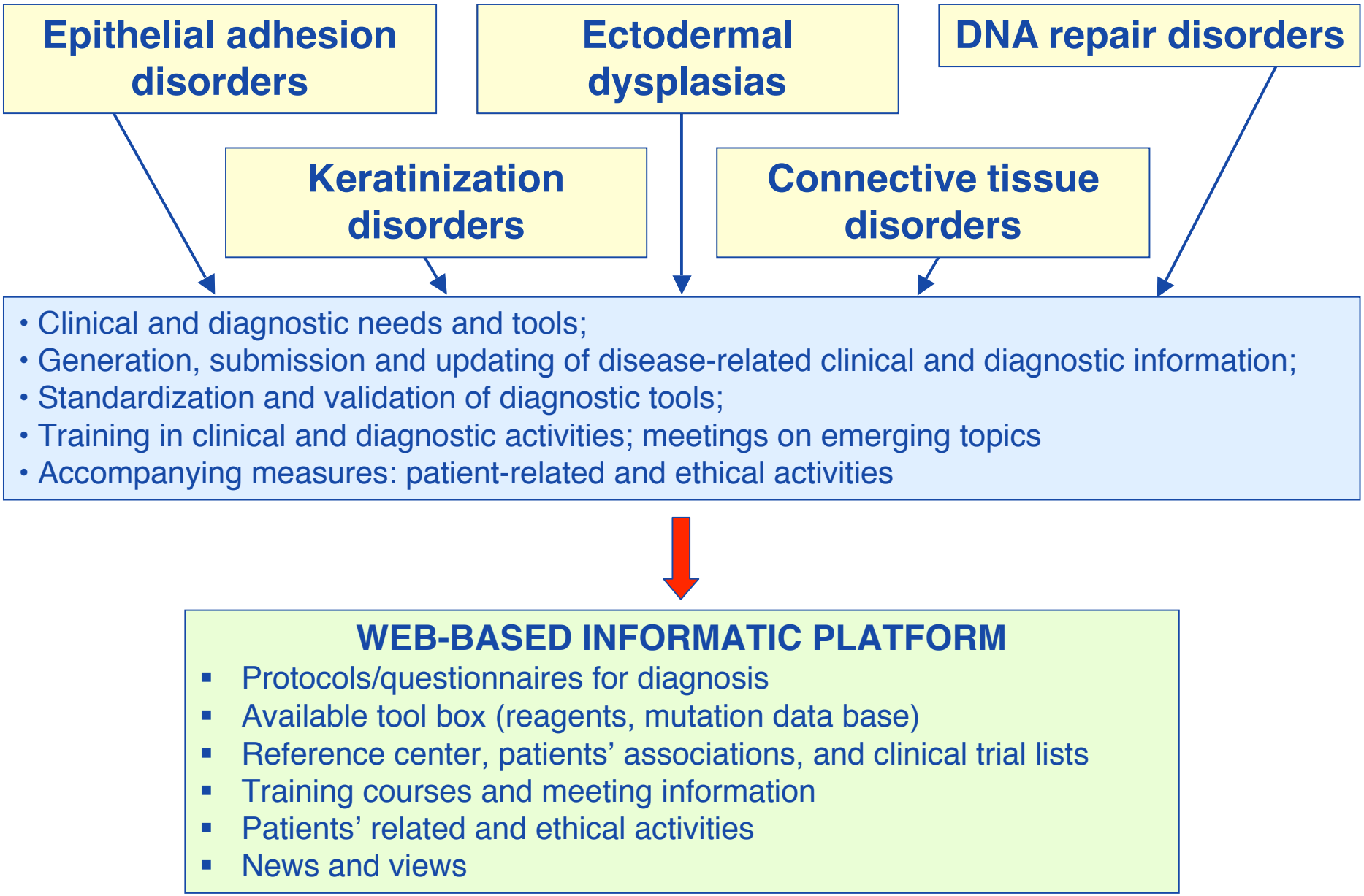
26 Prof. Sarolta Karpati, Budapest, Hungary

27 Prof. Anders Vahlquist, Uppsala, Sweden

GENESKIN achievements

- Development of an **European network** for **five major groups** of genetic skin diseases that, through a **dedicated website**, is contributing to disseminate disease knowledge and awareness, and improve diagnosis and management
- Novel, validated **diagnostic tools**; **fostering** of **research** on genetic skin diseases
- Organization of **training** activities on specific disease groups, and experts' **meetings** on specific topics (17 events in 8 countries, 665 participants)
- Set up of a **ethical expert group** and development of **an ethical document** on **genetic counselling related to genodermatoses**

GENESKIN structure

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Keratinization disorders

Definition

Keratinization disorders refers to a large and heterogeneous group of disorders of cornification, the majority of which are genetically determined. Actually, the ichthyoses constitute the predominant portion of keratinisation disorders. The word « ichthyosis » derives from the Greek word « ichthys » which means fish. In most cases, the skin abnormalities appear since birth. The patients develop extensive, often generalized scaling of the skin, associated or not with redness of the skin. Other organs can be affected. The vast majority of ichthyosis are rare diseases due to mutations in one single gene (monogenic disorders). They are transmitted in an autosomal dominant, recessive or recessive X-linked manner.

Classification

Over the past decade, the defective genes underlying a majority of these disorders have been identified. These spectacular progresses allow a classification based on the undelying defect. A first group is caused by defects in **structural proteins or enzymes involved in cornified envelope formation**. This includes lamellar ichthyosis/non-bullous congenital ichtyosiform erythroderma, congenital ichthyosiform erythroderma and Vohwinkel syndrome without deafness, bullous congenital ichtyosiform erythroderma (or epidermolytic hyperkeratosis) and ichthyosis of Siemens. A second group includes disorders due to **defects in lipid metabolism**: in the **cholesterol** pathway, such as X-linked recessive ichthyosis, Conradi-Hünermann-Happle syndrome and CHILD syndrome; or in **fatty acids** metabolism, including lamellar ichthyosis/non-bullous congenital ichtyosiform erythroderma, Harlequin ichthyosis, Sjögren-Larsson syndrome, Chanarin-Dorfman syndrome and Gaucher disease. A third group includes ichthyoses due to defects in **gap junctions** impairing **intercellular communication**, such as Keratitis-Ichthyosis-Deafness (KID) syndrome, erythroderma variabilis and Vohwinkel syndrome with deafness. A fourth group is represented by defects in **epidermal proteases and their inhibitors** and includes Netherton syndrome and Papillon Lefevre syndrome. A fifth group comprises **peroxisomal disorders** (i.e. Refsum disease and Rhizomelic chondrodysplasia punctata). A sixth group consists in a disorder of **DNA repair**, namely Trichothiodystrophy- this type of ichthyosis belongs to the group of DNA-repair disorders and are discussed elsewhere in this website. A seventh group consists in an intracellular calcium pump disorder and comprises Darier and Hailey-Hailey diseases.

geneSkin

diseases list
disease group
clinical centres
diagnostic centres
research centres
clinical trials
patients' associations

geneSkin

http://geneskin.idi.it/

a website dedicated to rare genetic skin diseases

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Clinical centres

AUSTRIA

Department of Dermatology
Innsbruck Medical University
Anichstr. 35
Innsbruck
Austria
A6020
Prof. Matthias Schmuth
Dr. Robert Gruber
r.gruber@uibk.ac.at
Outpatient clinic for Genodermatoses or rare diseases

Divison of Biochemical and Paediatric Genetics
University Children's Hospital Vienna
Währinger Gürtel 18-20
1090 Vienna
Austria
Prof. Olaf Bodamer
olaf.bodamer@meduniwien.ac.at
Outpatient clinic for Genodermatoses or rare diseases (for Refsum disease, Sjögren Larsson syndrome and X-linked recessive ichthyosis).

Salzburger Landeskliniken
Molecular Dermatology/ eb-house austria
Müllner Hauptstraße 48

- ✓ Development of collaborations on the European level
- ✓ **The progress towards the development of centres of expertise for the 6 groups of diseases**
- ✓ **The progress in the assessment of needs of the patients and the costs of the diseases for the patients for the 6 groups of diseases**
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- ✓ The progress in the assessment of associations of patients and development of collaborative links
- ✓ The development of a national network
- ✓ The epidemiological data for the 6 groups of diseases

The Italian regulation on rare diseases

- Decree n. 279, 18/05/2001
- Rare disease definition: **prevalence below 1:2,000** (according to EU criteria)
- **List of 284** rare diseases and syndromes (approximately 5,000 are estimated to exist)
- Creation of a **national network** of **regional centres** and **interregional reference centres** for diagnosis and management of rare diseases
- Definition of the role of Istituto Superiore di Sanità (National Health Institute) in the field of rare diseases
- Updating of the decree every three years (**to date not done**)

The Italian regulation on rare diseases

Regional reference centers are in charge to:

- Perform **diagnosis**, including biochemical and molecular diagnosis, of specific diseases and release the related certification
- Assure patient proper **management** and follow-up, also through a collaboration with GPs
- Keep patients' records and **communicate** all new disease **cases** to the **regional registry**

Interregional reference centers are in charge to:

- **Coordinate** the activities of **regional centers** and insure application of diagnostic and therapeutic protocols/guidelines, whenever available
- Give support to GPs about rare diseases and available drugs
- Participate in **training** of healthcare personnel and in disease prevention
- Disseminate information and raise public awareness about rare diseases; keep contacts with patients' associations

National Centre for Rare Diseases at Istituto Superiore di Sanità (ISS): mission

- Coordination of epidemiological, clinical and research activities on rare diseases
- Collecting data from **regional registries** for rare diseases and organising them into a **national registry**
- Establishment of **guidelines** for rare disease management
- Coordination and granting of **research** projects

The **Agenzia Italiana del Farmaco** (Italian Medicines Agency) is in charge to promote investments in research and development and to guarantee, through the simplification of drug registration procedures, a rapid access to innovative medicinal products and orphan drugs for rare diseases

The Italian regulation on rare diseases

The National Health System covers:

- All costs related to examinations required to establish the genetic disease **diagnosis**, including **molecular diagnosis** and **prenatal diagnosis**
- Costs of laboratory examinations, specialists' consultations and hospitalization
- Costs of **drugs**, **medical devices** and (not in all regions) emollients, antiseptics, dietary supplements, sunscreens, bandages, etc
- **Transportation** is **not** covered

TAG genodermatoses included in the Italian rare disease list

- **Congenital ichthyoses** (including: X-linked ichthyosis, Netherton syndrome, all forms of lamellar ichthyosis and non-bullous congenital ichthyosiform erythroderma, Harlequin fetus and ichthyosis hystrix
- **Epidermolytic hyperkeratosis**
- Erythrokeratodermia simmetrica progressiva
- Erythrokeratodermia variabilis
- KID syndrome
- Sjögren-Larsson syndrome
- Refsum disease
- Conradi-Hunermann syndrome
- **Inherited epidermolysis bullosa**
- **Xeroderma pigmentosum**
- **Incontinentia pigmenti**
- **Neurofibromatosis**

TAG genodermatoses not included in the Italian rare disease list

Hypohidrotic ectodermal dysplasia

Palmoplantar keratodermas (PPK): only epidermolytic hyperkeratosis (and thus possibly epidermolytic PPK) and erythrokeratodermas are included in the list. Non epidermolytic PPK, Mal de Meleda, pachyonychia congenita, hidrotic ectodermal dysplasia, striate PPK, loricrin keratoderma, Naxos disease, Papillon-Lefèvre syndrome, etc are not cited

↓

Patients are not entitled to receive free diagnosis and care

No officially recognized reference centers

No epidemiological data collected

Reference centers for rare diseases

- All Italian **regions** have **identified regional reference centers** for rare diseases and **activated rare disease registries**
- The **reference centre list** is **available at the National Center for Rare Diseases** (NCRD) **website** (http://www.iss.it/cnmr/), and, for some regions, at the regional website (e.g. Emilia Romagna - http://www.saluter.it/malattierare/)
- First epidemiological data should be available by NCRD in autumn 2009
- To date **no interregional reference centers** for genodermatoses have been **identified**

Regional reference centers for rare diseases

- Inherited epidermolysis bullosa: 35 centers at present recognised
- Congenital ichthyoses: 43 centers
- Neurofibromatosis: 62 centers
- Xeroderma pigmenosum: 31 centers
- Incontinentia pigmenti: 38 centers

Dyshomogeneous regional criteria for center recognition,
no checking of center activity,
no specific funding for centers

National guidelines/recommendations for rare disease management

- The **NCRD** at ISS is in charge of establishing **evidence-based guidelines/recommendations** for rare disease diagnosis, monitoring and treatment
- Guidelines are prepared by **groups of experts following the Delphi consensus development method** (systematic literature review and evidence level grading, followed by recommendation preparation and subsequent rounds of discussion for consensus achievement)
- **A panel of 18 experts** (dermatologists, pediatricians, medical geneticists, molecular biologists, ethicists and a representative of patient association) has been working during the past two years on the **diagnostic guidelines for inherited epidermolysis bullosa** (will be released by summer 2009)

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Italian patients associations

- Epidermolysis bullosa: DEBRA Italy (http://www.debraitaliaonlus.org/)
- Ichthyoses: UNITI (http://www.ittiosi.it/)
- Neurofibromatosis: ANANas (http://www.ananasonline.it/); ANF (http://www.neurofibromatosi.org/); IOCISONO (http://www.associazioneiocisono.it/); LINFA (http://www.associazionelinfa.it/); AMINF (http://www.associazioni.milano.it/itsos/aminf/index.html
- Palmoplantar keratoderma: no association
- Xeroderma pigmentosum: no association
- Hypoidrotic ectodermal dysplasia: ASSOANDE (http://www.assoande.it/)
- Incontinentia pigmenti: no association

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Towards the development of a national network

- A collaborative national network for epidermolysis bullosa has been built up during the past years
- Collaborative links already exist for other genodermatoses and need to be further developed
- The recently established ADOI (Associazione Dermatologi Ospedalieri Italiani) task force on rare diseases (27 members) will help in developing networks for other genodermatoses