Acta Derm Venereol 2004; 84: 337–338

Taylor & Francis
healthsciences

In this issue...

Gene chips: A giant leap – or the Emperor's new clothes?

Dr. Susanne Gabrielsson and her co-workers have studied differences in gene expression between atopic eczema and healthy controls on the "immature monocyte" cell level (p. 339). They have wisely avoided some pitfalls as they have a very well-defined cell population and not a mixture of cells. They convincingly demonstrate differences in "pro-inflammatory" cytokines and adhesion molecules, and they have discovered that atopic immature monocytes have upregulated levels compared with "healthy" immature monocytes – although not always. A few experiments are lacking: Would negatively selected "immature monocytes" show the same or would the selection process itself influence the results? I would have liked to see normal immature monocytes incubated with "atopic eczema serum" in order to see the significance of specific IgE.

Differential gene expression is a new technique which in principle could be an important step forward. If you have a "diseased cell" and can compare this cell to a normal one, then you could focus your research on the differentially upregulated genes. But – which cell is the "central cell" for atopic eczema? Immature monocytes as defined by the authors? I am not so sure. A recent study seems to indicate this. Skin biopsies from atopic dermatitis were compared with those from psoriasis and the following genes were significantly downregulated using the GeneChip microarray: human beta defensin 2, inducible NO synthetase, and IL-8 (1).

The "gene differential display technique" has a fancy name, is very expensive and requires expertise interpretation, but it could bring very interesting aspects into focus in the future, if the "right cell" is studied. Time will tell.

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Kristian Thestrup-Pedersen
Section Editor

Atopic eczema and "genes" – a complex conundrum

In this issue, too, Dr Annette Haagerup and her colleagues present their results from a genome screen of patients with atopic dermatitis (p. 346). Other investigations have been conducted along similar lines. However, this group has chosen to focus on "extrinsic atopic dermatitis" where type I allergies were present. They found three loci significantly associated with atopic eczema [3p (MLS = 2.14), 4p (MLS = 2.00) and 18q (MLS = 2.25)], one of them new (4p) (see Fig.). Eight additional regions showed weak although significant associations. Apparently they didn't find an association with the IgE locus even though they only looked at extrinsic atopic dermatitis patients. This is certainly noteworthy.

Why is it that a disease, which is certainly determined by genetic factors (see Schultz-Larsen's study on monozygous vs. dizygous twins) is so difficult to pinpoint? As recently reviewed by Thomas Bieber (forthcoming supplementum of Acta) there seems now to be an overlap between atopic eczema and psoriasis regarding the genes behind the diseases. These genes may be grouped as "inflammatory genes". So, not only should you have the "atopic gene(s)" but you need to have other "supportive" genes for the immune system to get activated.

We have recently described the clinical symptoms of patients with a completely different disorder, Papillon-LeFevre syndrome (1). We are about to publish the genotypes of this disorder, which is caused – or at least heavily associated with – a mutation within the Cathepsin C gene. Over 40 different mutations have now been described within this gene. One of the families we observed had a new genotype, a 189/189 mutation (2). Three children were affected having the exact same genetic 189/189 mutation. However, we also observed how the clinical phenotype of one child changed over the course of three months with spreading dyskeratosis (psoriasis-like) of her skin. Bernie Ackerman once used the term "*the lives of lesions*" – emphasizing that phenotypes can change and especially so in dermatological disorders. This makes it even more difficult for the geneticists in their selection of patients. So, like Papillon-LeFevre syndrome, atopic eczema may not just be atopic

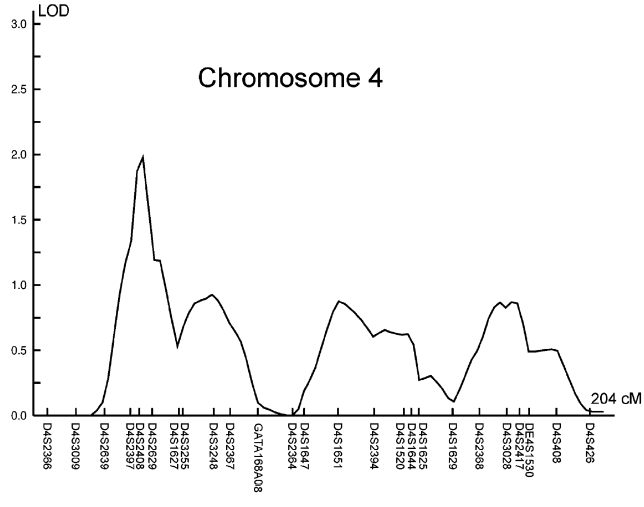

Fig. 1. Maximum likelihood IBD (MLS) curves. Taken from the original article, p. 348.

 ISSN 0001-5555
DOI: 10.1080/00015550410023202

eczema. There are still much to be learned about the genetic background in atopic eczema patients.

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A little light risk

The efficacy of a therapy is important but, perhaps of particular importance in dermatology, is safety. Safety is of special concern for several reasons. First, many of the disorders dermatologists treat are not life threatening. An adverse effect that threatens life is a major issue if it arises from a therapy for a disease such as atopic dermatitis or psoriasis. The oncologist is used to a different risk-benefit ratio. Second, many skin diseases are chronic, and the risks of therapy often long term. Even if the duration of therapy is short, toxicity may appear decades later. The paper in this issue of the Journal by Weischer and co-workers (p. 370) should be read with this in mind: how dangerous is ultraviolet B phototherapy?

The authors have followed up a modest number of patients (under 200), for a maximum of ten years (although the majority were followed up for a shorter length of time). The number of tumours were compared with the number predicted based on cancer registry data. The authors fail to show any statistically significant increase in cancer risk for those treated with broadband or narrow-band UVB. How should we assimilate their findings with current knowledge and practice?

First, as the authors acknowledge, the data are limited in power, principally because of the duration of follow up, and because details about the individual patients and their therapy was extremely limited. What happens to many of these patients after the study period is critical: we think of UVB as being a cumulative carcinogen and recognise that the biggest determinant of cancer risk is age — or to be more precise — cumulative UV exposure, and that the relation with dose of UVB is greater than linear. Second, returning to the theme of a lifelong disease, we should recall the therapies some of these patients may be exposed to later on. If some patients receive methotrexate or cyclosporin, or even some of the new biologics, will their prior phototherapy act as a latent factor for a later increased cancer risk? These are questions easy to pose and hard to answer. Difficult to answer not because of issues beyond our understanding, but because most health care systems (and research studies) usually manage *episodes* of disease rather than *life-histories* of disease. In any meaningful sense measures of risk can only come from clinical, rather than laboratory studies.

In the meantime the authors' data, coupled with those from others that they quote, is reassuring about any potential harm of phototherapy. Given the inconvenience and cost of hospital admission for treatment with dithranol or tar, and the clear efficacy of phototherapy, its place as a therapy for all but mild psoriasis remains reasonable. Probably, that is.

Jonathan Rees
Section Editor

Is eczema in infancy always atopic eczema?

Dr. Regina Fölster-Holst and her colleagues from Kiel (P. 410) have looked at *eczema infantum* and its development. Now, many of us do not use this term, but as presented here it is "non-specific eczema" in an infant, i.e. less than two years of age (the authors have a three-year limit). As stated by the authors, "eczema" in infancy may be atopic eczema, seborrhoic eczema, intertrigo, napkin dermatitis, or scabies. But one group of children does not belong to any of these categories, and this is why the diagnosis of *eczema infantum* has been used.

It is interesting to see that the eczema of two thirds of the children develop into atopic eczema, whereas in a third it disappears. And – as suggested by the authors – it may have been early atopic eczema, which disappears quickly. It is quite surprising that over an eight-year period they only find 49 children falling into the diagnosis of *eczema infantum* as their clinic must have seen quite a number of atopic eczema cases. So, it is a "rare" diagnosis.

But – if one third of "eczema" in childhood is not atopic eczema, do we not have a problem in questionnaire investigations like the BAMSE study in Stockholm, where up to 25% of parents report "atopic eczema"? (1). This is why I find the Fölster-Holst et al. study interesting. Can we – with certainty – diagnose atopic eczema in infant children, i.e. below the age of two years? We are helped by "pruritus" and eczema on "wrists, ankles, back of hands, neck, earlobes and anterior chest". So consider your atopic eczema diagnosis in an infant; it may not be that easy.

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