

DANGEROUS INTERACTION OF GENES AND LIFESTYLE

When hearing the term "body surface", most people think of the skin. However, the mucous membranes of the intestine, the respiratory passages and the lungs are also barrier surfaces to the outer world and with 300 m² are considerably larger than that of the skin (1.4 m²). These are the barrier surfaces where the body has to deal with many hostile envi-



Lena Bossen (Schreiber group)

ronmental factors. In particular, the mucous membranes of the intestine and the respiratory passages provide an entry portal for pathogens. That is why these tissues have a number of defense mechanisms for building up a barrier against the outside world. These include specialized proteins which fend off invading bacteria, viruses or fungi and also "guards", like the intestinal flora. Our intestine's dense population of bacteria prevents pathogens from being able to settle there. The mucous membranes also have a highly complex and differentiated immune system, the so-called mucous associated defense system.

DRAGNET SEARCH FOR THE RESPONSIBLE GENES

In the genome network Diseases due to Environmental Factors all research focuses on chronic inflammatory diseases in organs which exercise a barrier function against our environment. Among these are diseases such as allergies, asthma, chronic inflammatory intestinal diseases (Crohn's disease, ulcerative colitis), atopic dermatitis, the lung disease sarcoidosis, psoriasis and chronic obstructive respiratory diseases. To be sure, they affect different organs, but they all

have a hereditary aspect to them. Moreover, they all have in common that they can be triggered by lifestyle factors in industrialized societies. In recent decades there has been a great increase in the incidence of asthma and atopic dermatitis in children as well as of chronic inflammatory intestinal diseases – a clear indication that alongside disease genes,

environmental factors play a significant role as well. "In our network we are systematically searching for disease genes that together with external influences can trigger disease. We even believe that the seemingly so different environmental diseases are based in part on the same genetic factors," says Professor Stefan Schreiber, coordinator of the genome network. Scientists at the three locations of the network – Kiel, Berlin and Munich – are collaborating closely with the Systematic-Methodological Platforms DNA and Genetic Epidemiological Methods (GEMs). "Alone in

the first NGFN funding period of our network over four million single nucleotide polymorphisms (SNPs) were typed," Stefan Schreiber says. These include substantial scientific breakthroughs, such as the identification of the first and second disease genes for Crohn's disease or the discovery of the first disease gene for sarcoidosis.

SARCOIDOSIS – OFTEN NOT RECOGNIZED

Sarcoidosis is an inflammatory disease. Due to the formation of inflammatory lesions, so-called granulomas, it destroys the lungs. Immunologically, there is a hyperactivity of macrophages and CD4 T helper cells. Granulomas can occur everywhere in the body and interfere with the function of the respective organs. Often, however, the lungs are affected. Therefore, scientists suspect that substances from the inhaled air activate the immune system of genetically disposed persons. In Germany an estimated 30,000 people suffer from sarcoidosis. "But most likely there is a high number of unreported cases," says Dr. Jochen Hampe of the University of Kiel, who as young scientist together with his colleague Dr. Ruta Valentonyte discovered the first gene for sarcoidosis. "Due



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to unspecific symptoms like coughing, joint pain and fever, the disease frequently goes unrecognized."

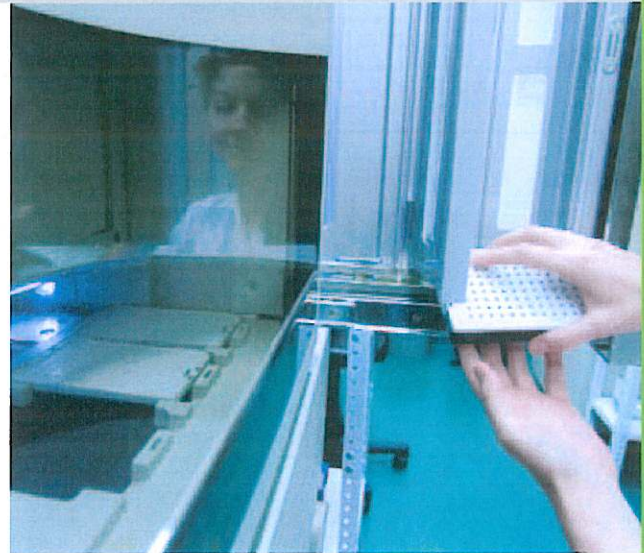
DISEASE GENE DISCOVERED

Scientists have had indications that sarcoidosis is hereditary for quite some time. There are families in which several family members suffer from the disease, while in other families it almost never occurs. In 2001 Dr. Manfred Schürmann of the University of Lübeck came a step closer to illuminating the genetic causes of the disease when he studied 63 families with known sarcoidosis. He discovered that genetic changes on a segment of chromosome 6 play a role in the genesis of the disease. Together with the Institute for Human Genetics in Lübeck, the Research Center Borstel, the Institute for Molecular Biotechnology in Jena and the Department of Pneumology of the University Hospital Freiburg, the Kiel scientists have now tracked down the culprit: The disease gene's name is butyrophilin-like 2 (*BTNL2*). Through an exchange of nucleotides a premature stop codon develops in its mRNA. The protein resulting from this lacks important domains for anchoring in the cell membrane. "This loss could lead to the fact that *BTNL2* as co-activator stimulates the T cells too strongly and that thus an autoimmune disease is triggered," Jochen Hampe speculates.

If an allele of the *BTNL2* gene exhibits this nucleotide exchange, the risk of sarcoidosis increases by 60 percent. If both alleles show this variant, the affected persons fall ill with sarcoidosis three times more often than people with "healthy" *BTNL2* variants. As next step the scientists want to elucidate the exact role of *BTNL2*, in order to create a solid



Jochen Hampe



Robotics in genome research

basis for new therapy approaches for sarcoidosis. "The discovery of the *BTNL2* gene is a breakthrough for clinical research on sarcoidosis," says Professor Joachim Müller-Quernheim, lung specialist at the University Hospital Freiburg. "Our long-term objective, to predict the course of the disease and the success of therapy, is thus closer to being realized."

NOT EVERY DISEASE HAS ITS OWN GENE

Already during the first experiments to circle in on disease genes for chronic barrier inflammation, the scientists noticed that diseases which attack different organs show considerable overlap. Now the discovery of the disease genes provides certainty: The Munich working group of Dr. Michael Kabesch found out that the gene *CARD15 (NOD2)* and *CARD4 (NOD1)* not only are significant for Crohn's disease, the chronic inflammation of the intestine, but also for asthma, periodontitis and joint inflammation in psoriasis. The Berlin researchers in the working group of Professor Young-Ae Lee report a gene localization for atopic dermatitis which overlaps with a localization for psoriasis. "This will result in completely new possibilities for therapy," Stefan Schreiber says. "The medical implementation of these results means that we must take a holistic view to solve the problem of 'inflammation' across all organ systems."

References

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