Identification of an allergen and identification of possible genetic predispositions by clinical data

Axel Schnuch,

IVDK,
University of Göttingen, Germany

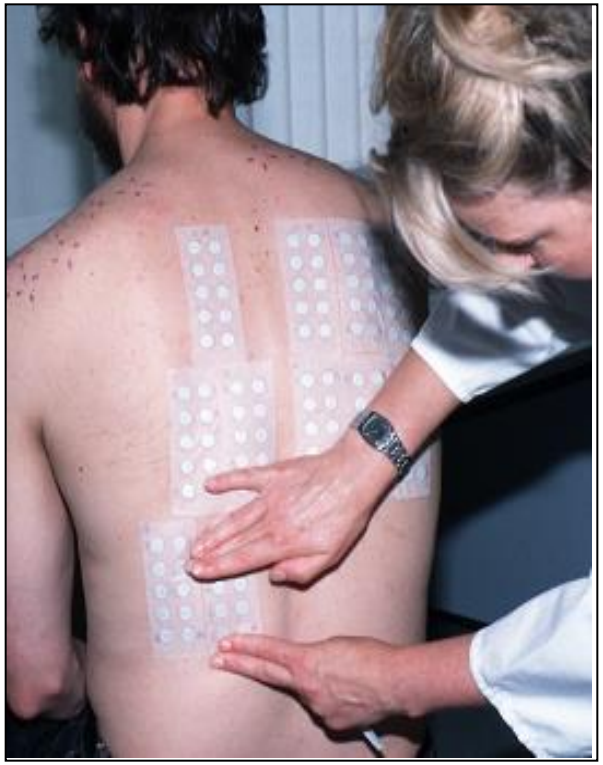
IDEA Workshop Characterization & Categorization of Fragrance Allergens;
September 23-25, 2014; Genval, Belgium

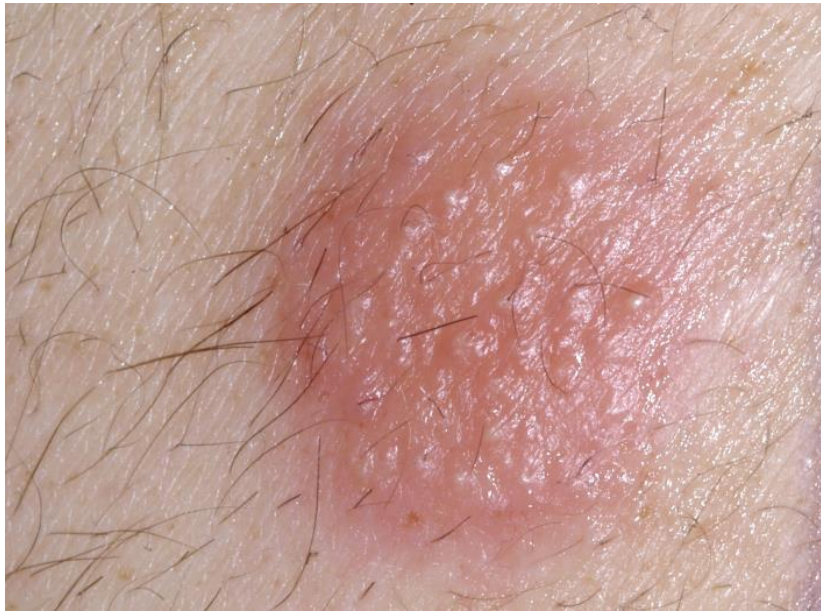
Face evidence

> 80% of young women are pierced

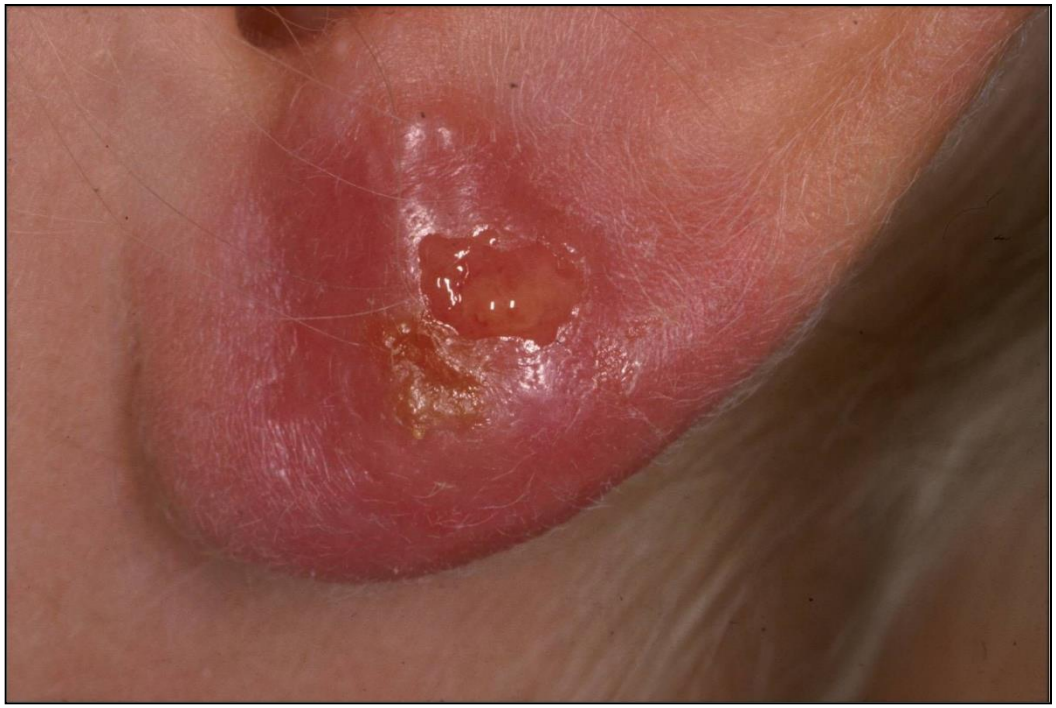
Face evidence

> 20% were shown to be sensitized to nickel





Face evidence



<< 5% develop manifest disease

Genetics in ACD

The outline

I. Traditional Studies in the Genetics of ACD

II. The phenotype to be studied

III. Genetic variation in ACD

IV. Perspectives

I. Traditional Studies in the Genetics of ACD

Family studies

Forsbeck, Skog, Yterborn (1966/1971)
Fleming, Burden& Forsyth (1999)
Walker, Smith, Maibach (1967)

Twin studies

Forsbeck, Skog, Yterborn (1968)
Menné and Holm (1983)
Bryld et al (2004)

Immunogenetic markers (HLA-Polymorphisms)

Many studies, no convincing picture

Family studies

Walker, Smith, Maibach (1967)

Experimental induction with NDMA (p-nitroso-dimethylaniline)

and

DNCB (2,4-dinitro-chlorobenzene)

(99 Families; 301 Individuals)

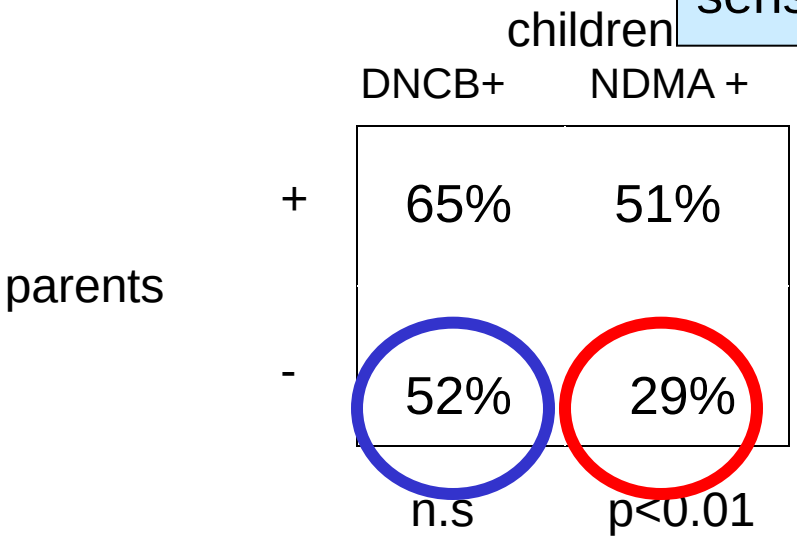
Family studies

Walker, Smith, Maibach (1967)

Experimental Sensitization to NDMA and DNCB

Children were sensitized to DNCB regardless of sensitization in parents

Children were sensitized to NDMA more often if parents were also sensitized



NDMA: p-Nitro-dimethylanilin; DNCB: Dinitrochlorbenzol

Family studies

Walker, Smith, Maibach (1967)

Experimental Sensitization to NDMA and DNCB

Conclusion explaining the difference:

A very potent allergen (e.g. DNCB) can “overpower” genetic influences.

In contrast, genetic factors seem to play a more prominent role
in sensitization to weaker allergens (e.g. NDMA)

Twin studies

Menné und Holm (1983)
(Danish Twin Register)

115 pairs with Nickel allergy

were investigated

Among MZ and DZ pairs

concordance rate for Ni-allergy

differed significantly

→ genetic influence !

Twin studies

Menné und Holm (1983)
(Danish Twin Register)

115 pairs with Nickel allergy

were investigated

Among MZ and DZ pairs

concordance rate for Ni-allergy

differed significantly

→ genetic influence !

Bryld et al **(2004)**

(Danish Twin Register)

630 twins (females) / 146 Ni +

Only

„ ... A small tendency
for larger OR among MZ...“

(OR: 1.28, 95% CI 0.33-5.00)

→ **No** genetic influence !

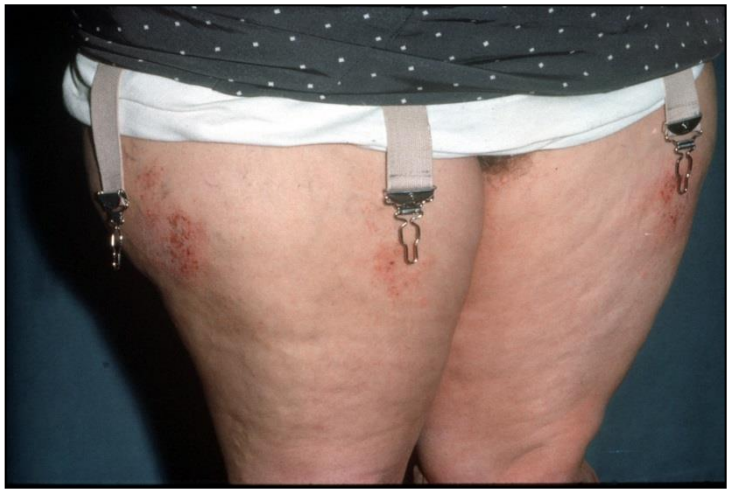
How to explain the diverging results ?

Different exposures ?

Menné und Holm **(1983)**

Genetics: +

suspenders



Bryld et al **(2004)**

Genetics: -

ear piercing

How to explain the diverging results ?

Different exposures ?

Menné und Holm **(1983)**

Genetics: +

suspenders

1. Nickel is a medium potent sensitizer. Genetic factors should play a role

Bryld et al **(2004)**

Genetics: -

ear piercing

2. But intense exposure may overrule genetic influences

I. Traditional Studies in the Genetics of ACD

Core message

Family studies

Twin studies

genetic factors may play a role in CA

Particularly in sensitization to **less potent** allergens and less intense exposure ?

Immunogenetic markers (HLA-Polymorphisms)

No further insights

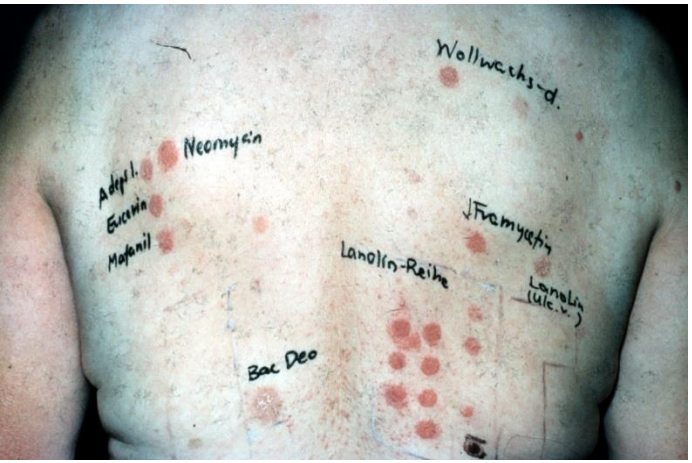
II. The appropriate **phenotype** in contact allergy:

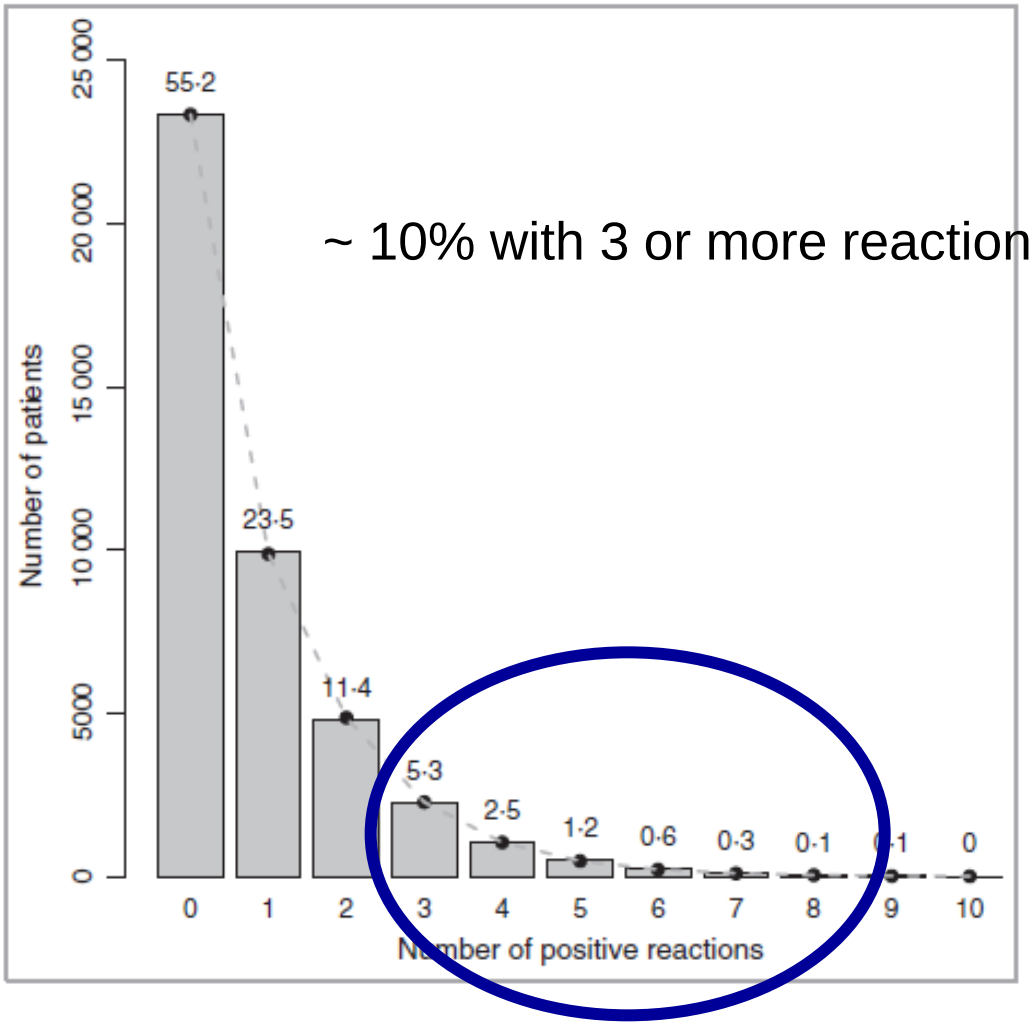
Polysensitization

Polysensitization

In a large patch test population (IVDK)

Number of positive reactions in 126.943 patients





~ 10% with 3 or more reactions

Schwitulla J, Gefeller O, Schnuch A, Uter W:
Risk factors of polysensitization to contact allergens.
British Journal of Dermatology 169, 611-617 **(2013)**

Polysensitization

Background

The study on genetics of complex diseases focus on **extreme phenotypes** (genetic influences more pronounced).

In hypertension it would be very high blood pressures

In ACD it could be polysensitization as a sign of increased susceptibility

II. The appropriate **phenotype** in contact allergy:

Polysensitization =/> 3 sensitizations

in experimental settings
(see Peter Friedmann)

DNCB

Diphenylcyclopropenone

In large patch test populations

Copenhagen/Gentofte

IVDK

Clinical profile of the PS subgroup

Polysensitization

In large patch test populations

Polysensitization is associated with:

- An increased risk for further sensitization *(INDUCTION)*
- Stronger allergic reactions *(ELICITATION)*
- Sensitization to even **weak allergens** (e.g. parabens)
- increased response to the irritant SLS

- and with a number of clinical characteristics (age, sex, AD, site of eczema)*

* B. Carlsen et al (Gentofte); J Schwitulla et al (IVDK)

II. Polysensitization

Based on

- Experimental studies (*Clin Exp Immunol 1985; 61: 232-41; Contact Dermatitis 2010; 63:10-14)*

- Clinical epidemiology in > 100,000 patients (Gentofte, IVDK)

Polysensitization can be regarded as a clinical sign of **increased susceptibility**

III. Genetic variation in ACD

Some basic explanations

- **Mutations** e.g. insertion, deletion, duplication or single base pair substitution occur **in less than 1%**

- A **polymorphism** is a genetic variation located in specific DNA sequences **found in > 1%** in the population e.g.
  a „SNP“ = single nucleotide polymorphisms

In the case of the *TNF* –308 G→A polymorphism, the “G” (guanosine) at position –308 of the DNA sequence normally present in the TNF gene is replaced by “A” (adenosine)

Genetic variation in ACD

Two main approaches:

1. **'candidate gene approach**'

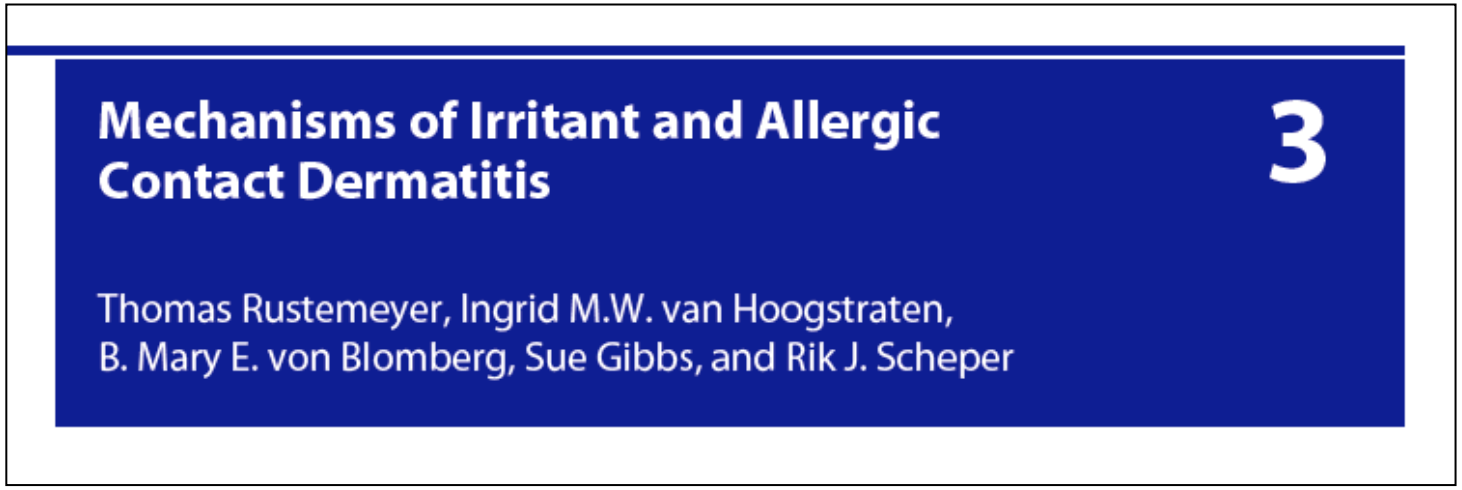
The gene products (e.g. cytokine) suggest from a pathogenetic point of view a role in ACD - thus hypothesis-driven research.

The responsible genes can be considered as candidate genes

2. Genome-wide association studies (**GWAS**),

an *a priori* 'agnostic' approach regarding the genes involved

Functionally relevant steps in the pathogenesis of CA and candidate genes to be studied



In: Jeanne Duus Johansen, Peter J. Frosch, Jean Pierre Lepoittevin (eds.)
Contact Dermatitis, Fifth Edition, Springer, Berlin 2011

Contact dermatitis: from pathomechanisms to immunotoxicology

Stefan F. Martin

Exp. Dermatol. 2012; 21: 382

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

1. Factors influencing the availability of the allergen	
barrier structure and function	Filaggrin Late cornified envelope Claudin-1
metabolism of the allergen (toxification/detoxification)	*N*-Acetytransferase I and II, Glutathione-*S*- transferase

Deletions in the *LCE3B* and *LCE3C*
Molin et al 2011

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

1. Factors influencing the availability of the allergen	
barrier structure and function	Filaggrin Late cornified envelo Claudin-1
metabolism of the allergen (toxification/detoxification)	*N*-Acetytransferase I Glutathione-*S*- transferase

Decreasing or increasing risk in fragrance and nickel allergies
Ross-Hansen et al 2013;

Studies of candidate genes in ACD: Results

1. **Filaggrin** null mutations*
   (combined genotypes for R501X and 2282del4)

Results inconclusive:

In several studies not associated with ACD

Lerbaek A, et al Br J Dermatol 2007; 157: 1199-204.
Brown SJ, et al Br J Dermatol 2008; 158: 1383-4.
deJongh CM, et al Br J Dermatol 2008; 159: 621-7.
Novak N, et al J Invest Dermatol 2008; 128: 1430-5.
Ross-Hansen K. et al Contact Dermatitis 2010; 64: 24
Carlsen B. et al Contact Dermatitis 2010; 63: 89
Thyssen JP, et al Br J Dermatol 2010; 162: 1278-1285
Carlsen B. et al Br. J. Derm. 2011; 36: 467 .

Studies of candidate genes in ACD: Results

1. **Filaggrin** null mutations*
   (combined genotypes for R501X and 2282del4)

…But the risk of **Ni allergy** was increased **in specific situations:**

in combined allergic and irritant contact dermatitis (Molin S et al Br.J Derm 2009; 161:801)

- in women with nickel dermatitis (!) and without ear piercing (Thyssen et al 2010)

…and the risk of contact sensitization (other than Ni and thiomersal) increased in individuals with "dermatitis" (unspecified hand eczema and / or atopic dermatitis) (Thyssen J. et al Contact Dermatitis 2013; 68; 273)

Studies of candidate genes in ACD: Results

1. **Filaggrin** null mutations
   (combined genotypes for R501X and 2282del4)

The risk was increased:
- in women with nickel dermatitis and **without ear piercing**

Hypothetical explanations:

In piercing nickel is *‚bypassing‘* the Ni-chelating action of filaggrin (Thyssen / Ross-Hansen), thus blurring genetic differences)

Or, compatible with our more general concept, that genetic factors play a role in less intensive allergen exposure….

See twin studies (Menné & Holm (1983) versus Bryld et al (2004))

Studies of candidate genes in ACD: Results

1. **Filaggrin** null mutations
   (combined genotypes for R501X and 2282del4)

The risk for contact sensitization was increased:

- in **combined** allergic and irritant contact dermatitis (Molin S 2009)
- in individuals with "dermatitis" (Thyssen J 2013

Hypothetical explanation:

The risk conferred by *FLG* mutations is increased by additional risk factors:

⟶ **Mutations plus inflammatory state**

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

1. Factors influencing the availa	
barrier structure and function	
metabolism of the allergen (toxification/detoxification)	*N*-Acetytransferase I and II, Glutathione-*S*- transferase

Risk increased in rapid acetylators (4 publications)
Schnuch et al 1998, Westphal et al 2000, M. Nacak et al 2006), Najim RA, et al (2005)

No associations
Blömeke et al 2009

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

1. Factors ir	
barrier struct	
metabolism of the allergen (toxification/detoxification)	*N*-Acetytransferase I and II, Glutathione-*S*- transferases

Combined deletions (M + T) more frequent
in allergics to mercury compounds (org. and unorg)
Westphal et al 2000 or chromate
Wang et al 2007

No associations with “contact allergies” (!)
Ross-Hansen K et al. ***2012***

Evidence that polymorphisms of xenobiotic metabolizing enzymes may act as **substance-specific (!) risk factors** with probably no impact on contact allergy in general

Glutathione *S*-transferase *M1* and *T1*

Comment on:

B.J. Wang et al Contact Dermatitis 57: 309 (2007)

Possible consequences of not considering exposure (see also Westphal et al 2003):

Individuals with high susceptibility but without allergen exposure (and thus not sensitized) may be allocated to the control group

In Wang‘s et al study all were

- exposed to cement and had
- the same chance (risk) to become sensitized.
- the different outcome (sensitization to Cr) was probably due to different susceptibility (identified as a GST polymorphism

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

2. Factors interfering with inflammatory pocesses	
Reactive oxygen species (ROS)	Manganese superoxide dismutase
Metabolism of in (neuro)peptides	scavenges potentially toxic superoxide radicals. No association. Brans R, et al 2005

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

2. Factors interfering with inflammatory pocesses	
Reactive oxygen species (ROS)	Manganese superoxide dismutase
Metabolism of inflammatory (neuro)peptides	Angiotensin Converting Enzyme

cleaves substance P, beta-endorphins and other peptides

modulate Langerhans cells and T-lymphocyte functions.

Risk increased in the variant (I/I) with low levels of ACE (= less inactivation)

Nacak M, et al. 2007;

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

3. Immunological factors (with impact on)	
antigen processing migration and maturation of APC presentation of the allergen (MHC), chemotaxis of lymphocytes. T-cell subpopulations (activating or regulating)	Various cytokines: TNF, IL1β, IL1β RA, IL4, IL6, IL10, IL16

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

3. Immunological factors (with impact on)	
	Various cytokines: TNF,

in polysensitized !

TNF –308 G [illegible] A (*G/A and *A/A comb) polymorphism more frequent in ACD (para- group and Chromate)

Westphal GA, 2003, Wang BJ, et al *2007;* Blömeke B et al 2009

No association (parthenium dermatitis)

Khatri R et al *2011*

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

3. Immunological factors (with impact on)

Various cytokines:

IL16

IL16-295 T→C polymorphism in ACD **(polysensitized !)** more frequent

Reich K. , Westphal et al *2003*

Functionally relevant steps in the pathogenesis of CA and candidate genes having been studied

3. Immunological factors (with impact on)

Various cytokines:

IL10,

T-cell responses to allergens are suppressed by L10

Two polymorphisms (*IL10 -1082 G→A and IL10 - 819 C→T)*

associated with a decreased IL10 expression and

a predisposition to dermatitis

(Kathri R et al 2011

Genetic variation in ACD

1. **‘candidate gene approach’**

„Breaking News“

Preliminary results from an ongoing study of the IVDK in collaboration with the IPA (Institute for Prevention and Occupational Medicine), Bochum/Germany

Genetic variation in ACD

candidate gene approach

Ongoing study IVDK/ IPA

Database total:

n=613

Minus:
- leg dermatitis
- cross reactions
- not identified

Total corrected:

n=542

- 345 Controls (Bood donors)
- 170 patients zero sensitization
- 372 Sensitized ,
  - **133 Mono/Oligo (1 and 2 Sensitization)**
  - **239 Poly (3 and more)**

Genetic variation in ACD

Ongoing study IVDK/ IPA

One outstanding result: ***CXCL11 G→A*** in polysensitized

Lokus	Kontrollen (N=345)		Mono- (N=115)		Poly-Sensibilisierte (N=173)			Alle Sensibilisierten (N=288)		
CXCL11(rs6817952)	N	(%)	N	(%)	N	(%)	p	N	(%)	p
GG	249	(72,2)	88	(76,5)	117	(68,8)		205	(71,2)	
GA	94	(27,2)	24	(20,9)	47	(26,2)		71	(24,7)	
AA	**2**	**(0,6)**	**3**	**(2,6)**	**9**	**(5,2)**	**0,0012**	**12**	**(4,2)**	**0,0024**
G	592	(85,8)	200	(85,9)	281	(81,2)		481	(83,5)	
A	98	(14,2)	29	(14,1)	65	(18,8)		95	(16,5)	

CXCL11 (interferon-inducible T-cell alpha chemoatractant)
a CXCR3 ligand expressed on - Th1 cells and on
- innate lymphocytes (e.g. NKT)

→ Infiltrate into inflamed tissues

Genetic variation in ACD

Ongoing study IVDK/ IPA

One outstanding result: ***CXCL11 G→A*** in polysensitized

Lokus	Kontrollen (N=345)		Mono- (N=115)		Poly-Sensibilisierte (N=173)			Alle Sensibilisierten (N=288)		
CXCL11(rs6817952)	N	(%)	N	(%)	N	(%)	p	N	(%)	p
GG	249	(72,2)	88	(76,5)	117	(68,8)		205	(71,2)	
GA	94	(27,2)	24	(20,9)	47	(26,2)		71	(24,7)	
AA	**2**	**(0,6)**	**3**	**(2,6)**	**9**	**(5,2)**	**0,0012**	**12**	**(4,2)**	**0,0024**
G	592	(85,8)	200	(85,9)	281	(81,2)		481	(83,5)	
A	98	(14,2)	29	(14,1)	65	(18,8)		95	(16,5)	

In genome expression analysis of ACD lesions (compared to AD and psoriasis) CXCL 11 (among others*) was exclusively upregulated

Quaranta M et al Sci Transl.Med 6, 244ra (2014)

* IL-1ß, AIM2, CXCL9, CXCL10

Genetic variation in ACD

Ongoing study IVDK/ IPA

Further (significant) polymorphisms:

Will probably be lost after correction

IL1B-31,

IL16-295, *IL16* P343S,

IL18-607, *IL18–137* → ***CXCL11 G→A***

TLR4 (D299G)

MDR1 3435

Multidrug Resistance Protein 1
(P-Glykoprotein /
ABC-Transporter)

NFκB-94 ins/ins

No associations:

TNF !

IL12RB1, *IL23R*,
MIF,
CTSB,
TGFB1,

FLG,
NAT2.

Genetic variation in ACD

Ongoing study IVDK/ IPA

IL18*-607, *IL18–137 ⟶ ***CXCL11 G→A***

IL18 Serum levels are increased in patients with ACD

(Gangemi et al J Dermaol Sci 2003; 33:187)

IL18 promotes allergen-induced migration of LCs

(Antonopoulos et al J Leukoc Biol 2008; 83:361)

IL-18 enhances IFN-γ induced production of…CXCL11 in keratinocytes

(Kanda N et al Eur J Immunol 2007; 37:338)

IL-18 (and IL-1ß) induced via inflammasome activation

(Watanabe et al J Invest Dermatol 2007;127: 1956)

Genetic variation in ACD

Only one Genome-wide association study (**GWAS**) has been done

A Genome-Wide Association Study in Koreans Identifies Susceptibility Loci for Allergic Nickel Dermatitis

Dae Suk Kim[a] Dong Hyun Kim[b] Hemin Lee[a] Hyunjoong Jee[a] Young Lee[c]
Min-youl Chang[d] Taek-jong Kwak[d] Chul-Hong Kim[e] Young-Ah Shin[f]
Jeung-Hoon Lee[c] Tae-jin Yoon[g] Min-Geol Lee[a]

Int Arch Allergy Immunol **2013**; 162:184

24 Ni + and 52 Ni - were genotyped

Using Axiom Genome-Wide Assay Chip Plate ® (Affymetrix, Santa Clara)

Genetic variation in ACD

Genome-wide association study (**GWAS**) (Kim et al 2013)

No SNPs with a significant association (**p value <1 x 10^{-7}**) were detected

Two novel SNPs were found:

NTN4 (*netrin4*) (p3.7 x 10^{-6}) (chromosome 12q22)

PELI1 (*Pellino homolog 1*) (7.7 x 10^{-5}) (chromosome 2p.13.3)

PELI1 in **Ni ++** : 7.1 x 10^{-6} **!**

Genetic variation in ACD

Genome-wide association study (**GWAS**) (Kim et al 2013)

NTN4 (*netrin4*) (p3.7 x 10^{-6})

Netrin-4: extracellular matrix molecule with homology to laminin amino-terminal domains

Biological relevance to Nickel dermatitis ??

Genetic variation in ACD

Genome-wide association study (**GWAS**) (Kim et al 2013)

PELI1 (*Pellino homolog 1*) (**p value: 7.7 x 10^{-5}**)

Not small enough to confirm an association with Ni allergy

Pellino-1: **-ubiquitin ligase** (attaches ubiquitin to a lysine on target proteins)

- involved in TLR/IL-1R (TIR) signalling.
- catalyzes polyubiquitylation of e.g. IL1 receptor associated kinase (IRAK) molecules and thereby regulates
- activation of NF-κB (and other transcription factors) and MAPK (which in turn promote gene profiles tailored towards efficient removal of the invading microbe (activation of an IL1-/ IL18 pathway))

„a crucial element in the regulation of innate immune signaling“

Genetics of allergic contact dermatitis

Summary I

1. Genetics/ Polymorphisms may play a role in

- Sensitization to moderate/weak allergens *(Potency)*
- In lower exposure conditions *(Dose)*
- In combination with further risk factors

Potent allergens or high dose (e.g. through „intense“ exposure) may overule genetic presdispositions

Genetics of allergic contact dermatitis

Summary II

2. Polymorphic genes of

- Structural proteins (Filaggrin)
- Xenobiotic metabolizing enzymes (NAT, GST)
- Factors interfering with inflammatory processes (ACE)
- Polymorphisms of relevant cytokines (e.g. *TNF , IL-16*) and chemokines (*CXCL11*)

may play a role

Genetics of allergic contact dermatitis

Summary III

3. Polysensitized individuals

= *phenotypically* high degree of sensitization

appear to represent a

genetically ‚high-risk' group

(*TNF -308 (?), IL16-295, IL18-607, CXCL11, NF-kB*)

IV. Perspectives

The Future

IV. Perspectives

1. **Candidate gene approach**

2. **Genome-wide association studies** (**GWAS**)

3. A combination of both:
   Genomic profiling in lesions identifies common and allergen specific molecular responses.

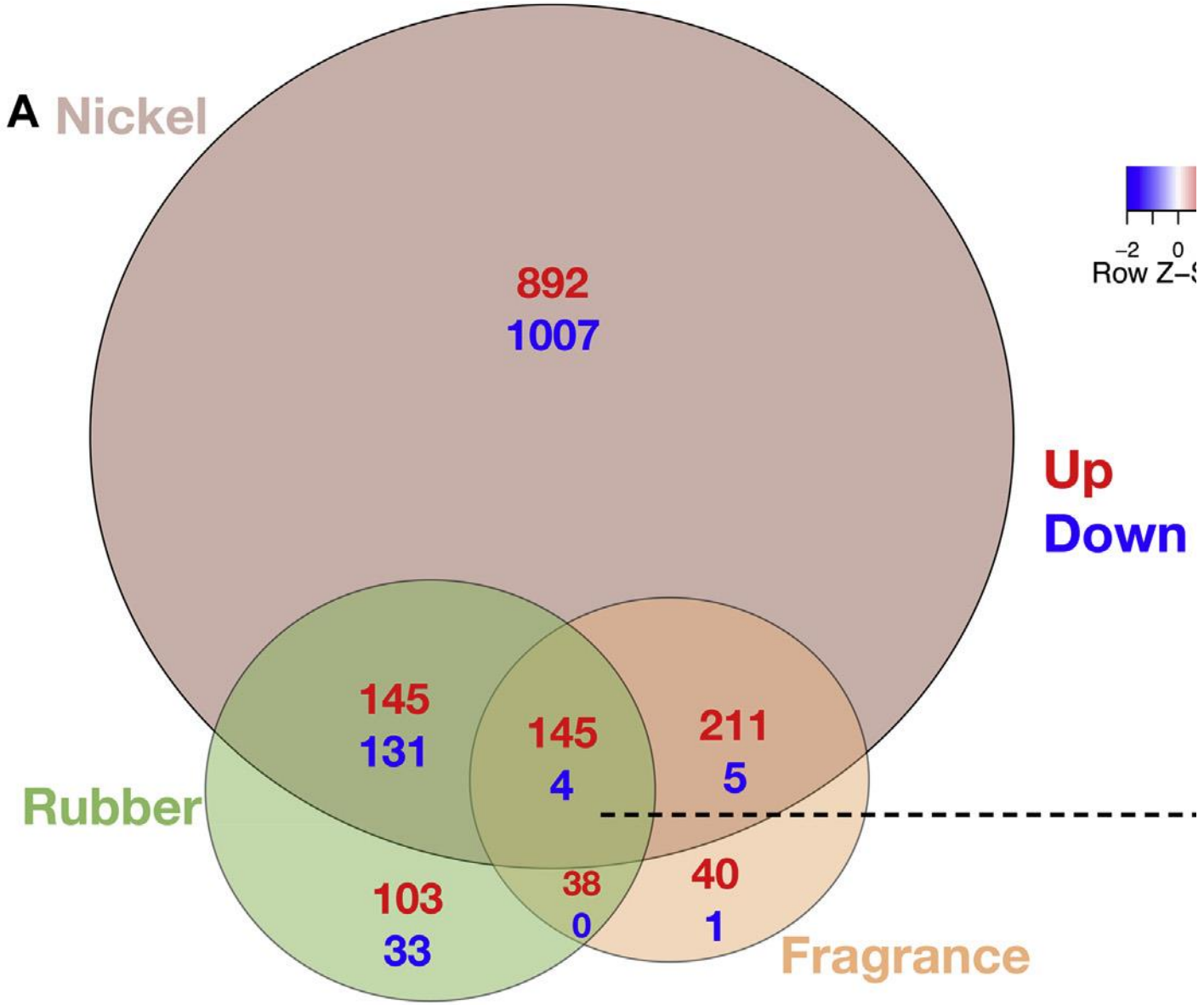
   They may (as candidate genes) be subject to studies of genetic variation

IV. Perspectives

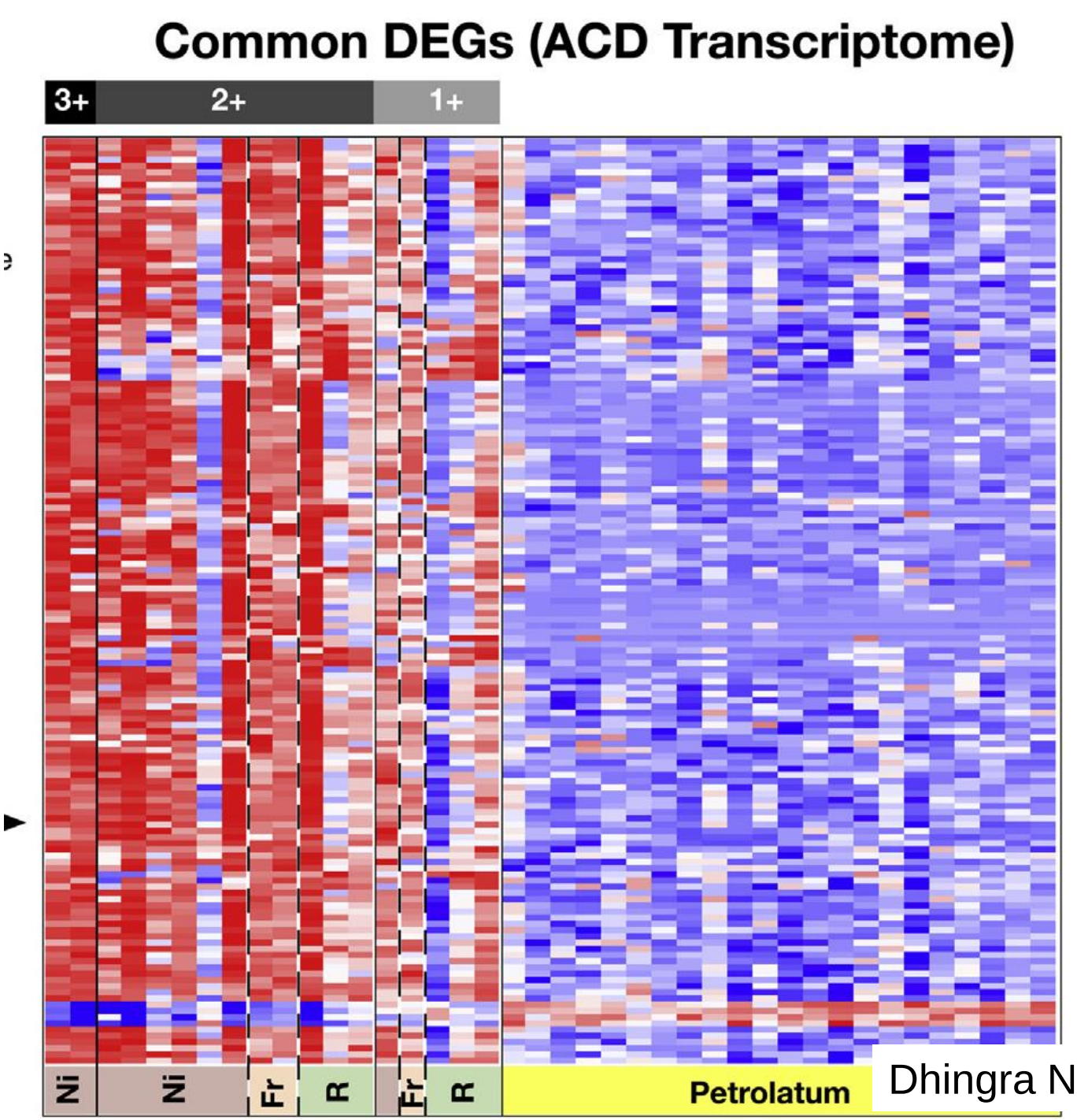
Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response

Dhingra N et al JACI 2014

Differentially expressed genes



Dhingra N et al JACI 2014



Dhingra N et al JACI 2014

IV. Perspectives

Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response

149 genes were differentially expressed in all lesions induced by Nickel, rubber, and fragrances.

Nickel induced innate immunity, Th1/ Th17 and Th22 components

Fragrances (and rubber) demonstrated a strong Th2 bias and a smaller Th1/Th17 contribution

Dhingra N et al JACI 2014

The future

Broadening the focus on pathology

Again back to candidate genes from a different perspective

The future: Broadening the focus on pathology

Background:

One genomic interval may be associated *with two or more* diseases. They may share

Clinical symptoms,

Pathogenesis,

Genetics and

Epidemiology

Ichthyosis vulgaris, AD, ICD and filaggrin mutations

The future: Broadening the focus on pathology

ACD may share e.g. symptoms, pathogenesis and epidemiology…

ACD was found to be associated with other diseases (phenotypes):

- Irritant contact dermatitis

- Leg (stasis) dermatitis

Respiratory symptoms ?

The future: Broadening the focus on pathology

Result of an epidemiological study in Denmark:

Contact sensitization to nickel (and other unrelated, not airborne) allergens) was associated with an **increased risk of respiratory symptoms**

after exposure to various airborne chemicals (laser printer, drying paint, car exhaust, newspaper)

Elberling J, et al Airborne chemicals cause respiratory symptoms in individuals with contact allergy. Contact Dermatitis 2005; 52: 65-72

The future: Broadening the focus on pathology

AND FURTHER:

The risk of respiratory symptoms increased with the number of positive patch tests
(polysensitization)

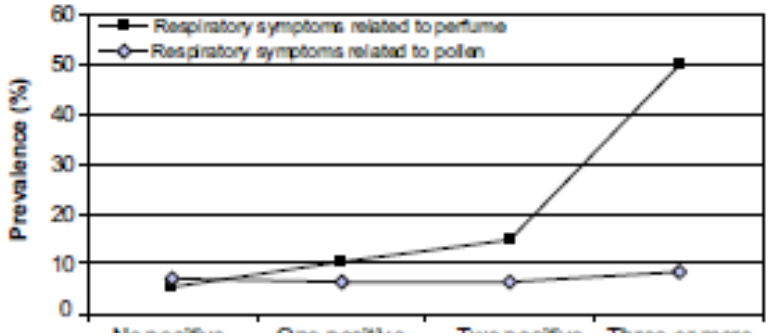
Elberling J, et al Airborne chemicals cause respiratory symptoms in individuals with contact allergy. Contact Dermatitis 2005; 52: 65-72

The future: Broadening the focus on pathology

Prevalence of perfume-related respiratory symptoms and ACD

J. Elberling et al. / Int. J. Hyg. Environ. Health 212 (2009) 670–678

Prevalence



0 1 2 =/> 3 positive patch tests

The risk increased with the number of positive patch tests **(polysensitization)**

Elberling J, et al A twin study of **perfume-related respiratory symptoms** Int J Hyg Environ Health 2009; 212: 670

The future: Broadening the focus on pathology

Relation between respiratory symptoms and ACD:

Respiratory symptomy associated with CA (OR 1.54 (1.10 – 2.17)

(and also with hand eczema, atopic dermatitis and asthma) (Log. Regr)

The significant associations are **not** attributable to shared genetic or shared environmental/ familial factors (except for AD)

Elberling J, et al A twin study of perfume-related respiratory symptoms Int J Hyg Environ Health 2009; 212: 670

The future: Broadening the focus on pathology

A hypothesis:

Polysensitization may be regarded as a phenotype of increased susceptibility to inflammatory diseases/states

Increased susceptibility to inflammatory diseases/states in general might be a general trait (a genetically driven characteristic)

Elberling et al (2009) suggested (also) that an „intrinsic environment related to tissue inflammation increases the sensitivity to inhaled perfume chemicals“

The future: Broadening the focus on pathology

Associations between

asthma and inflammatory bowel disease

Bjermer L. Time for a paradigm shift in asthma treatment:
from relieving bronchospasm to controlling systemic inflammation.
J Allergy Clin Immunol 2007; 120: 1269-75

The future: Broadening the focus on pathology

- psoriasis and systemic inflammatory diseases

Davidovici BB et al

Psoriasis and systemic inflammatory diseases:

potential mechanistic links between skin disease and co-morbid conditions.

J Invest Dermatol 2010; 30(7):1785-96

Associations between
psoriasis and cardiovascular diseases

Prodanovich S, et al. Arch Dermatol 2008; 144: 1518-9.

Federman DG, et al. Br J Dermatol 2009; 160: 1-7

The future: Broadening the focus on pathology

Thus, the genetics of CA is embedded in the larger context of the genetics of other diseases.

- The study of the genetics of ACD may contribute to reasearch in other diseases, and vice versa

- To find the *shared* molecular and genetic basis will be the challenge for the future

The future: Broadening the focus on pathology

"The textbooks of medicine need to rewritten to account for the **interconnectivity of the molecular basis** underlying distinct diseases"

Frazer KA, SS Murray, NJ Schork, EJ Topol.
Human genetic variation and its contribution to complex traits.
Nat Rev Genet 2009; 10: 241-51.

Greetings
from
Göttingen

...to be kissed by every
graduated student
who finishes a doctorate

„The most kissed girl in the world“