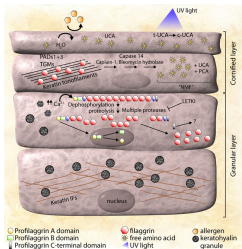


AD Genetics



Alan Irvine, Trinity College Dublin
ISAD Nottingham May, 2014

Allergy runs in families..

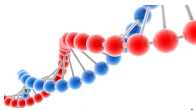


0.23 - 0.86



0.15 - 0.5

Edfors-Lubs M-L. Allergy in 7000 twin pairs. *Acta Allergologica* 1971;26:249-285.
Schultz Larsen FV, Holm NV. Atopic dermatitis in a population based twin series. Concordance rates and heritability estimation. *Acta Derm Venereol Suppl (Stockh)* 1985;114:159.
Larsen FS, Holm NV, Henningsen K. Atopic dermatitis. A genetic-epidemiologic study in a population based twin sample. *J Am Acad Dermatol* 1986;15:487-494.
Strachan DP, Wong HJ, Spector TD. Concordance and interrelationship of atopic diseases and marker of allergic sensitization among adult female twins. *J Allergy Clin Immunol* 2001;108:901-907.
van Beijsterveldt CE, Boomsma DI. Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. *Eur Respir J* 2007;29:516-521.



AD Genetics:
Possible benefits?

- Greater understanding of pathogenesis
- Prevent disease?
- Molecular phenotyping
- Targeted and novel therapies
- Prediction of treatment response

Genetics of complex disease

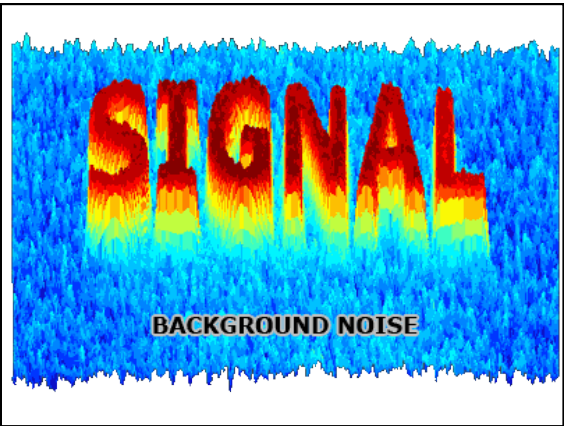
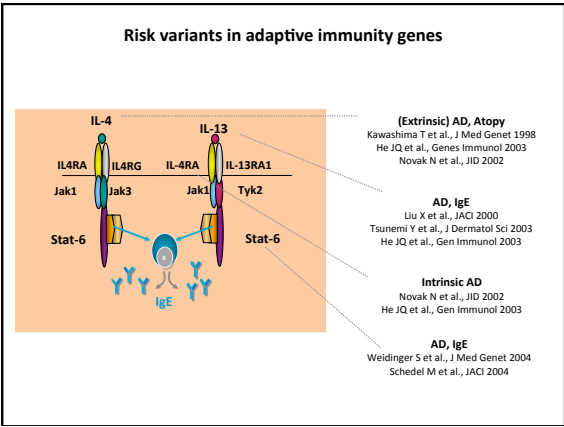
LETTER

doi:10.1038/nature12873

Genetics of rheumatoid arthritis contributes to biology and drug discovery

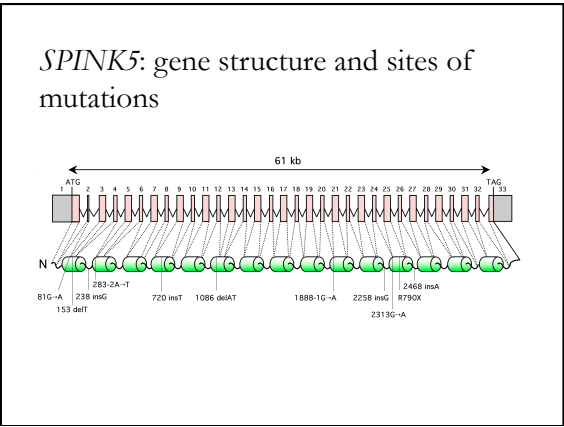
A list of authors and their affiliations appears at the end of the paper

Table 1. Novel rheumatoid arthritis risk loci identified by trans-ethnic GWAS meta-analysis in ~200,000 subjects											
SNP	Chr	Genes	ALF2		P	Trans-ethnic		European		Asian	P
			10	10		10	10	10	10		
rs227163	1	ITPR3	C/T	1.04 (-0.0215)	3.9 × 10 ⁻⁸	1.00 (-0.0713)	9.3 × 10 ⁻⁸	1.01 (-0.1667)	3.1 × 10 ⁻⁸		
rs105352	1	MTF	C/T	1.01 (-0.0815)	6.9 × 10 ⁻⁸	1.02 (-0.0815)	6.9 × 10 ⁻⁸	1.01 (-0.0815)	6.9 × 10 ⁻⁸		
rs105325	1	LOC100506023	C/T	1.12 (-0.0815)	3.9 × 10 ⁻⁸	1.12 (-0.0815)	3.9 × 10 ⁻⁸	1.11 (-0.0815)	3.9 × 10 ⁻⁸		
rs10157958	2	LBH	A/G	1.08 (-0.0615)	1.1 × 10 ⁻⁸	1.09 (-0.0615)	4.2 × 10 ⁻⁸	1.07 (-0.0215)	6.4 × 10 ⁻⁸		
rs10157958	2	LBH	A/G	1.08 (-0.0615)	1.1 × 10 ⁻⁸	1.09 (-0.0615)	4.2 × 10 ⁻⁸	1.07 (-0.0215)	6.4 × 10 ⁻⁸		
rs1615284	2	CFAR-CA302	G/C	1.15 (-0.1015)	1.8 × 10 ⁻⁸	1.15 (-0.1015)	2.5 × 10 ⁻⁸	1.14 (-0.1015)	2.5 × 10 ⁻⁸		
rs1615284	2	CFAR-CA302	G/C	1.15 (-0.1015)	1.8 × 10 ⁻⁸	1.15 (-0.1015)	2.5 × 10 ⁻⁸	1.14 (-0.1015)	2.5 × 10 ⁻⁸		
rs380624	3	EDMS	G/A	1.08 (-0.0515)	8.6 × 10 ⁻⁸	1.08 (-0.0515)	2.8 × 10 ⁻⁸	1.06 (-0.0914)	1.4 × 10 ⁻⁸		
rs380624	3	EDMS	G/A	1.08 (-0.0515)	8.6 × 10 ⁻⁸	1.08 (-0.0515)	2.8 × 10 ⁻⁸	1.06 (-0.0914)	1.4 × 10 ⁻⁸		
rs13142500	4	CLNK	C/T	1.01 (-0.0713)	3.0 × 10 ⁻⁸	1.01 (-0.0615)	2.4 × 10 ⁻⁸	1.01 (-0.0615)	2.8 × 10 ⁻⁸		
rs13142500	4	CLNK	C/T	1.01 (-0.0713)	3.0 × 10 ⁻⁸	1.01 (-0.0615)	2.4 × 10 ⁻⁸	1.01 (-0.0615)	2.8 × 10 ⁻⁸		
rs978815	6	IRF4	C/G	1.09 (-0.0615)	1.7 × 10 ⁻⁸	1.09 (-0.0515)	1.4 × 10 ⁻⁸	1.01 (-0.0415)	2.3 × 10 ⁻⁸		
rs2234067	6	ETV7	C/T	1.15 (-0.1015)	1.6 × 10 ⁻⁸	1.14 (-0.0915)	1.1 × 10 ⁻⁸	1.22 (-0.1614)	7.0 × 10 ⁻⁸		
rs2234067	6	ETV7	C/T	1.15 (-0.1015)	1.6 × 10 ⁻⁸	1.14 (-0.0915)	1.1 × 10 ⁻⁸	1.22 (-0.1614)	7.0 × 10 ⁻⁸		
rs7625040	7	AZT1	T/C	1.10 (-0.0714)	3.7 × 10 ⁻⁸	1.11 (-0.0714)	2.6 × 10 ⁻⁸	1.02 (-0.0415)	8.5 × 10 ⁻⁸		
rs7625040	7	AZT1	T/C	1.10 (-0.0714)	3.7 × 10 ⁻⁸	1.11 (-0.0714)	2.6 × 10 ⁻⁸	1.02 (-0.0415)	8.5 × 10 ⁻⁸		
rs98871	8	TPD52	T/C	1.08 (-0.0515)	1.9 × 10 ⁻⁸	1.09 (-0.0515)	6.6 × 10 ⁻⁸	1.02 (-0.0615)	4.9 × 10 ⁻⁸		
rs98871	8	TPD52	T/C	1.08 (-0.0515)	1.9 × 10 ⁻⁸	1.09 (-0.0515)	6.6 × 10 ⁻⁸	1.02 (-0.0615)	4.9 × 10 ⁻⁸		
rs1516971	8	PTT1	T/C	1.15 (-0.1015)	1.3 × 10 ⁻⁸	1.16 (-0.1112)	1.2 × 10 ⁻⁸	1.03 (-0.0615)	2.6 × 10 ⁻⁸		
rs1516971	8	PTT1	T/C	1.15 (-0.1015)	1.3 × 10 ⁻⁸	1.16 (-0.1112)	1.2 × 10 ⁻⁸	1.03 (-0.0615)	2.6 × 10 ⁻⁸		
rs973108	10	DNF48	T/C	1.08 (-0.0515)	1.3 × 10 ⁻⁸	1.07 (-0.0415)	6.1 × 10 ⁻⁸	1.04 (-0.0414)	4.4 × 10 ⁻⁸		
rs973108	10	DNF48	T/C	1.08 (-0.0515)	1.3 × 10 ⁻⁸	1.07 (-0.0415)	6.1 × 10 ⁻⁸	1.04 (-0.0414)	4.4 × 10 ⁻⁸		
rs1061662	10	WDR4	A/G	1.07 (-0.0515)	2.8 × 10 ⁻⁸	1.06 (-0.0315)	2.6 × 10 ⁻⁸	1.01 (-0.0514)	8.9 × 10 ⁻⁸		
rs1061662	10	WDR4	A/G	1.07 (-0.0515)	2.8 × 10 ⁻⁸	1.06 (-0.0315)	2.6 × 10 ⁻⁸	1.01 (-0.0514)	8.9 × 10 ⁻⁸		
rs1061662	11	FAO51-FAO52-FAO53	C/T	1.12 (-0.0714)	1.8 × 10 ⁻⁸	1.12 (-0.0714)	1.8 × 10 ⁻⁸	1.11 (-0.0714)	1.8 × 10 ⁻⁸		
rs1061662	11	FAO51-FAO52-FAO53	C/T	1.12 (-0.0714)	1.8 × 10 ⁻⁸	1.12 (-0.0714)	1.8 × 10 ⁻⁸	1.11 (-0.0714)	1.8 × 10 ⁻⁸		
chr1:107,000,139	11	ATM	A/G	1.21 (-0.1315)	1.4 × 10 ⁻⁸	1.21 (-0.1315)	1.1 × 10 ⁻⁸	1.14 (-0.0812)	4.1 × 10 ⁻⁸		
chr1:107,000,139	11	ATM	A/G	1.21 (-0.1315)	1.4 × 10 ⁻⁸	1.21 (-0.1315)	1.1 × 10 ⁻⁸	1.14 (-0.0812)	4.1 × 10 ⁻⁸		
rs773125	12	CDK2	A/G	1.09 (-0.0615)	1.1 × 10 ⁻⁸	1.09 (-0.0615)	2.1 × 10 ⁻⁸	1.14 (-0.0417)	1.1 × 10 ⁻⁸		
rs773125	12	CDK2	A/G	1.09 (-0.0615)	1.1 × 10 ⁻⁸	1.09 (-0.0615)	2.1 × 10 ⁻⁸	1.14 (-0.0417)	1.1 × 10 ⁻⁸		
rs9036136	13	COG6	C/T	1.10 (-0.0713)	1.6 × 10 ⁻⁸	1.11 (-0.0714)	2.8 × 10 ⁻⁸	1.08 (-0.0214)	1.0 × 10 ⁻⁸		
rs9036136	13	COG6	C/T	1.10 (-0.0713)	1.6 × 10 ⁻⁸	1.11 (-0.0714)	2.8 × 10 ⁻⁸	1.08 (-0.0214)	1.0 × 10 ⁻⁸		
rs373872	14	PRKCH	A/G	1.14 (-0.0915)	2.2 × 10 ⁻⁸	1.17 (-0.0913)	1.4 × 10 ⁻⁸	1.14 (-0.0915)	4.4 × 10 ⁻⁸		
rs373872	14	PRKCH	A/G	1.14 (-0.0915)	2.2 × 10 ⁻⁸	1.17 (-0.0913)	1.4 × 10 ⁻⁸	1.14 (-0.0915)	4.4 × 10 ⁻⁸		
rs178030	16	TNRC1C1	T/G	1.07 (-0.0515)	4.1 × 10 ⁻⁸	1.09 (-0.0513)	8.7 × 10 ⁻⁸	1.03 (-0.0815)	2.5 × 10 ⁻⁸		
rs178030	16	TNRC1C1	T/G	1.07 (-0.0515)	4.1 × 10 ⁻⁸	1.09 (-0.0513)	8.7 × 10 ⁻⁸	1.03 (-0.0815)	2.5 × 10 ⁻⁸		
rs178030	17	MDI1	T/G	1.09 (-0.0615)	1.9 × 10 ⁻⁸	1.09 (-0.0513)	1.3 × 10 ⁻⁸	1.03 (-0.0414)	3.2 × 10 ⁻⁸		
rs178030	17	MDI1	T/G	1.09 (-0.0615)	1.9 × 10 ⁻⁸	1.09 (-0.0513)	1.3 × 10 ⁻⁸	1.03 (-0.0414)	3.2 × 10 ⁻⁸		
chr1:97,107,1941	19	ILF3	C/T	1.47 (-0.1617)	8.6 × 10 ⁻⁸	1.47 (-0.1617)	8.8 × 10 ⁻⁸	1.03 (-0.0815)	2.9 × 10 ⁻⁸		
chr1:97,107,1941	19	ILF3	C/T	1.47 (-0.1617)	8.6 × 10 ⁻⁸	1.47 (-0.1617)	8.8 × 10 ⁻⁸	1.03 (-0.0815)	2.9 × 10 ⁻⁸		
rs1803932	21	UBASH3A	A/C	1.11 (-0.0814)	7.2 × 10 ⁻⁸	1.11 (-0.0715)	9.8 × 10 ⁻⁸	1.06 (-0.0215)	8.9 × 10 ⁻⁸		
rs1803932	21	UBASH3A	A/C	1.11 (-0.0814)	7.2 × 10 ⁻⁸	1.11 (-0.0715)	9.8 × 10 ⁻⁸	1.06 (-0.0215)	8.9 × 10 ⁻⁸		
rs11096637	22	UBXK1-UBXK2	T/G	1.08 (-0.0515)	2.1 × 10 ⁻⁸	1.01 (-0.0615)	2.0 × 10 ⁻⁸	1.06 (-0.0215)	8.9 × 10 ⁻⁸		
rs11096637	22	UBXK1-UBXK2	T/G	1.08 (-0.0515)	2.1 × 10 ⁻⁸	1.01 (-0.0615)	2.0 × 10 ⁻⁸	1.06 (-0.0215)	8.9 × 10 ⁻⁸		
chr7:7646456	X	POR1C1	A/C	1.11 (-0.0715)	35 × 10 ⁻⁸	1.16 (-0.0715)	4.6 × 10 ⁻⁸	1.11 (-0.0715)	36 × 10 ⁻⁸		

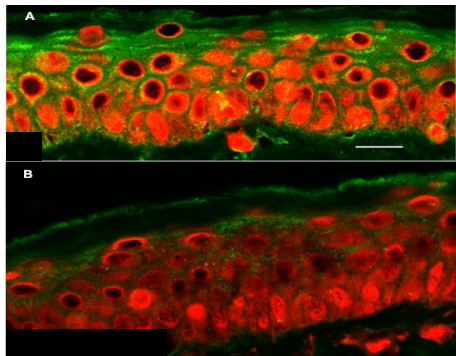


In established AD
the skin barrier is
very
dysfunctional

..both at
'affected' and
'unaffected' skin



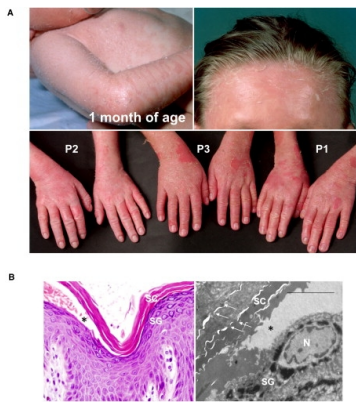
↑↑↑ Serine Protease Activity in NS



REPORT

Loss of Corneodesmosin Leads to Severe Skin Barrier Defect, Pruritus, and Atopy: Unraveling the Peeling Skin Disease

Vinzenz Oji,^{1,8} Kaija-Martina Eckl,^{2,3,8} Karin Aufenvenne,¹ Marc Nöthbus,² Tatjana Tarinski,¹ Katharina Ackermann,⁴ Natalia Seller,¹ Dieter Metz,¹ Gudrun Nürnberg,² Regina Fölster-Holst,⁵ Monika Schäfer-Korting,⁴ Ingrid Hausser,⁶ Heiko Traupe,¹ and Hans Christian Hennies^{2,7,*}

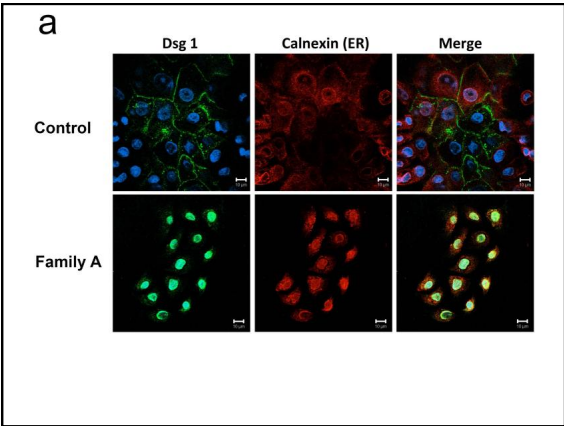


REPORT

Mutations in the Fatty Acid Transport Protein 4 Gene Cause the Ichthyosis Prematurity Syndrome

Joakim Klar,¹ Martina Schweiger,² Robert Zimmerman,² Rudolf Zechner,² Hao Li,³ Hans Törmä,³ Anders Vahlquist,³ Bakar Bouadjar,⁴ Niklas Dahl,^{1,*} and Judith Fischer⁵





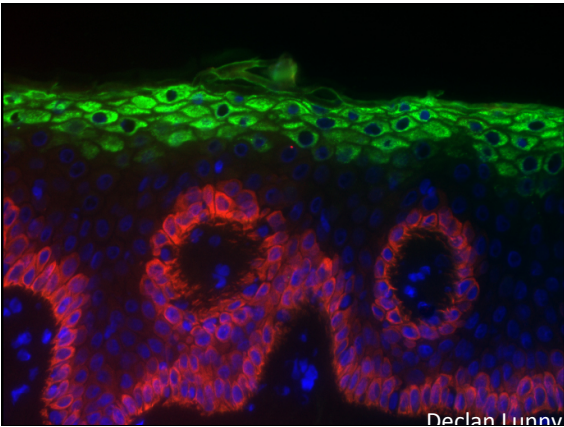
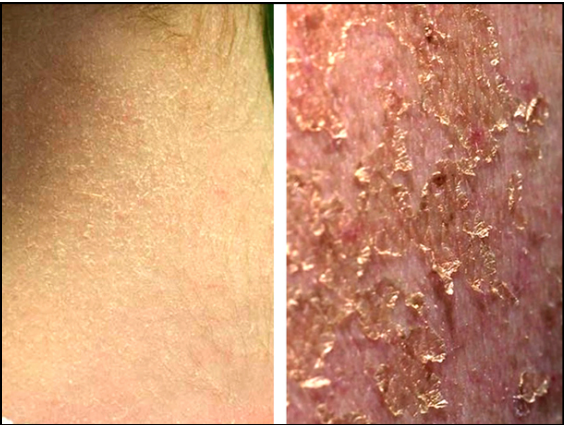
nature genetics

Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting

Liat Samuelov^{1,20}, Ofer Sarig^{1,20}, Robert M Harmon^{2,20}, Debora Rapaport³, Akemi Ishida-Yamamoto⁴, Ofer Isakov⁵, Jennifer L Koetsier⁶, Andrea Gat⁶, Ilan Goldberg¹, Reuven Bergman^{7,8}, Ronen Spiegel^{8,9}, Ori Eytan^{1,10}, Shamir Geller¹, Sarit Peleg^{8,11,12}, Noam Shomron¹, Christabelle S M Goh¹³, Neil J Wilson¹³, Frances J D Smith¹³, Elizabeth Pöhler¹³, Michael A Simpson¹⁴, W H Irwin McLean¹⁵, Alan D Irvine¹⁵⁻¹⁷, Mia Horowitz², John A McGrath¹⁸, Kathleen J Green¹⁹ & Eli Sprecher^{1,10}

Conclusions from Mendelian genetics:

Severe inherited epidermal barrier disruptions are sufficient to cause AD and systemic atopic manifestations



Filaggrin

From Ichthyosis Vulgaris...

...to Atopic Eczema and Asthma

nature genetics 38:337-342, March 2006

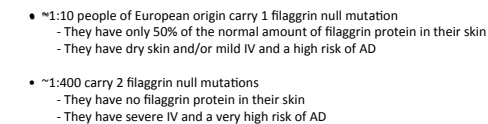
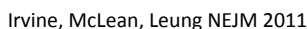
Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris

nature genetics 38:441-446, April 2006

Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis

nature genetics 39:650-654, April 2007

Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema



But what sets filaggrin apart is:

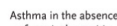
Common

Semi-dominant

Neither necessary nor sufficient to cause AD/
Systemic allergy



1.5



1.0

Asthma in the presence

3.3



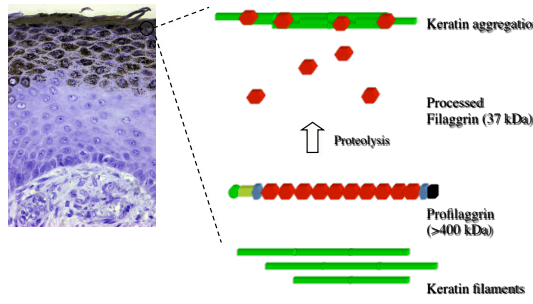
Peanut allergy

Odds Ratio is x 5.4,
x 3.3 corrected for AD

Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy

Sara J. Brown, MD,^{1,2,3,4} Yuka Asai, MD,^{5,6} Heather J. Cordell, DPhil,¹ Linda E. Campbell, MSc,⁴ Yiwei Zhao, MD, PhD,⁴ Haihui Liao, MD, PhD,⁴ Kate Northstone, PhD,⁴ John Henderson, MD,⁴ Reza Allizadehfar, MD,⁴ Moshe Ben-Shoshan, MD,^{1,1} Kenneth Morgan, PhD,¹ Graham Roberts, DM,¹ Laury J. N. Masthoff, MD,¹ Suzanne G. M. A. Pasmans, MD, PhD,¹ Peter C. van den Akker, MD,¹ Cisca Wijmenga, PhD,¹ Jonathan O.B. Hourihane, PhD,¹ Colin N. A. Palmer, PhD,¹ Gideon Lask, PhD,⁴ Ann Clarke, MD, MSc,^{1,6} Peter R. Hull, MD, PhD,¹ Alan D. Irvine, MD,^{1,2} and W. H. Irwin McLean, PhD, DSc⁴ ¹Dundee, Newcastle-upon-Tyne, Bristol, Southampton, and London, United Kingdom, ²Dublin and Cork, Ireland, ³Montreal, Quebec, and ⁴Saskatoon, Saskatchewan, Canada, and ⁵Utrecht and Groningen, The Netherlands

Filaggrin - filament aggregating protein



Keratin aggregation

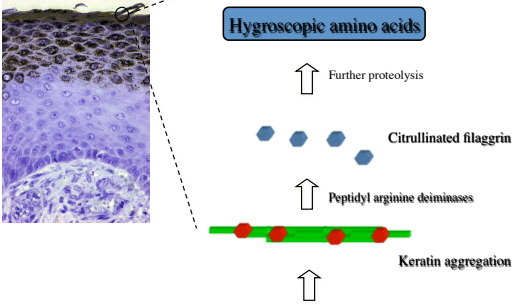
Processed Filaggrin (37 kDa)

Proteolysis

Profilaggrin (>400 kDa)

Keratin filaments

"Natural moisturizing factor"



Hygroscopic amino acids

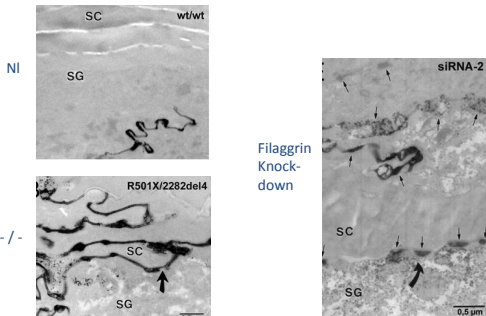
Further proteolysis

Citrullinated filaggrin

Peptidyl arginine deiminases

Keratin aggregation

Elias: Tracer Perfusion Reveals Extracellular Barrier Defect in IV



SC

SG

wt/wt

NI

R501X/2282del4

-/-

siRNA-2

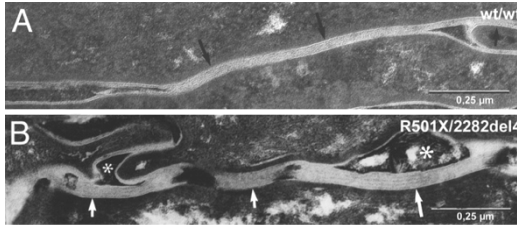
Filaggrin Knock-down

SC

SG

0.5 µm

Elias: Abnormal Lamellar Bilayers in IV Account for Barrier Defect



A

wt/wt

NI

0.25 µm

B

R501X/2282del4

-/-

0.25 µm

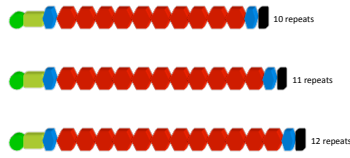
JOURNAL OF INVESTIGATIVE DERMATOLOGY

ORIGINAL ARTICLE

¹⁰Open

Intragenic Copy Number Variation within *Filaggrin* Contributes to the Risk of Atopic Dermatitis with a Dose-Dependent Effect

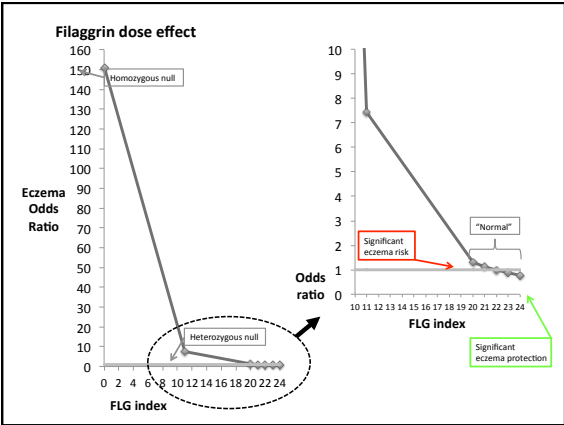
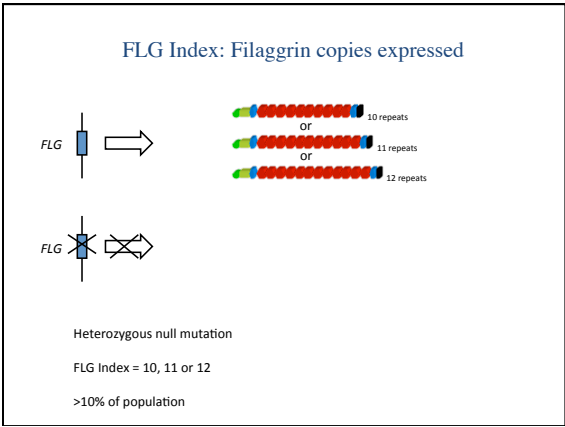
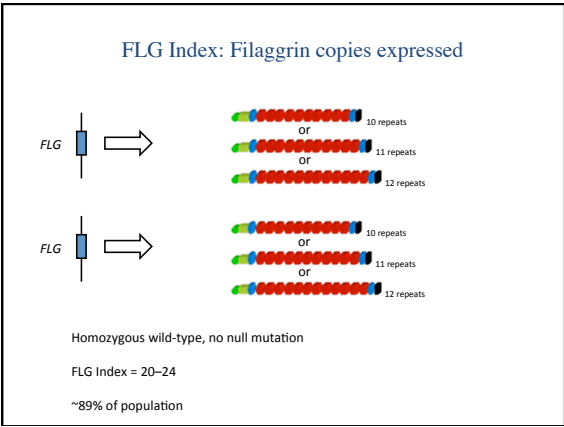
Sara J. Brown^{1,2,3,4}, Karin Kobotti¹, Aileen Sandilands¹, Linda E. Campbell¹, Elizabeth Pöhler¹, Sanja Kestic⁴, Heather J. Cordell¹, W.H. Irwin McLean¹ and Alan D. Irvine^{1,2}



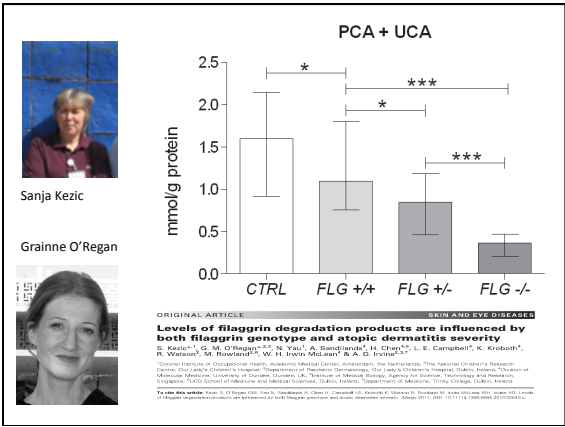
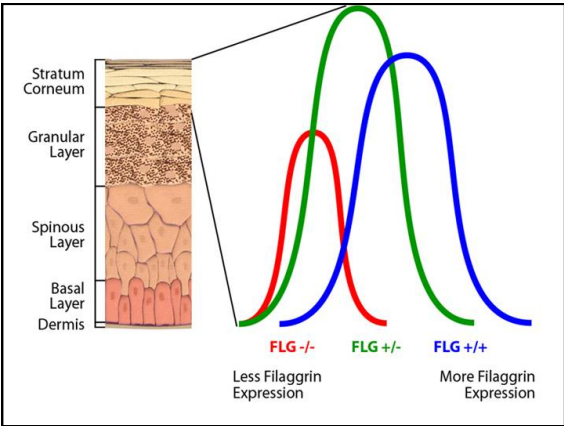
10 repeats

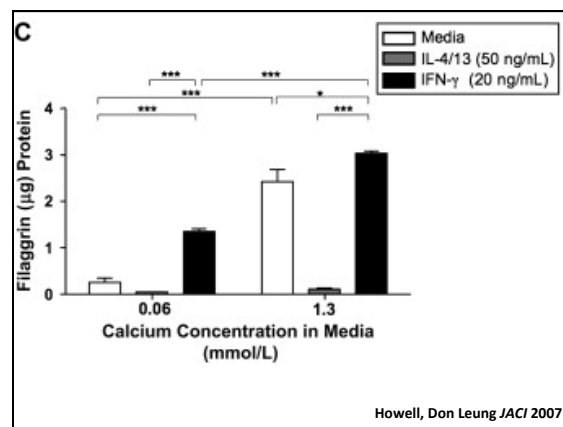
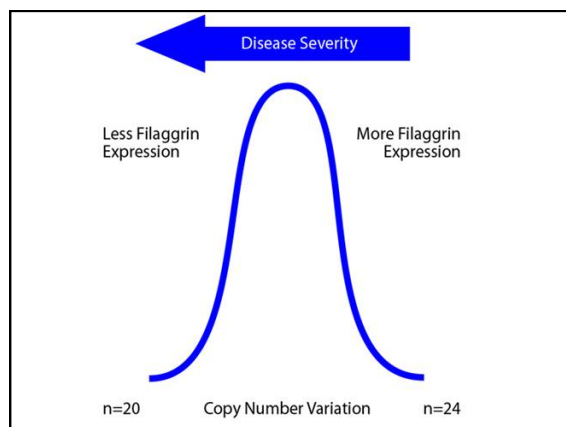
11 repeats

12 repeats



AD _{FLG}	Clinical Features	Biophysical Features
	Palmar Hyperlinearity More Persistent ↑Allergic Sensitization ↑Risk of Asthma ↑Severity ↑Eczema Herpeticum	Severe Decrease in Natural Moisturizing Factor (NMF) ↑pH ↑IL-1β
AD _{NON-FLG}	Clinical Features	Biophysical Features
	No Palmar Hyperlinearity Less Persistent Less Allergic Sensitization Lower Risk of Asthma	Mild Decrease in Natural Moisturizing Factor (NMF) pH Lower Compared to AD _{FLG} IL-1β Low Compared to AD _{FLG}





CLINICAL AND LABORATORY INVESTIGATIONS British Journal of Dermatology BJD

Interleukin-22 downregulates filaggrin expression and affects expression of profilaggrin processing enzymes

D. Gutowska-Owsiak, A.L. Schaupp, M. Salimi, S. Taylor* and G.S. Ogg

MRC Human Immunology Unit and *Computational Biology Research Group, University of Oxford, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, U.K.

Summary

Original Article

DOI:10.1111/j.1468-0425.2011.01412.x
www.blackwellpublishing.com/BJD

IL-17 downregulates filaggrin and affects keratinocyte expression of genes associated with cellular adhesion

Danuta Gutowska-Owsiak¹, Anna L. Schaupp², Maryam Salimi¹, Tharini A. Selvakumar¹, Tess McPherson¹, Stephen Taylor² and Graham S. Ogg¹

¹MRC Human Immunology Unit, University of Oxford, John Radcliffe Hospital, Oxford, UK; ²Translational Gastroenterology Unit, University of Oxford, John Radcliffe Hospital, Oxford, UK; ³Computational Biology Research Group, University of Oxford, John Radcliffe Hospital, Oxford, UK

Correspondence: Dr Danuta Gutowska-Owsiak, MRC Human Immunology Unit, University of Oxford, Weatherall Institute of Molecular Medicine, Oxford OX3 9DS, UK. Tel: +44(0)1865222334; Fax: +44 (0)1865222502; e-mail: danuta.gutowska-owsiak@ndm.ox.ac.uk

Population cohort analyses: penetrance of *FLG* null alleles is 38-42%

- That is to say approximately 60% of *FLG* null allele carriers do not develop atopic dermatitis
- What are the genetic and environmental modifiers?

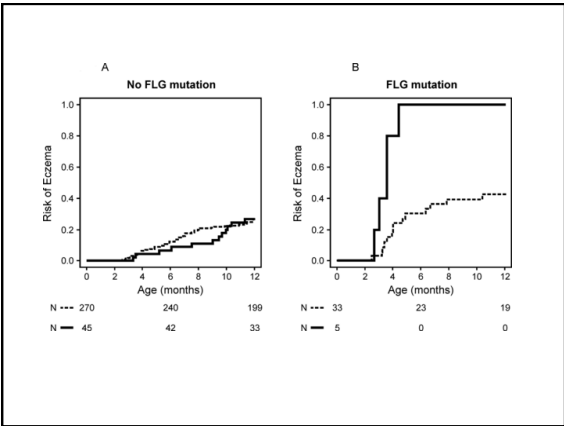
Environmental influences?

OPEN ACCESS Freely available online PLOS MEDICINE

Gene-Environment Interaction in the Onset of Eczema in Infancy: Filaggrin Loss-of-Function Mutations Enhanced by Neonatal Cat Exposure

Hans Bisgaard^{1*}, Angela Simpson², Colin N.A. Palmer³, Klaus Bonnelykke¹, Irwin McLean⁴, Somnath Mukhopadhyay⁵, Christian B. Pipper¹, Liselotte B. Halljaer¹, Brian Lipworth⁶, Jenny Hankinson⁷, Ashley Woodcock², Adnan Custovic²

PLOS Medicine June 2008



Environmental influences?

Atopic dermatitis and skin disease

Elder siblings enhance the effect of filaggrin mutations on childhood eczema: Results from the 2 birth cohort studies LISApus and GINplus

Claudia Cramer, MSc,^a Elke Link,^a Malika Horster, BSc,^a Sibylla Koletzko, MD,^b Carl-P. Bauer, MD,^{a,b} Dietrich Bardel, MD,^c Andrea von Berg, MD,^d Irina Lehmann, PhD,^e Olf Herbarth, PhD,^f Michael Borte, MD,^{g,h} Beate Schaaf, MD,^{g,h} Heidrun Behrendt, MD,ⁱ Chih-Mei Chen, PhD,^j Stefanie Sausenthaler, PhD,^j Thomas Illig, PhD,^k H.-Erich Wichmann, MD, PhD,^{l,m} Joachim Heinrich, PhD,^j and Ursula Krämer, PhD,^j for the LISApus Study Group and the GINplus Study Group ^aDüsseldorf, ^bMunich, ^cWesel, ^dLeipzig, and ^eBad Honnef, Germany

Elder siblings and daycare exposures increase AD risk in *FLG* mutation carriers



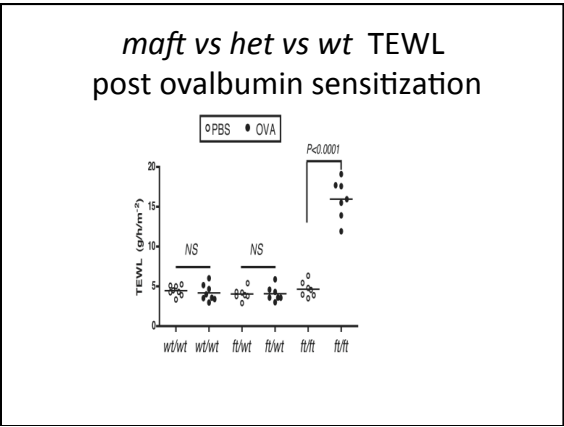
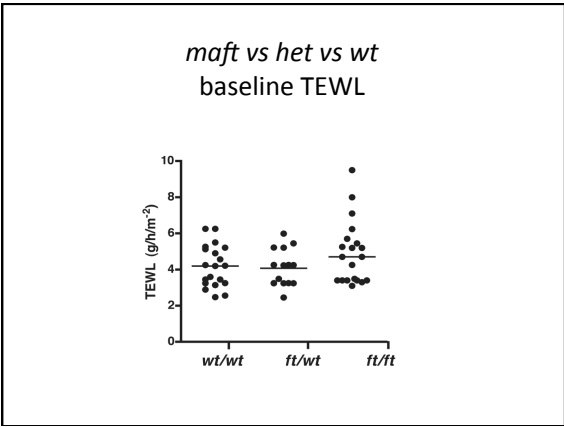
Filaggrin-deficient mice:

nature Genetics 41:602-608 (2009)

A homozygous frameshift mutation in the mouse *Flg* gene facilitates enhanced percutaneous allergen priming

Padraic G Fallon¹, Takashi Suzuki^{2,3}, Alice Sandford⁴, Linda E Campbell⁵, Sean P Saunders¹, Niamh M Mangan¹, John J Collins¹, Hiroshi Kawasaki⁶, Aiko Shinkuma^{2,3}, Aikawa Kaku⁶, John P Sundberg⁷, Richard B Probst^{8,9}, Philip Fleckman¹⁰, Nobuyoshi Shimizu⁶, Jun Kadoh¹¹, Alan D Irvine¹², Masayuki Amagai¹³ & W H Irwin McLean¹⁴

Padraic Fallon, Masa Amagai



Gene-environment interaction in Flg-deficient mice



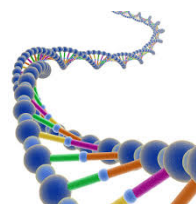
Caoimhe Fahy, Padraic Fallon



Mouse models

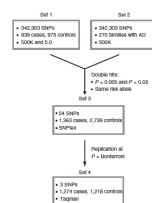
- Importance of immune activation on exacerbating pre-existing skin barrier defects
- Influence of immune background
- Show influence of environment

GWAS Studies

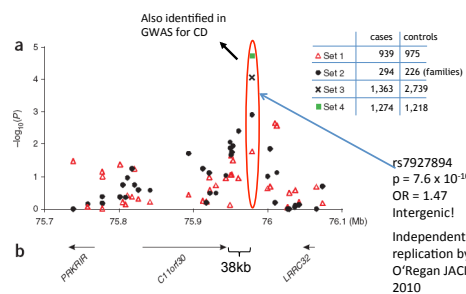


A common variant on chromosome 11q13 is associated with atopic dermatitis

Jorge Esparza-Gordillo^{1,2,3,4}, Stephan Weidinger^{1,4,5}, Regina Fölster-Holst¹, Anja Bauerfeind¹, Franz Rauschendorf¹, Giannino Paton¹, Klaus Rohde¹, Ingo Marenholz^{1,2}, Florian Schulz^{1,2}, Tamara Kerschke^{1,2}, Norbert Hübner¹, Ulrich Wahn¹, Stefan Schreiber^{6,7}, Andre Franke⁸, Rainer Vogler⁷, Simon Heuß^{1,2}, Hansjörg Baresch⁹, Natalija Novak¹⁰, Elke Rodriguez^{3,4}, Thomas Illig^{1,1}, Min-Ae Lee-Kirsch^{1,2}, Andrei Cechanowicz^{1,2}, Michael Kurck¹⁴, Tereza Piskackova¹⁵, Milan Mack¹⁵, Young-Ae Lee^{1,2} & Andreas Ruefher⁶

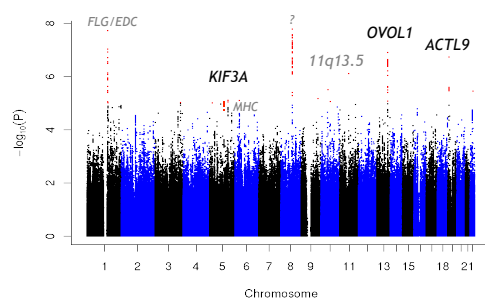


First European genome-wide association study: 11q13.5



Esparza and Weidinger Nat Genet 2009

Second European GWAS: KIF3A, OVOL1, ACTL9



Patemoster L et al. Nat Genet 2011



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Irwin McLean



University of Dundee