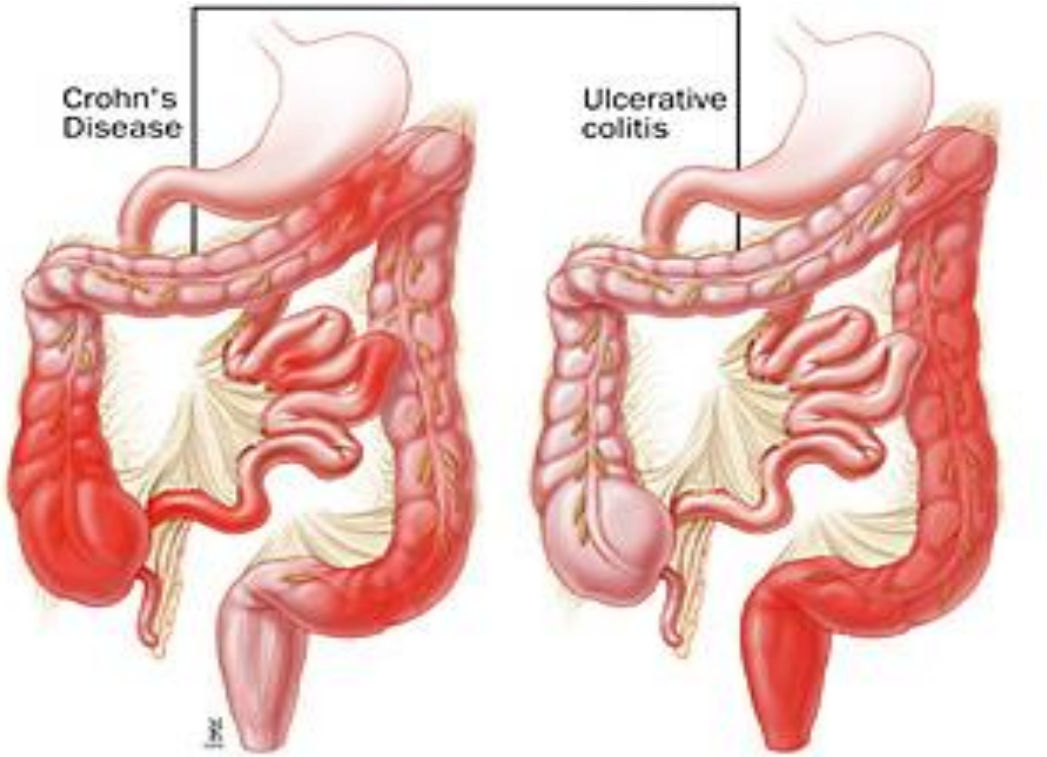
Genetik vid inflammatorisk tarmsjukdom

Elisabeth Norén

Biomedicinsk analytiker, doktorand, Jönköping

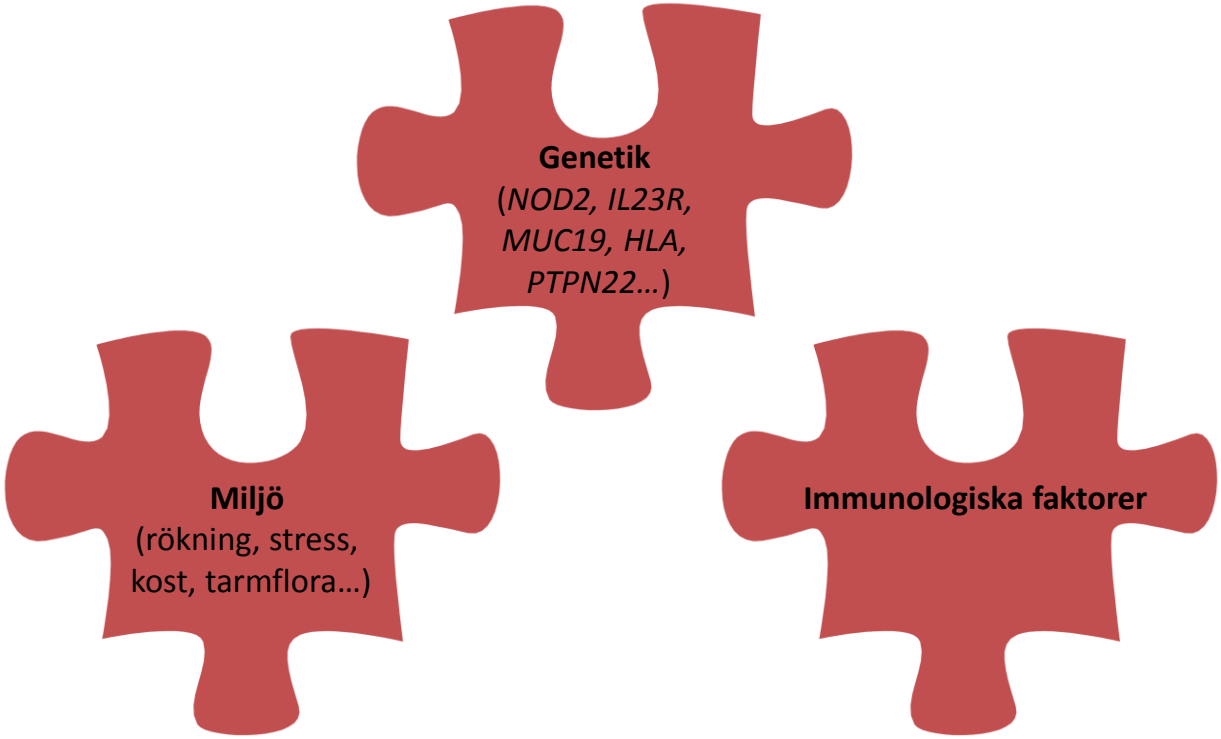
Handledare:
Sven Almer. Professor, överläkare. GastroCentrum, Karolinska universitetssjukhuset och KI, Stockholm
Jan Söderman. Docent, forskningsledare. Medicinsk diagnostik, Jönköping

Inflammatorisk tarmsjukdom (IBD)



http://iconsinmedicine.wordpress.com

Sjukdom med många frågetecken



NOD2 var den första genen som uppvisade association till Crohn's sjukdom

Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease

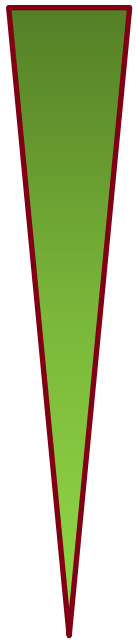
Jean-Pierre Hugot*†‡, Mathias Chamaillard*†, Habib Zouali*, Suzanne Lesage*, Jean-Pierre Cézard‡, Jacques Belaiche§, Sven Almer‖, Curt Tysk¶, Colm A. O'Morain#, Miquel Gassull☆, Vibeke Binder**, Yigael Finkel††, Antoine Cortot‡‡, Robert Modigliani§§, Pierre Laurent-Puig†, Corine Gower-Rousseau‡‡, Jeanne Macry‖‖, Jean-Frédéric Colombel‡‡, Mourad Sahbatou* & Gilles Thomas*†¶¶

A frameshift mutation in *NOD2* associated with susceptibility to Crohn's disease

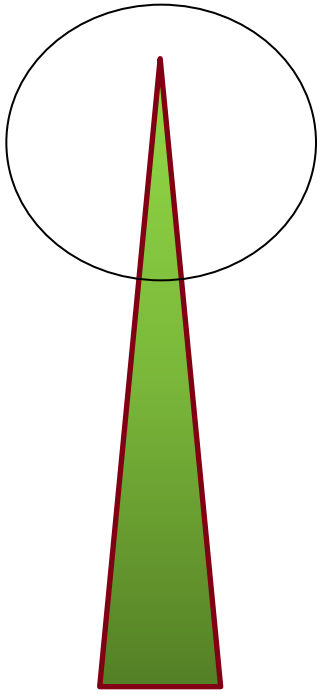
Yasunori Ogura*†, Denise K. Bonen‡†, Naohiro Inohara*, Dan L. Nicolae§, Felicia F. Chen*, Richard Ramos‡, Heidi Britton‡, Thomas Moran‡, Reda Karaliuskas‡, Richard H. Duerr‖, Jean-Paul Achkar¶, Steven R. Brant#, Theodore M. Bayless#, Barbara S. Kirschner☆, Stephen B. Hanauer‡, Gabriel Nuñez*†† & Judy H. Cho‡††

Geografisk heterogenitet

Nordeuropa



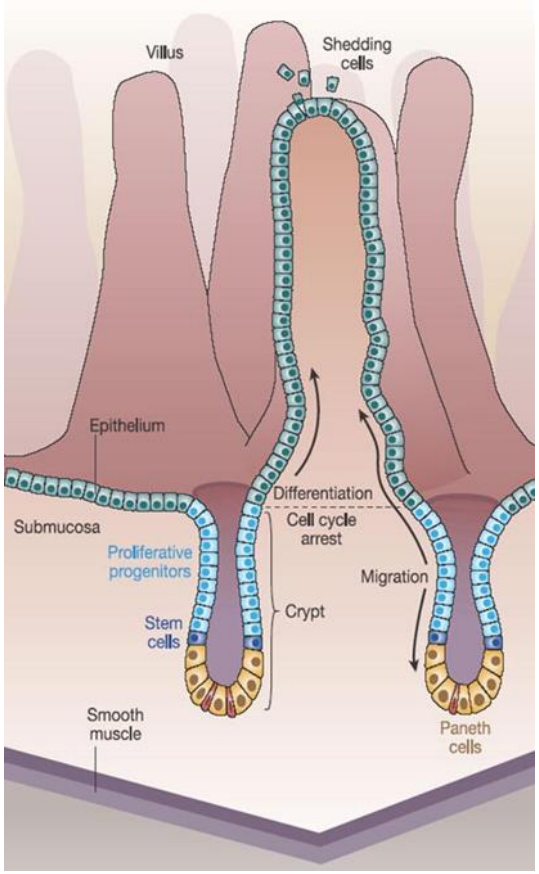
Prevalens av IBD

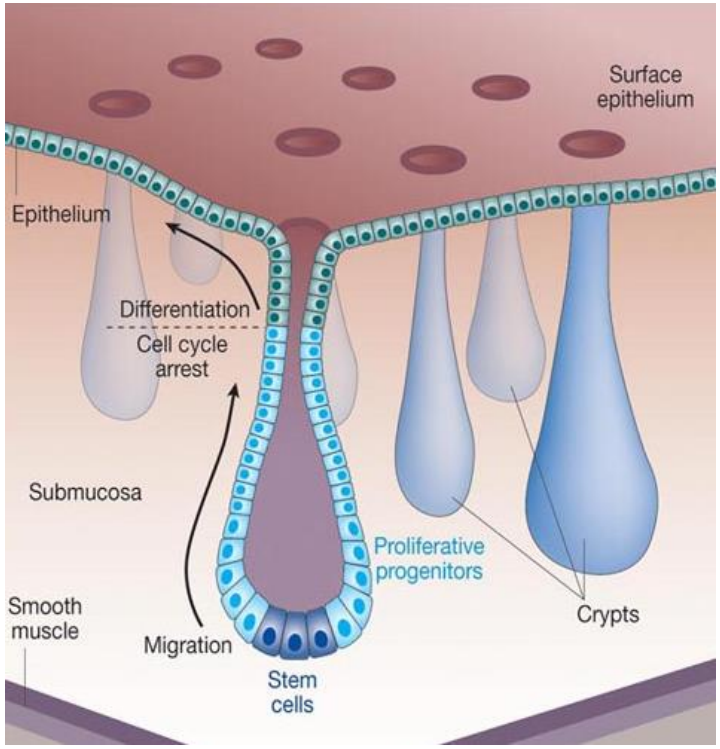


NOD2

Sydeuropa

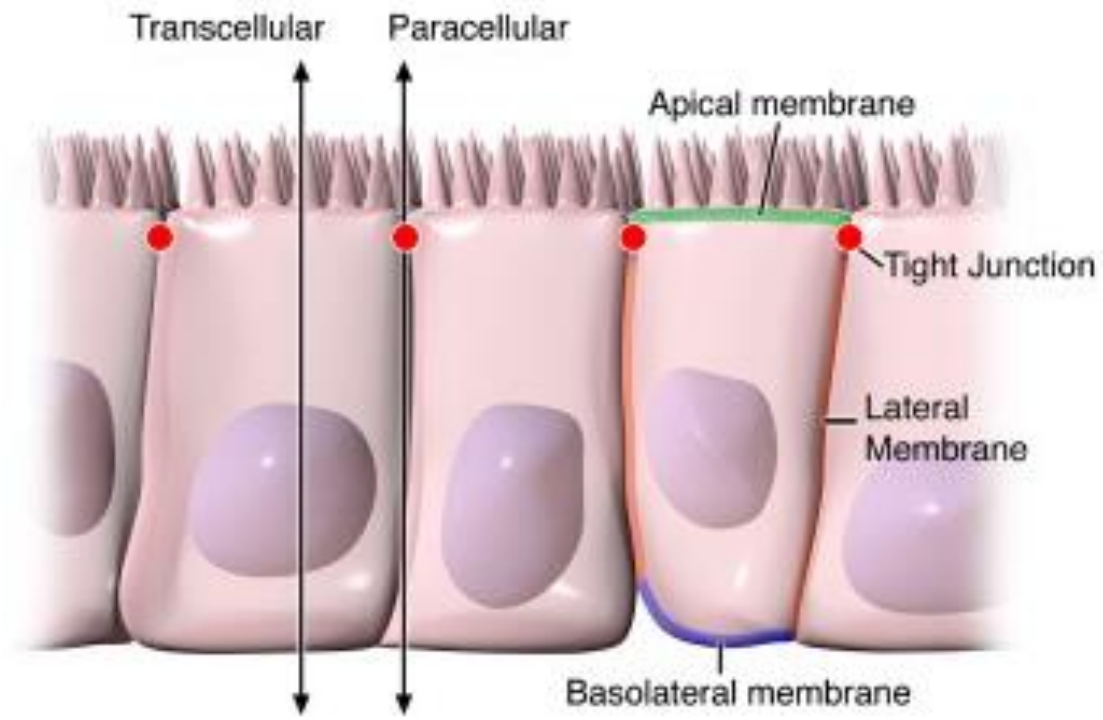
Nord-syd gradient:
Törkvist L *et al.* Digestion 2005



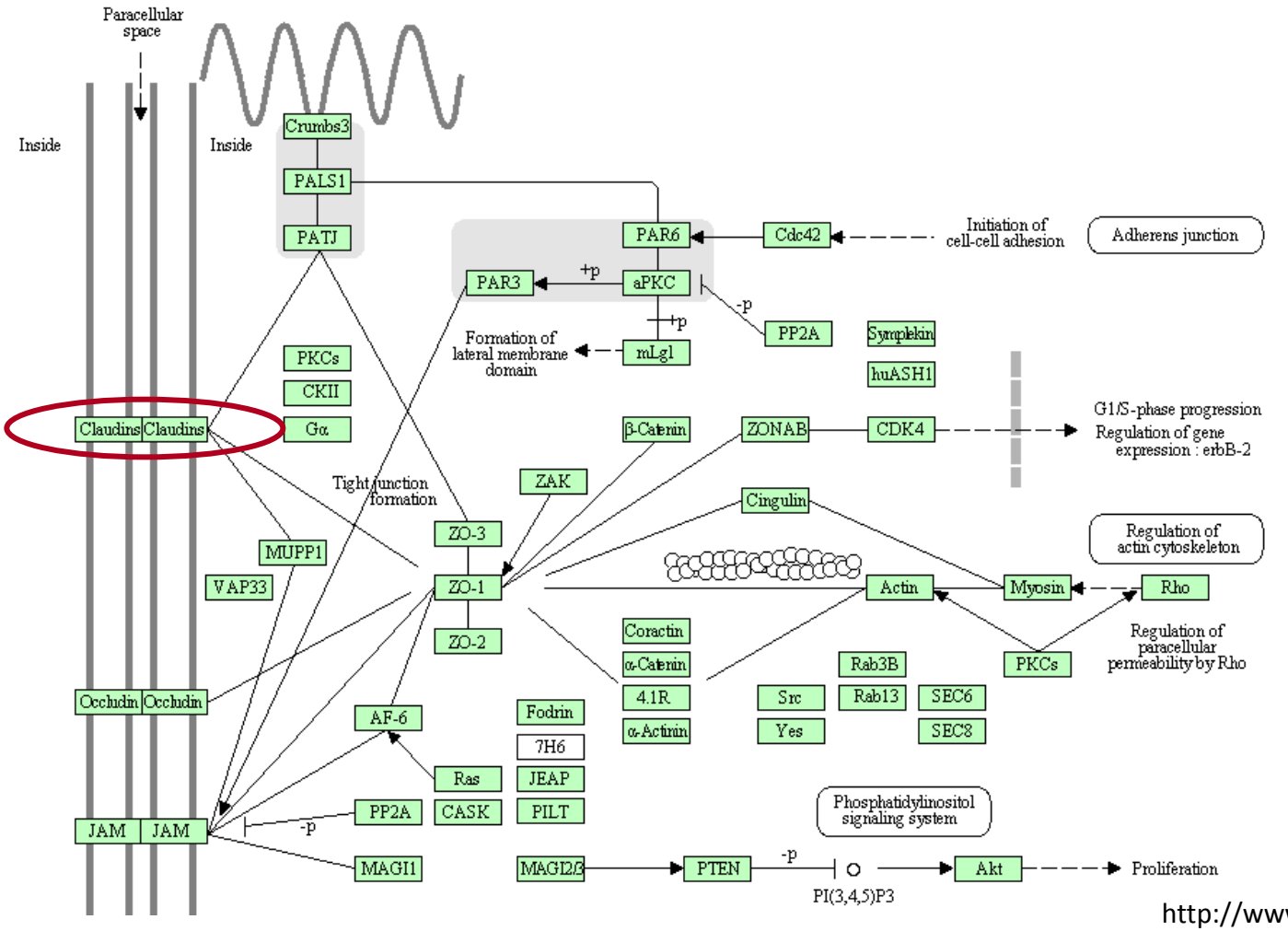


Tannishtha Reya and Hans Clevers, Nature, 2005

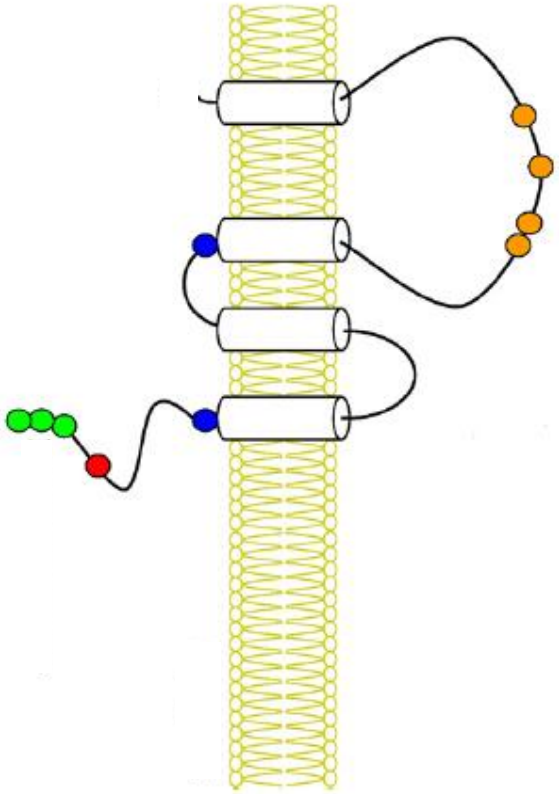
Epitelial integritet

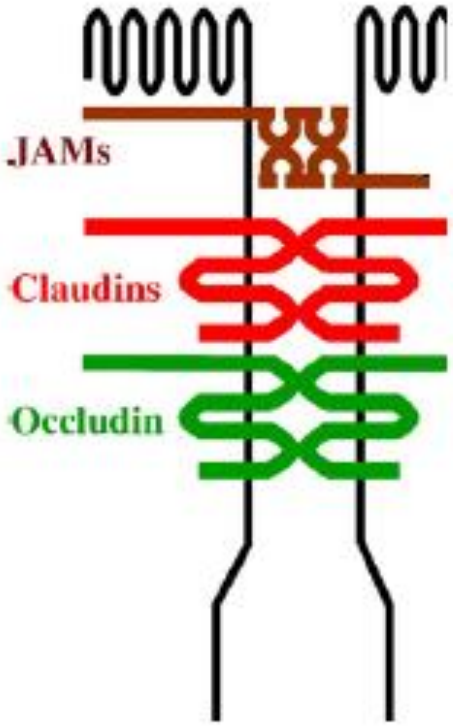


Katherine R. Groschwitz and Simon P. Hogan, 2009



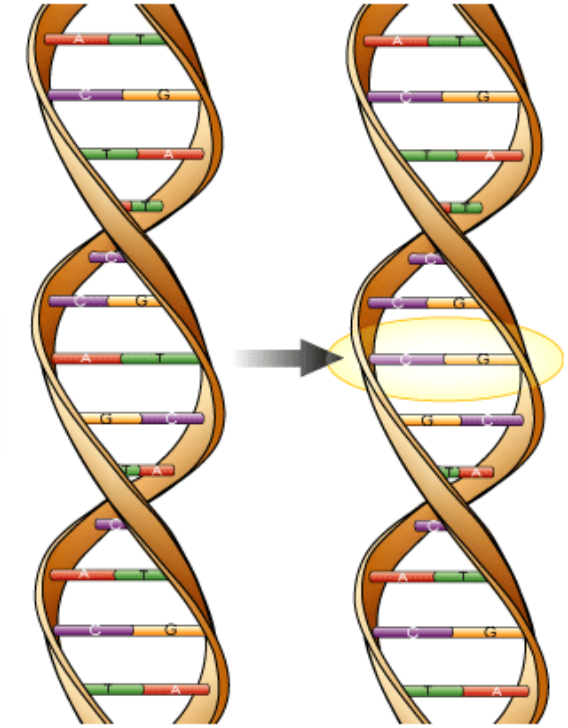
http://www.genome.jp/kegg/





Modifierad bild efter Chiba H *et al.* 2008

Single nucleotide polymorphism (SNP)



Mer än 1% av befolkningen bär på den genetiska avvikelsen (annars mutation)

www.scq.ubc.ca

Pilotstudie

Candidate gene	SNP rs number[1]
CLDN1	rs1491991
	rs3732923
	rs3732924
	rs9848283
	rs12629166
	rs7620166
	rs567408
	rs536435
CLDN2	rs4409525
	rs5917027
	rs12014762
CLDN4	rs4131376
	rs8629

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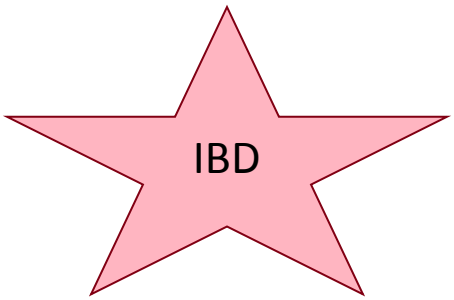


Europeiskt familjebaserat material

Svenska IBD patienter
fall kontroll studie

Familjebaserad
associations studie
(svenskar exkluderade)

		rs7620166 (*CLDN1*)		rs12014762 (*CLDN2*)		rs8629 (*CLDN4*)	
		allelic OR (95%CI)	*P* value	allelic OR (95%CI)	*P* value	allelic OR (95%CI)	*P* value
IBD	Swedish case-control	1.33 (1.04–1.72)	0.025	1.39 (0.95–2.01)	0.083	1.21 (0.89–1.65)	0.225
	Non-Swedish families	0.87 (0.72-1.06)	0.177	1.25 (0.89–1.77)	0.195	1.09 (0.88–1.33)	0.432
CD	Swedish case-control	1.17 (0.86–1.60)	0.319	1.98 (1.17-3.35)	0.007	1.25 (0.84–1.85)	0.258
	Non-Swedish families	0.80 (0.64-1.00)	0.052	1.37 (0.91–2.07)	0.126	1.14 (0.89–1.46)	0.287
UC	Swedish case-control	1.35 (0.98–1.84)	0.064	1.27 (0.80–2.02)	0.304	1.18 (0.80-1.73)	0.409
	Non-Swedish families	1.19 (0.77-1.84)	0.436	0.91 (0.39-2.14)	0.827	1.15 (0.75-1.77)	0.512

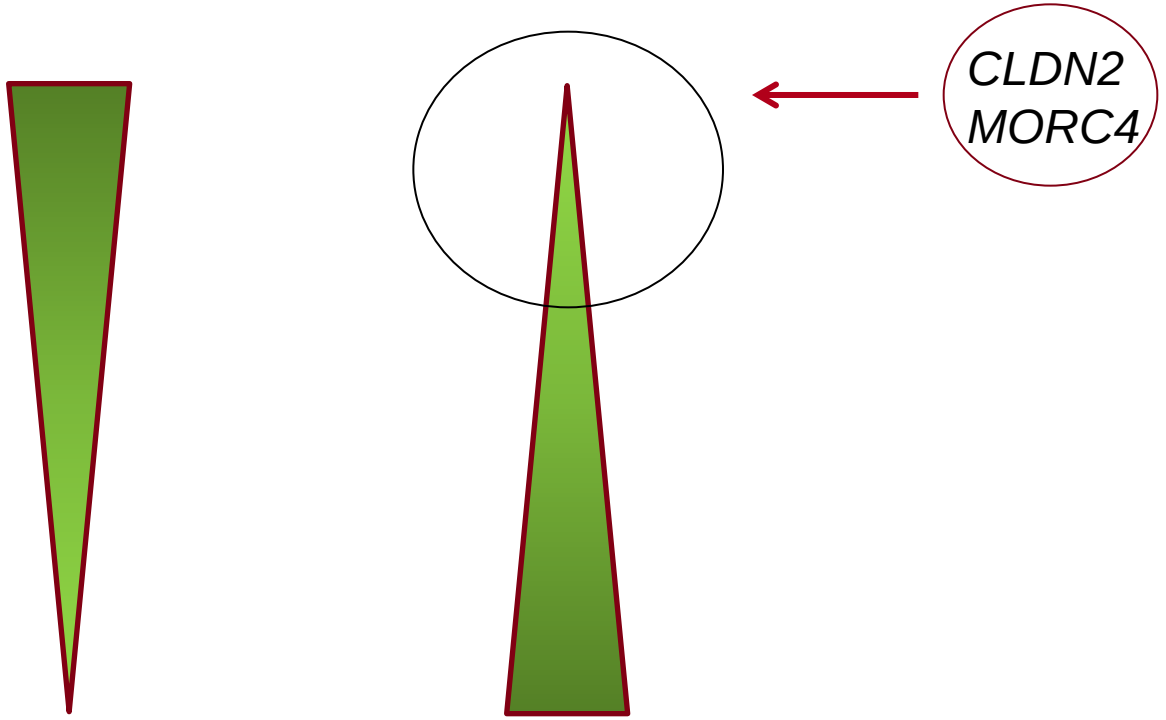
1. Sekvensering av *CLDN2* resulterade i två nya fynd lokaliserade i promotorregionen

2. Genen *MORC4* ligger på samma genetiska block som *CLDN2* varför en kodande icke-synonym SNP valdes ut för associationsstudie

	rs62605981 (*CLDN2*)		rs72466477 (*CLDN2*)		rs6622126 (*MORC4*)	
	allelic OR (95%CI)	*P* value	allelic OR (95%CI)	*P* value	allelic OR(95%CI)	*P* value
IBD	1.11 (0.71–1.73)	0.659	1.23 (0.79–1.91)	0.350	1.24 (0.91–1.70)	0.179
CD	0.83 (0.49–1.41)	0.501	1.16 (0.68–2.00)	0.584	1.61 (1.08–2.41)	0.018
UC	1.24 (0.69–2.26)	0.463	1.19 (0.68–2.06)	0.543	0.903 (0.61–1.33)	0.606

Geografisk heterogenitet

Nordeuropa



Sydeuropa

Nord-syd gradient:
Törkvist L *et al.* Digestion 2005

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
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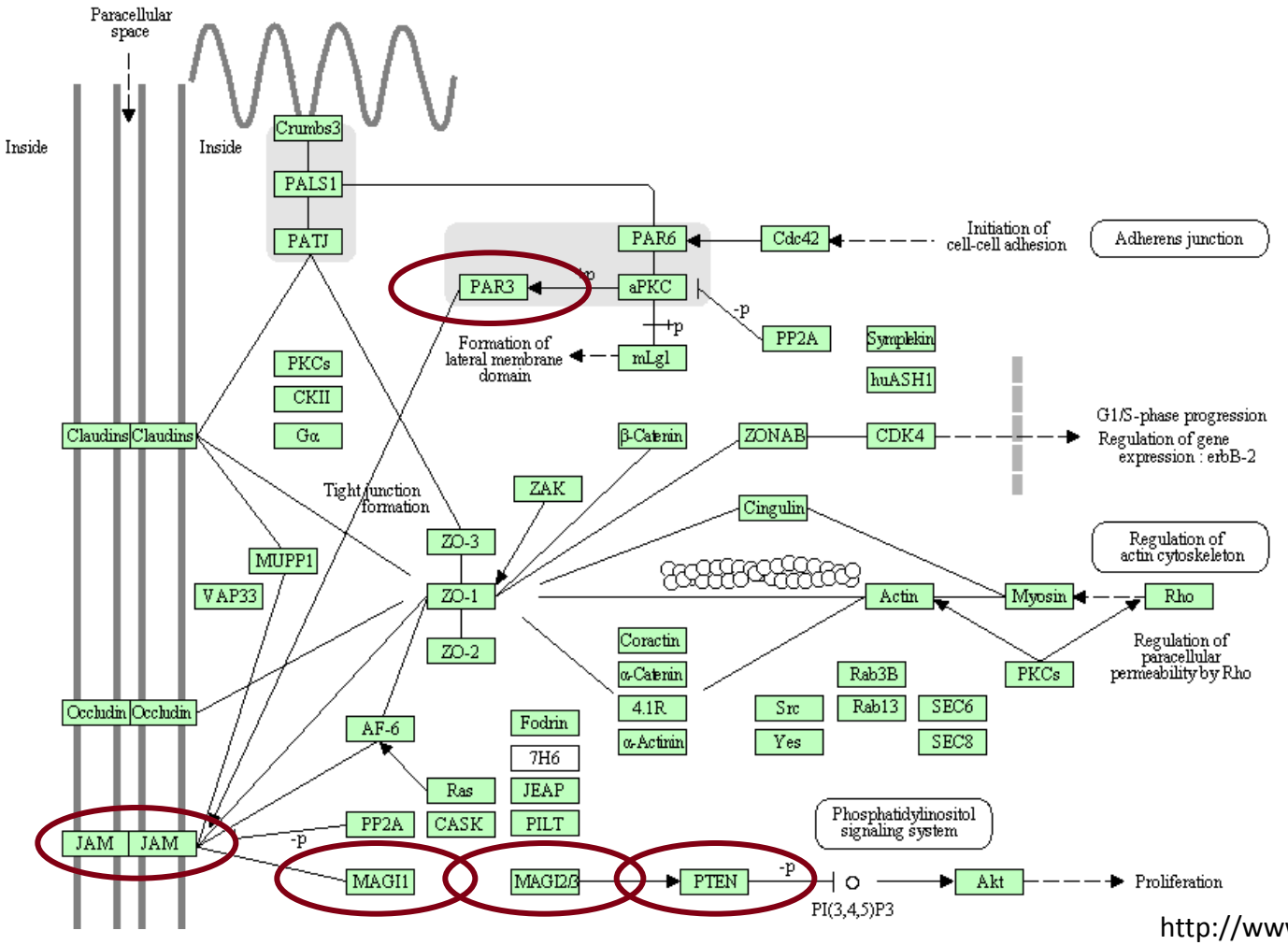
BRIEF ARTICLE

Analysis of single nucleotide polymorphisms in the region of *CLDN2-MORC4* in relation to inflammatory bowel disease

Jan Söderman, Elisabeth Norén, Malin Christiansson, Hanna Bragde, Raphaele Thiébaut, Jean-Pierre Hugot, Curt Tysk, Colm A O'Morain, Miquel Gassull, Yigael Finkel, Jean-Frédéric Colombel, Marc Lémann, Sven Almer

Linköping University
FACULTY OF HEALTH SCIENCES

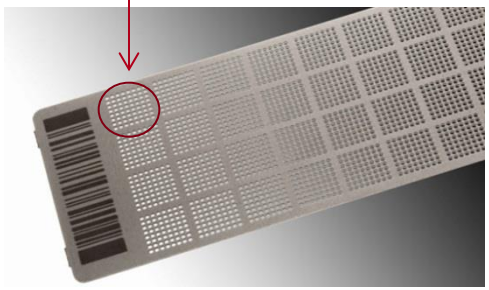
Medicinsk diagnostik
Landstinget i Jönköpings län



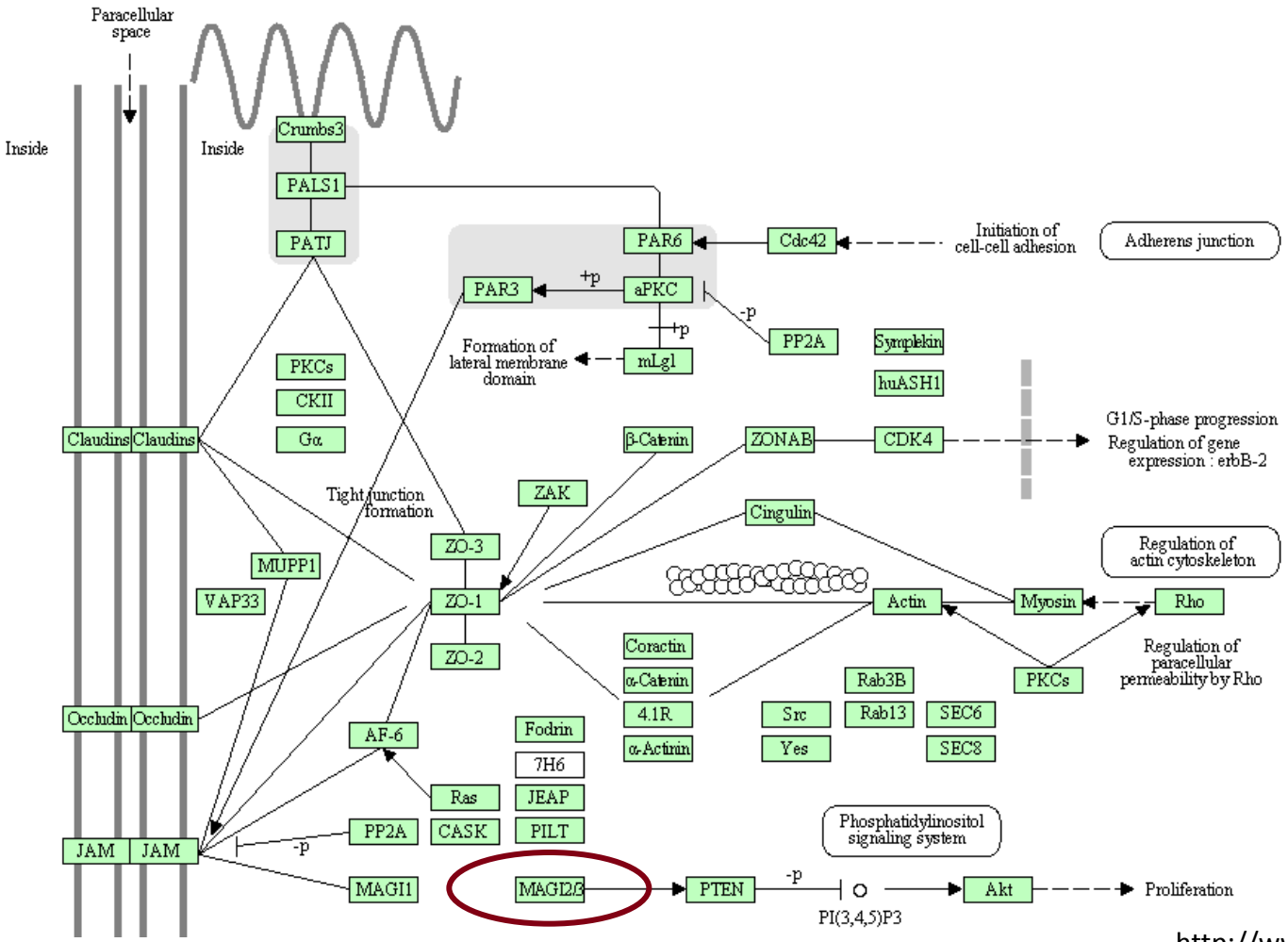
http://www.genome.jp/kegg/

OpenArray system

En individ, 64 SNPs



Gene	Marker	Trait	Number of controls	Number of cases	Allele OR	Lower CI	Upper CI	ChiSq Allele	Probe Allele
MAGI3	SNP1	CD_UC	410	229	1,464	1,143	1,874	9,150	0,002
MAGI3	SNP2	CD_UC	406	271	1,380	1,084	1,757	6,868	0,009
MAGI2	SNP3	CD_UC	410	265	0,749	0,602	0,933	6,685	0,010
F11R	SNP4	CD_UC	349	222	1,463	1,062	2,014	5,469	0,019
MAGI2	SNP5	CD_UC	406	282	0,778	0,627	0,965	5,205	0,023
MAGI1	SNP6	CD_UC	392	233	0,633	0,425	0,944	5,110	0,024
MAGI2	SNP3	CD	410	126	0,694	0,523	0,922	6,394	0,011
MAGI1	SNP6	CD	392	113	0,559	0,322	0,971	4,358	0,037
MAGI3	SNP1	UC	410	124	1,583	1,171	2,140	8,977	0,003
MAGI2	SNP5	UC	406	151	0,704	0,539	0,919	6,706	0,010
MAGI3	SNP2	UC	406	146	1,456	1,088	1,950	6,404	0,011
MAGI2	SNP7	UC	413	141	1,397	1,062	1,837	5,747	0,017
MAGI2	SNP8	UC	417	142	1,397	1,052	1,856	5,358	0,021
MAGI3	SNP9	UC	411	152	0,723	0,546	0,958	5,117	0,024
F11R	SNP4	UC	349	113	1,607	1,054	2,448	4,927	0,026
MAGI3	SNP10	UC	403	117	1,563	1,036	2,358	4,595	0,032
TSTD1;USF1	SNP11	UC	414	144	1,329	1,008	1,753	4,086	0,043



http://www.genome.jp/kegg/

Genuttrycket studeras utifrån lokal i tarmen samt korreleras mot genotyp

mRNA → cDNA → **Genuttryck**

Dataanalys pågår…

TACK!

Projektet stöds av:
Futurum - akademin för hälsa och vård
Länssjukhuset Ryhov, Jönköping

Linköping University
FACULTY OF HEALTH SCIENCES

Medicinsk diagnostik
Landstinget i Jönköpings län