

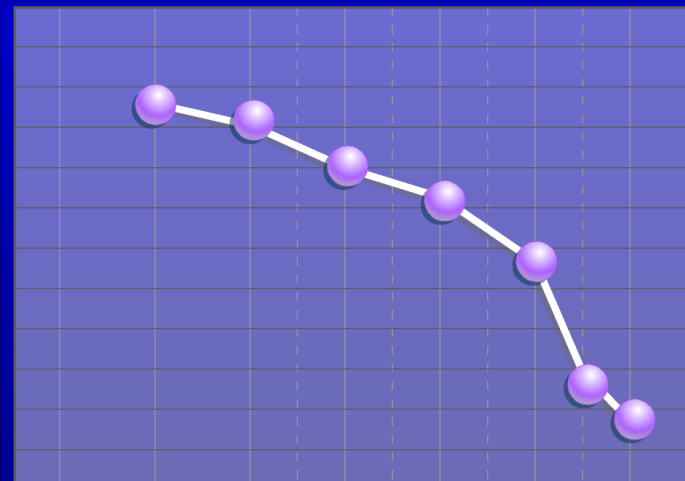
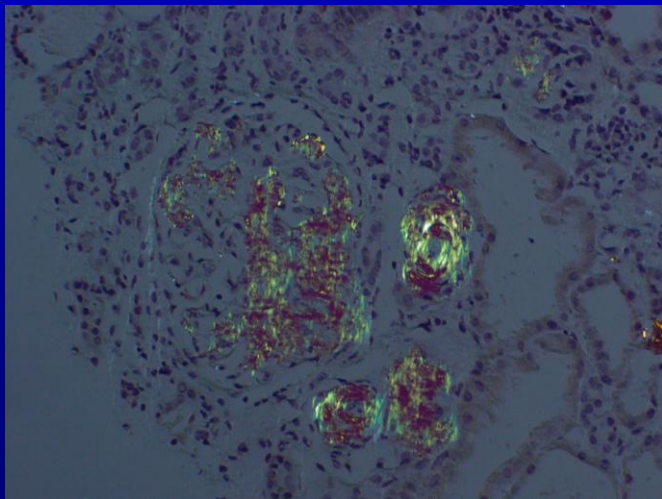
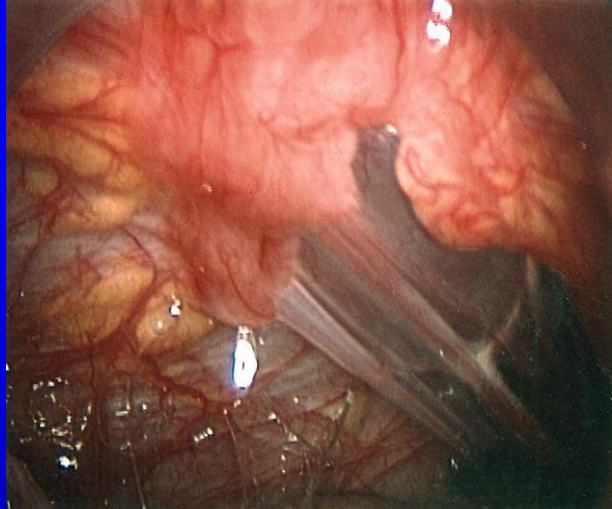
# Fevers, Genes, and Targeted Therapy: Adventures in the Genomics of Inflammation

Dan Kastner, MD, PhD

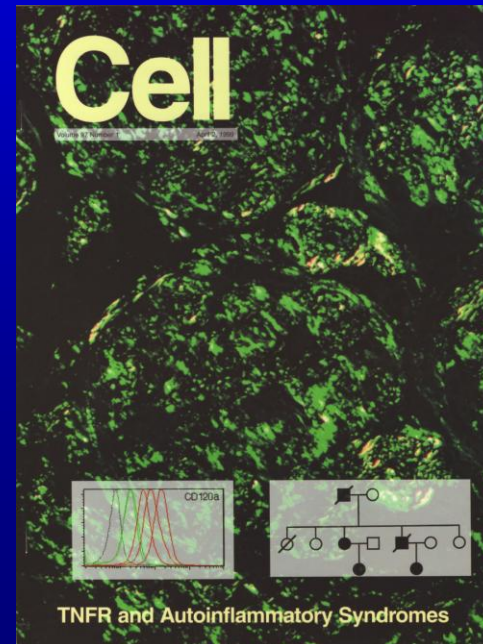
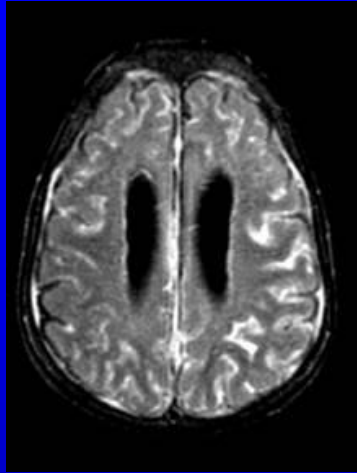
NHGRI/NIH/DHHS

February 11, 2011

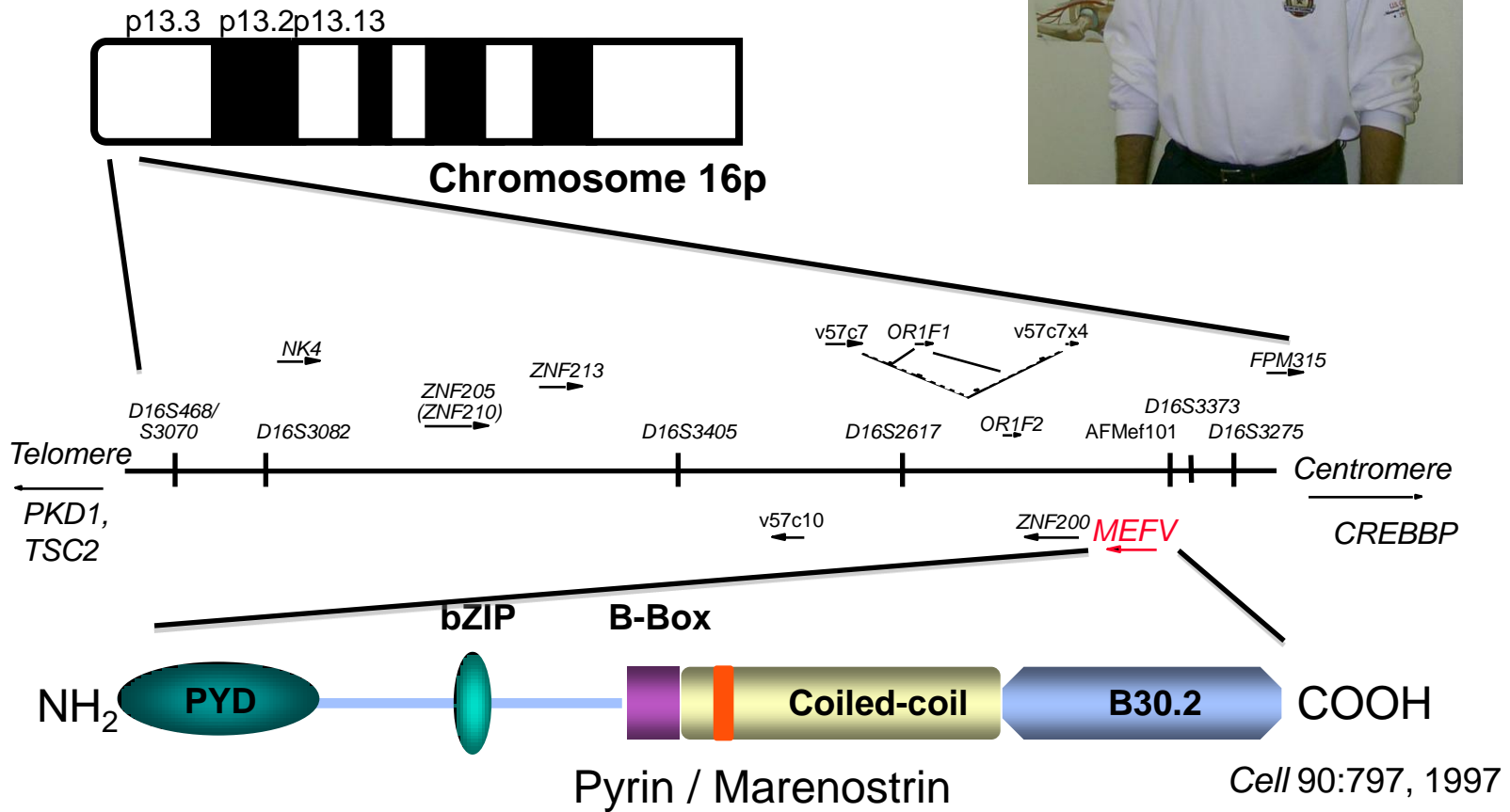
# Charting a Course for Genomic Medicine



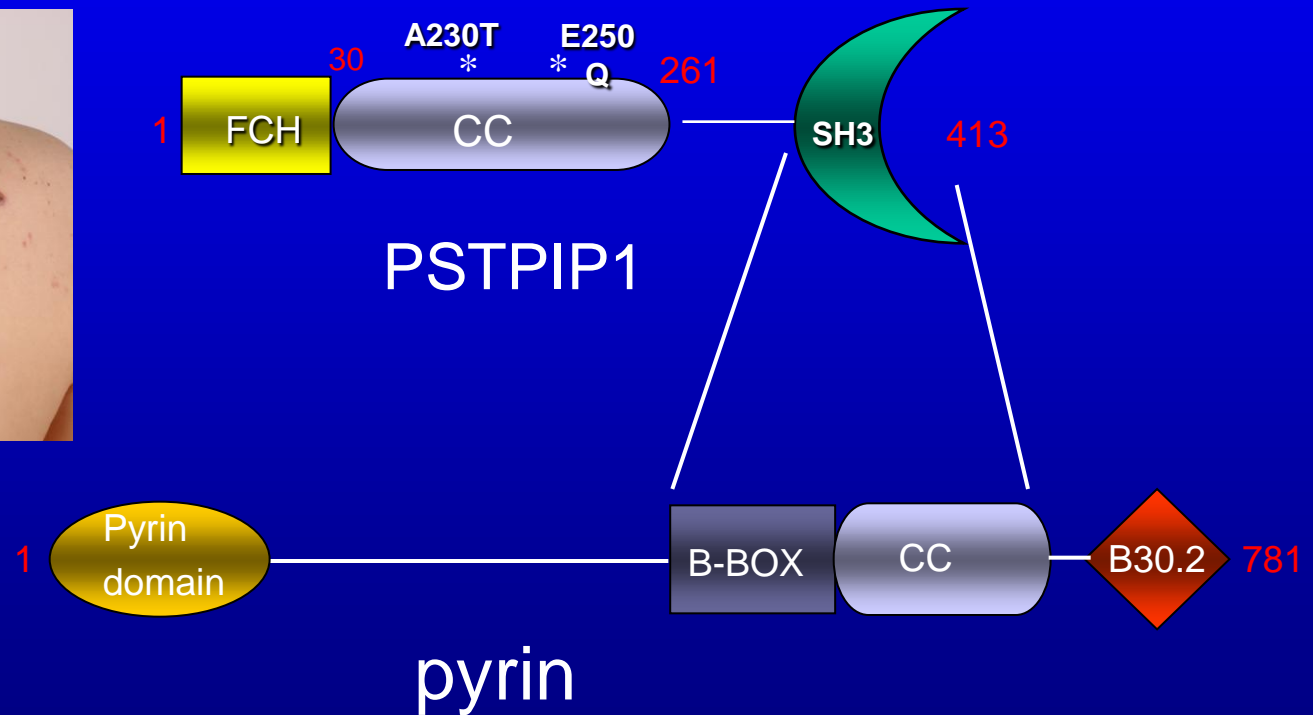
# Charting a Course for Genomic Medicine



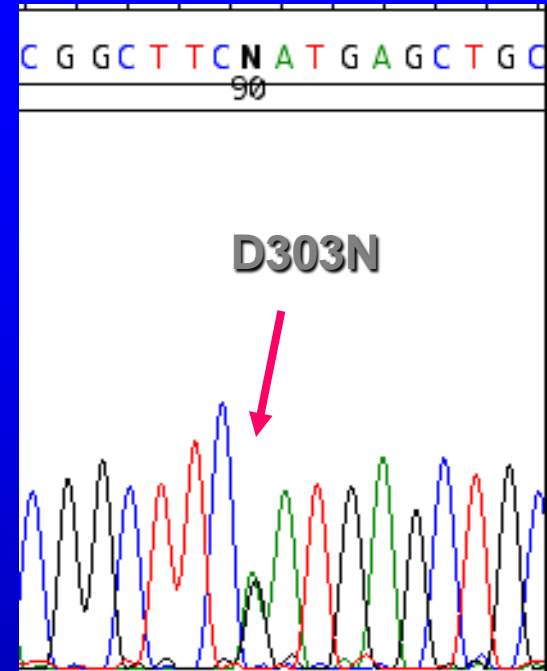
# Familial Mediterranean Fever (FMF)



# Extending the Pyrin Pathway: Proline Serine Threonine Phosphatase Interacting Protein 1 (PSTPIP1/CD2BP1)

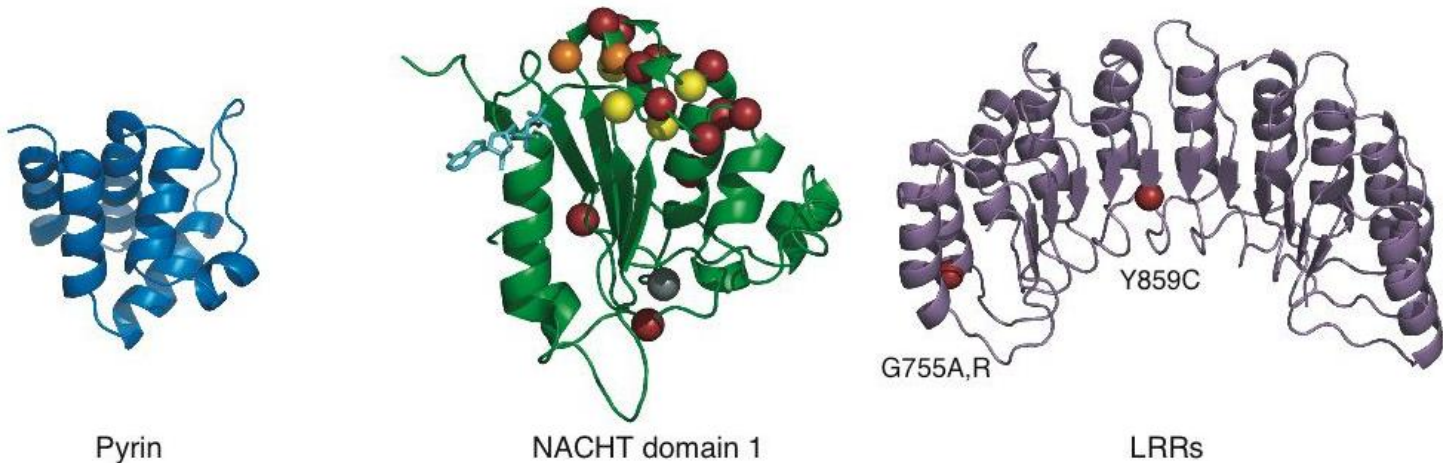


# NLRP3 Mutation in NOMID/CINCA



Aksentjevich et al, *Arthritis Rheum* 46:3340, 2002

B



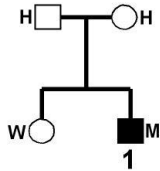
Aksentjevich et al *Arthritis Rheum* 56:1273, 2007

# Mutations in *IL1RN*, IL-1 Receptor Antagonist Gene



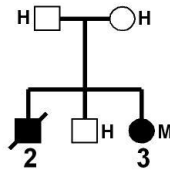
Newfoundland  
(N52KfsX25)

Family A

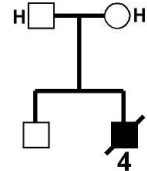


Netherlands  
(E77X)

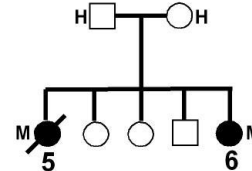
Family B



Family C

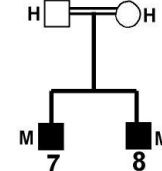


Family D



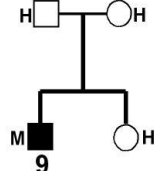
Lebanon  
(Q54X)

Family E

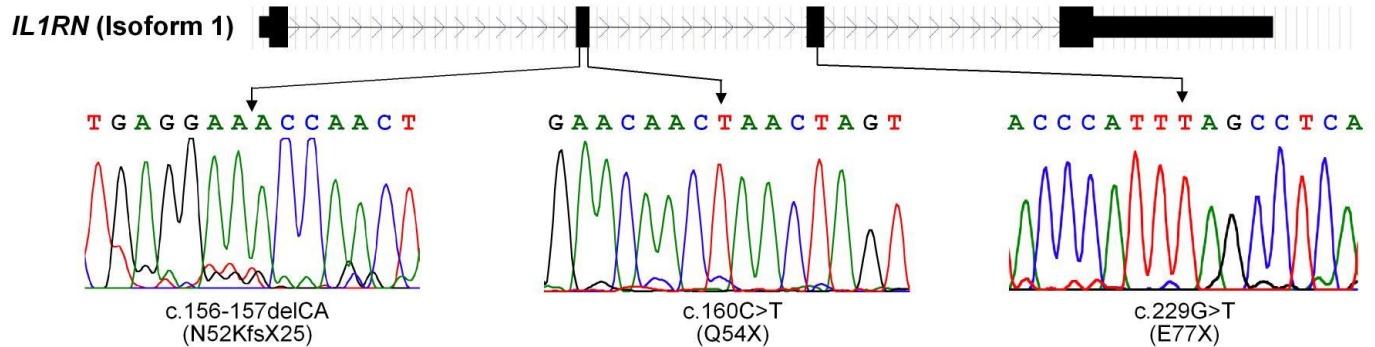


Puerto Rico  
(deletion)

Family F



B



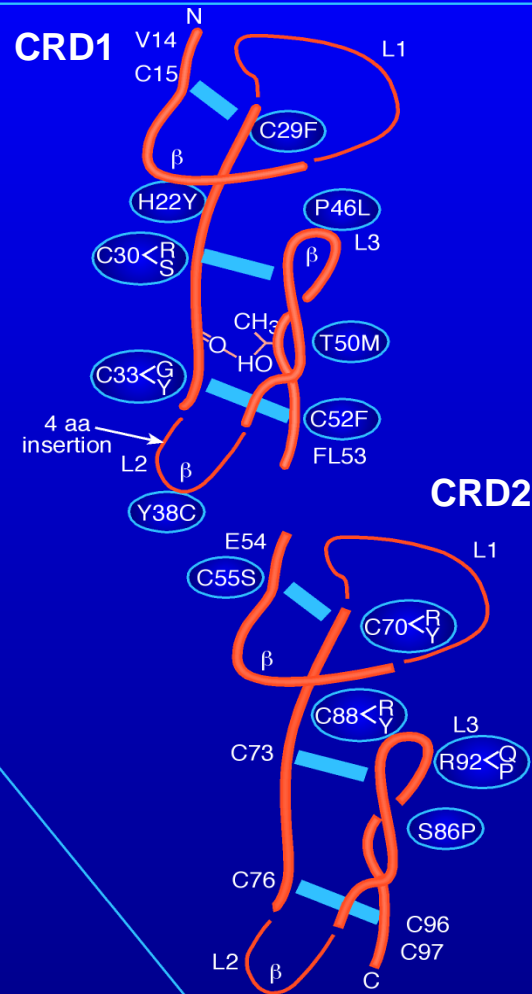
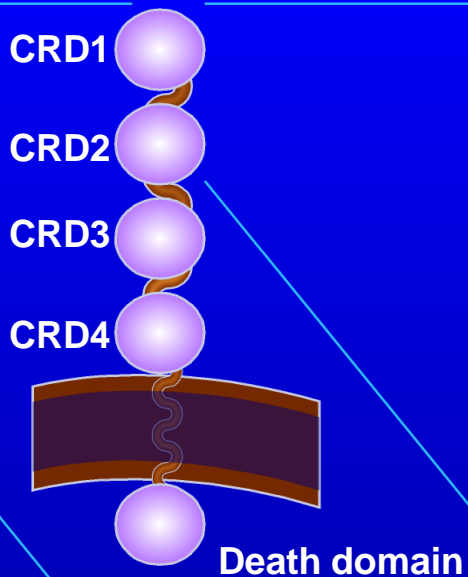
Aksentijevich I et al. *N Engl J Med* 360:2426-2437, 2009

## Deficiency of the IL-1 Receptor Antagonist (DIRA)

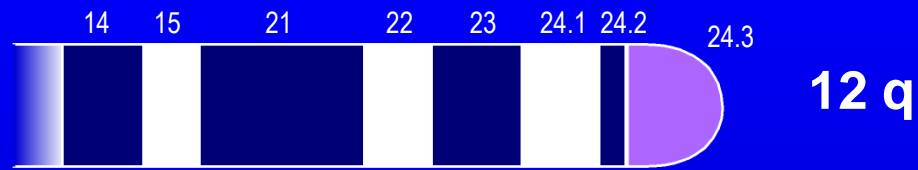
# TNFRSF1A Mutations Can Cause Dominantly Inherited Periodic Fever



**TNFRSF1A**

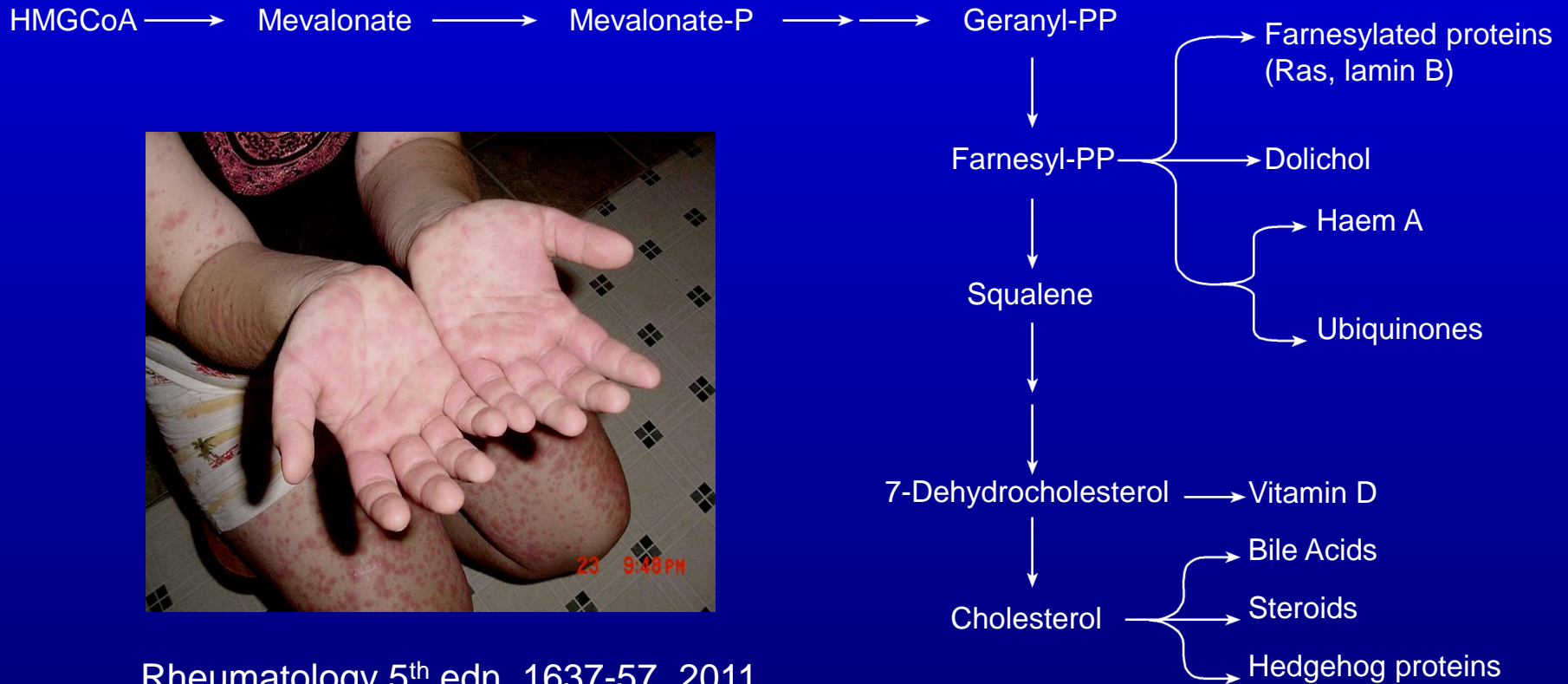






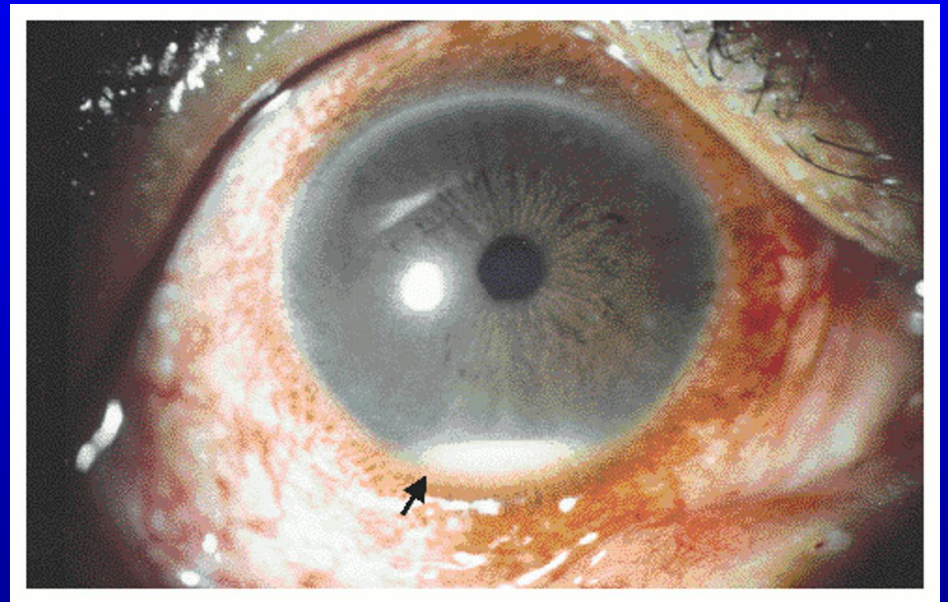
## Mutations in the Mevalonate Kinase Gene Cause HIDS

Mevalonate kinase (MK)



Rheumatology 5<sup>th</sup> edn, 1637-57, 2011

# Behçet's Disease: The Classic Triad of Clinical Findings

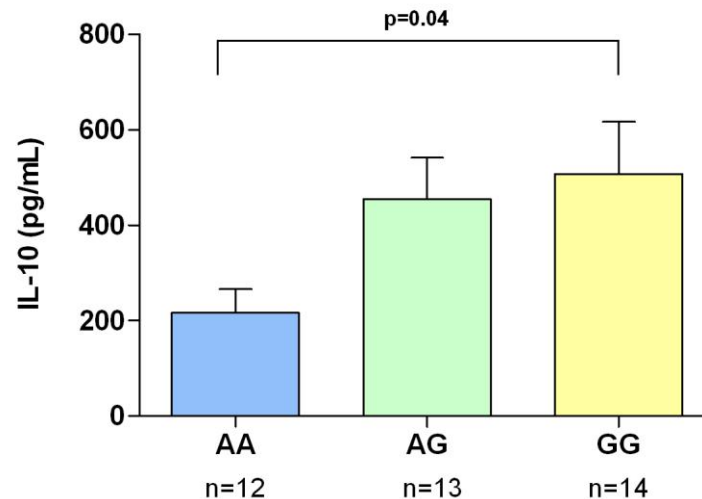


$$\lambda_s > 10$$

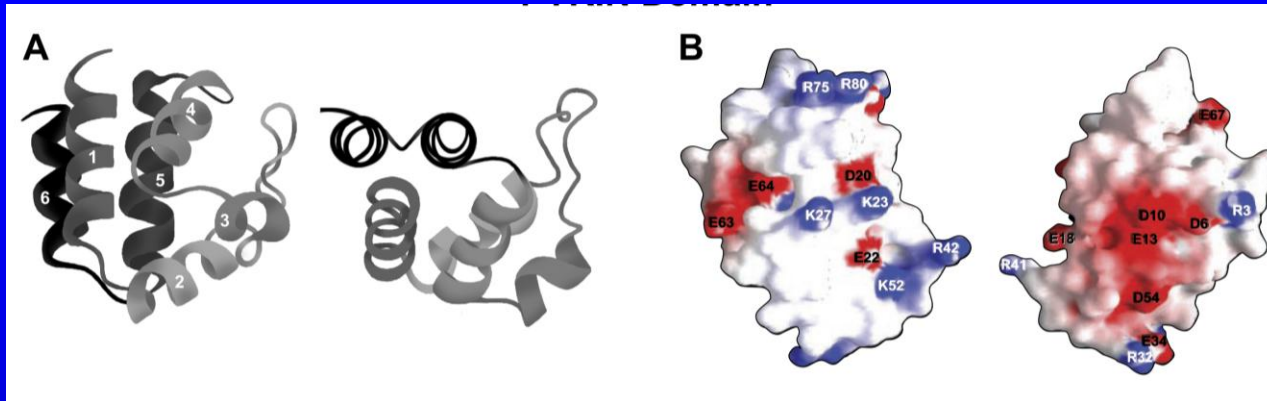
# Association of an *IL10* Variant with Behçet's Disease

Sample Collection	# cases	# controls	Allele freq		Chi-squared	ChiSq P- value	Odds ratio	(95% CI)
			cases	Allele freq ctrls				
<i>rs1518111 (IL10) A/G</i>								
Discovery - Turkish	1161	1221	0.38	0.30	31.62	<b>1.88E-08</b>	1.41	(1.25 - 1.59)
Replication - Turkish	110	224	0.30	0.31	(0.02)	0.689	0.97	(0.69 - 1.38)
Replication - Middle Eastern	188	163	0.35	0.26	7.15	0.007	1.56	(1.12 - 2.16)
Replication - Greek	107	84	0.40	0.27	7.21	0.007	1.41	(1.26 - 1.59)
Replication - UK Caucasian	120	119	0.31	0.22	4.49	0.034	1.56	(1.03 - 2.34)
Replication - Korean	77	52	0.71	0.66	0.57	0.450	1.23	(0.78 - 2.10)
Replication - Japanese	611	737	0.76	0.67	29.40	5.89E-08	1.60	(1.35 - 1.90)
CMH-Meta-analysis	2374	2600			75.56	<b>3.54E-18</b>	1.45*	(1.34 - 1.58)

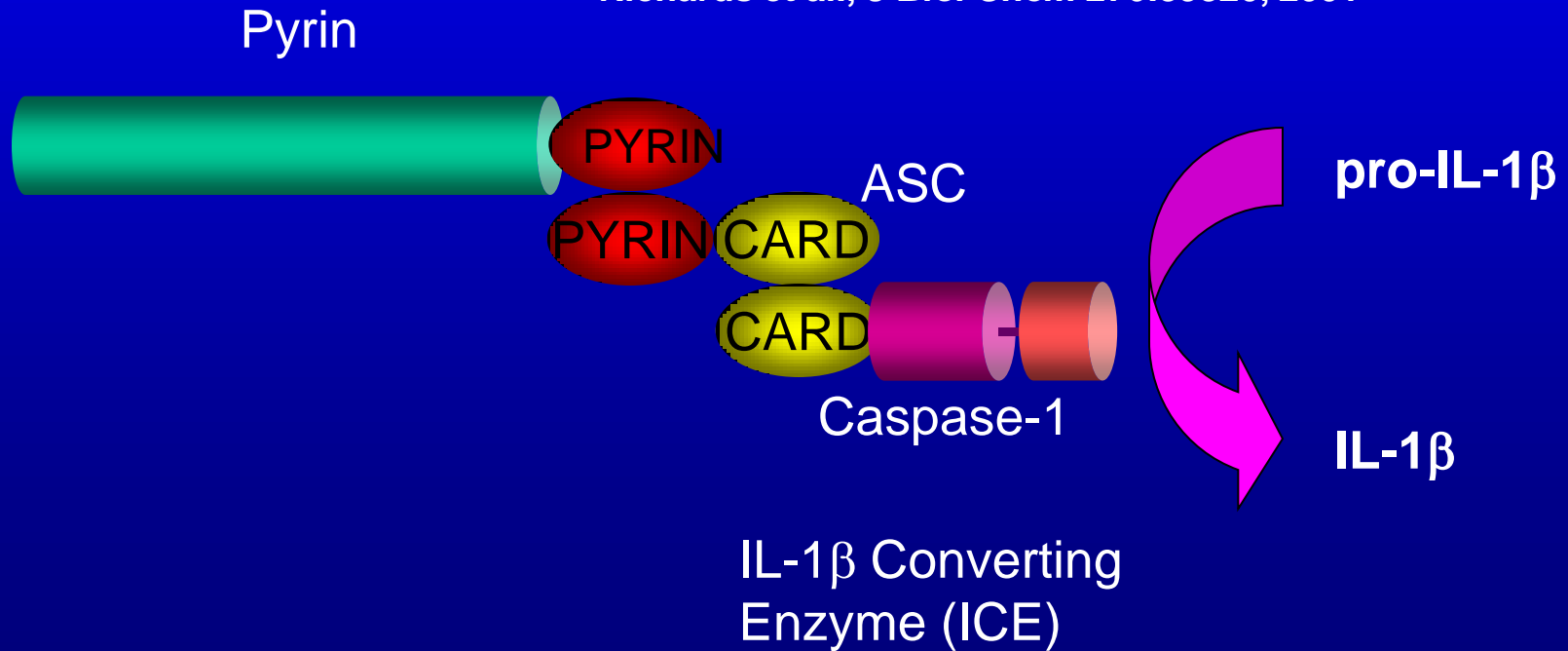
IL-10 Mean Change from CD14+ Monocytes (unstim vs. MDP+PAM)



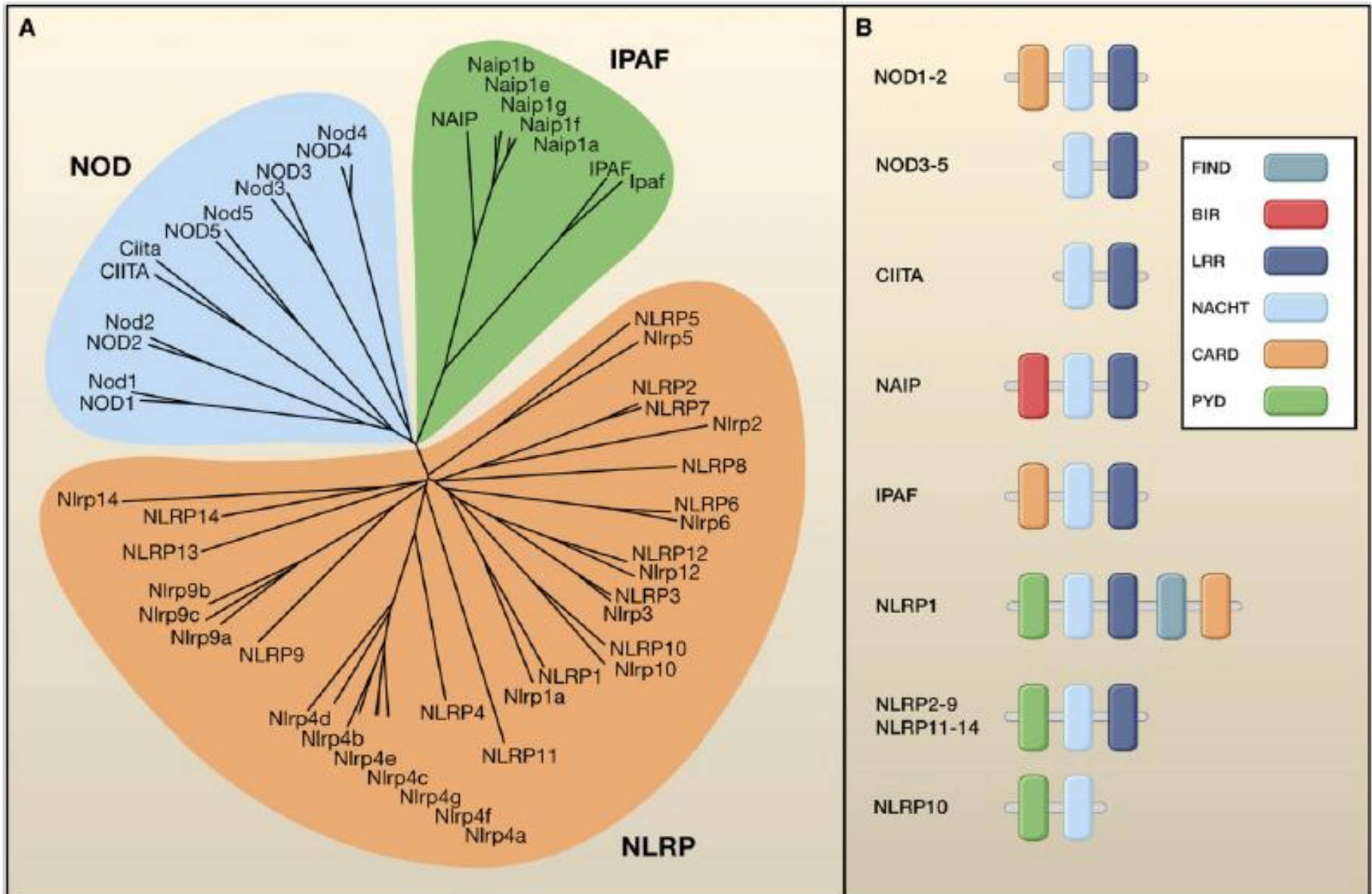
# The PYRIN Domain: A Cognate Interaction Motif



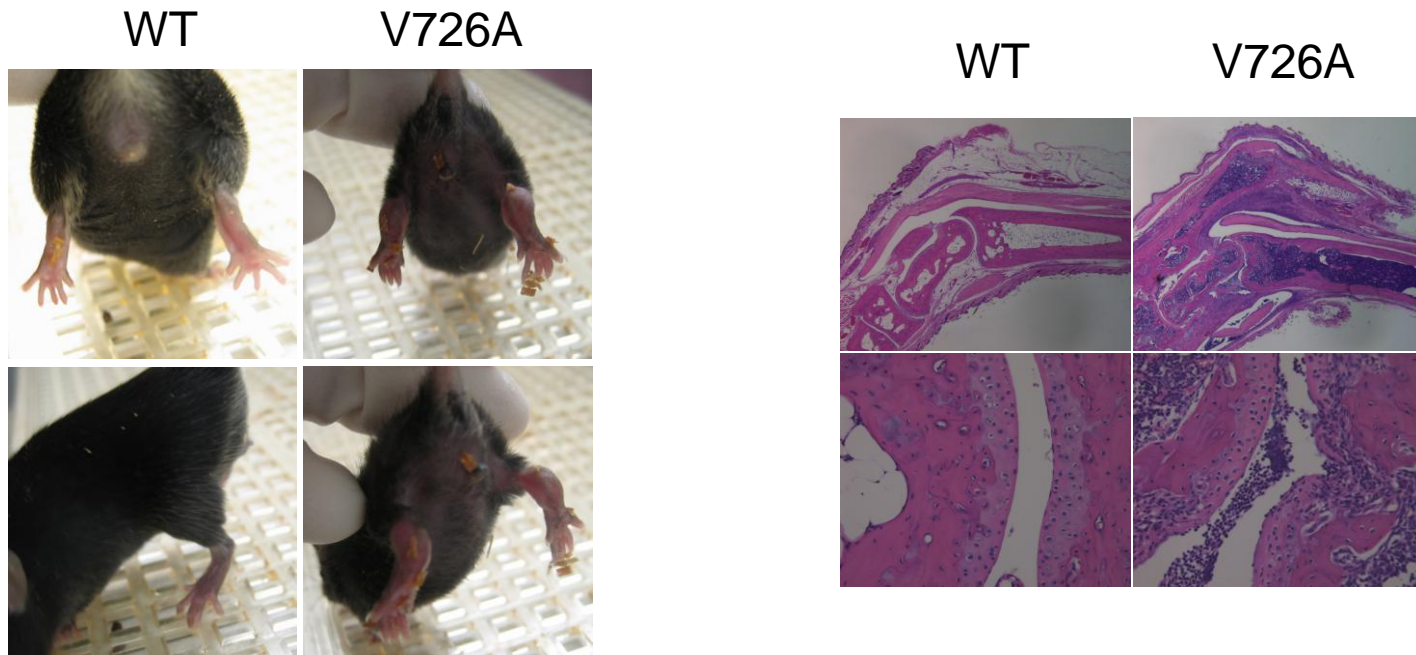
Richards et al., *J Biol Chem* 276:39320, 2001



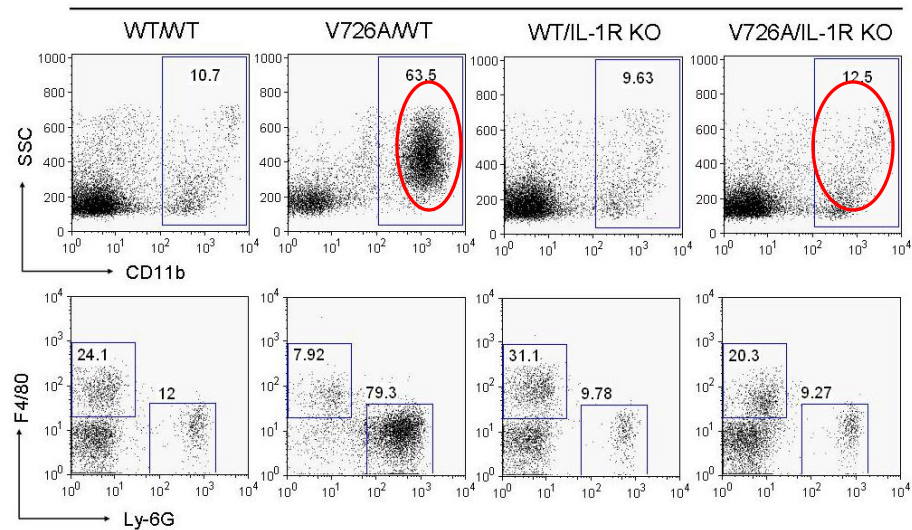
# Human and Mouse NLR Family Members



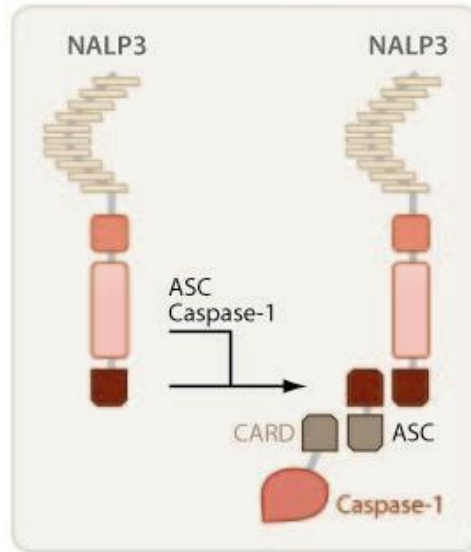
# FMF Knockin Mice: IL-Dependent Inflammation



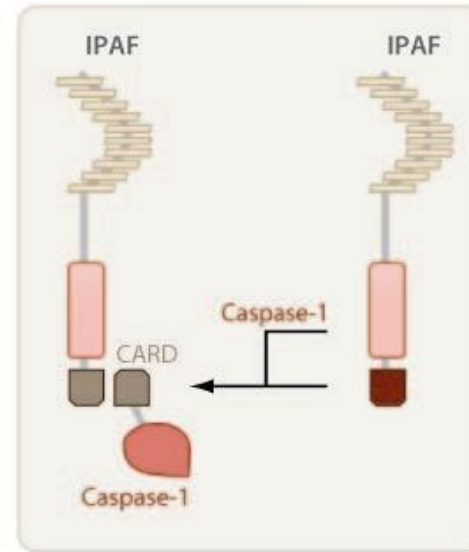
Peripheral blood



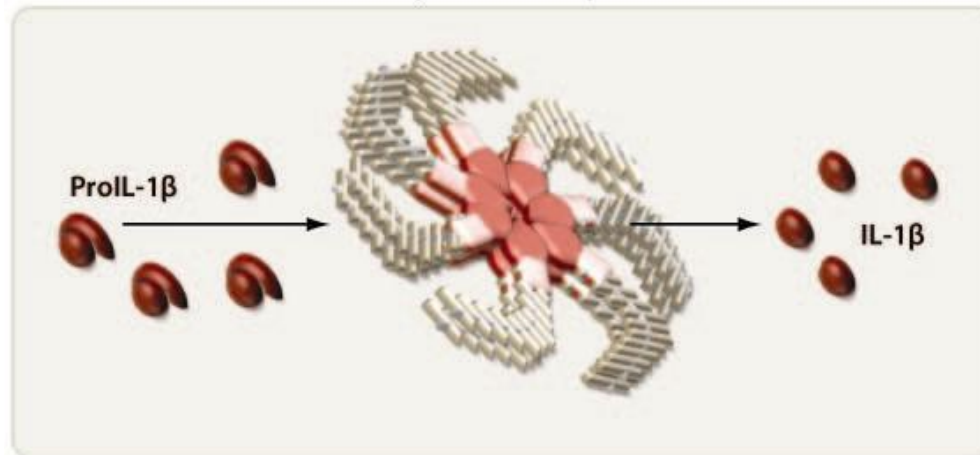
### NALP3 inflammasome



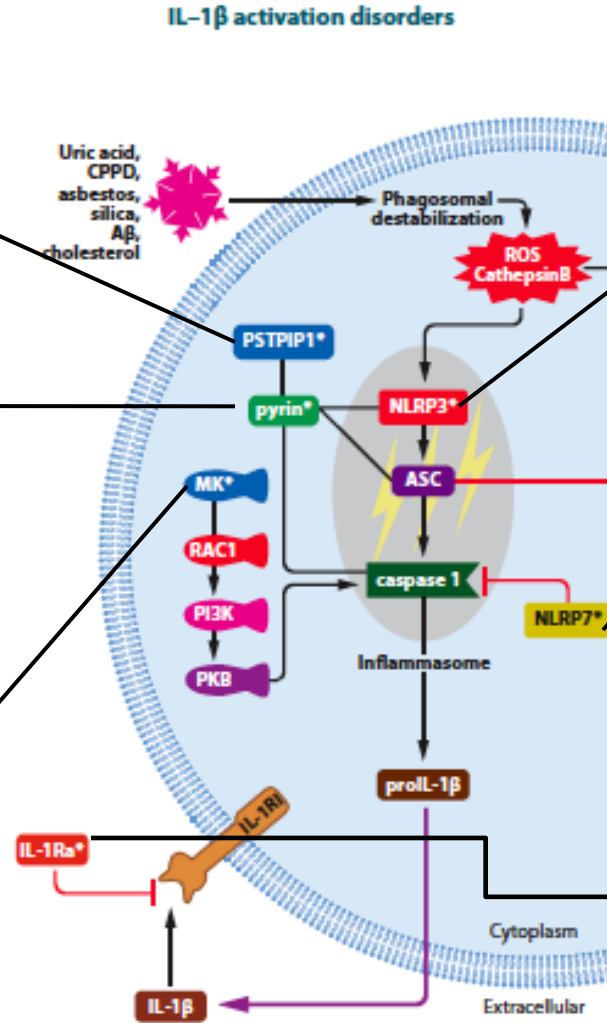
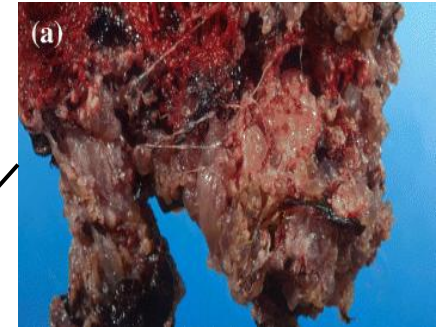
### IPAF inflammasome



### Inflammasome

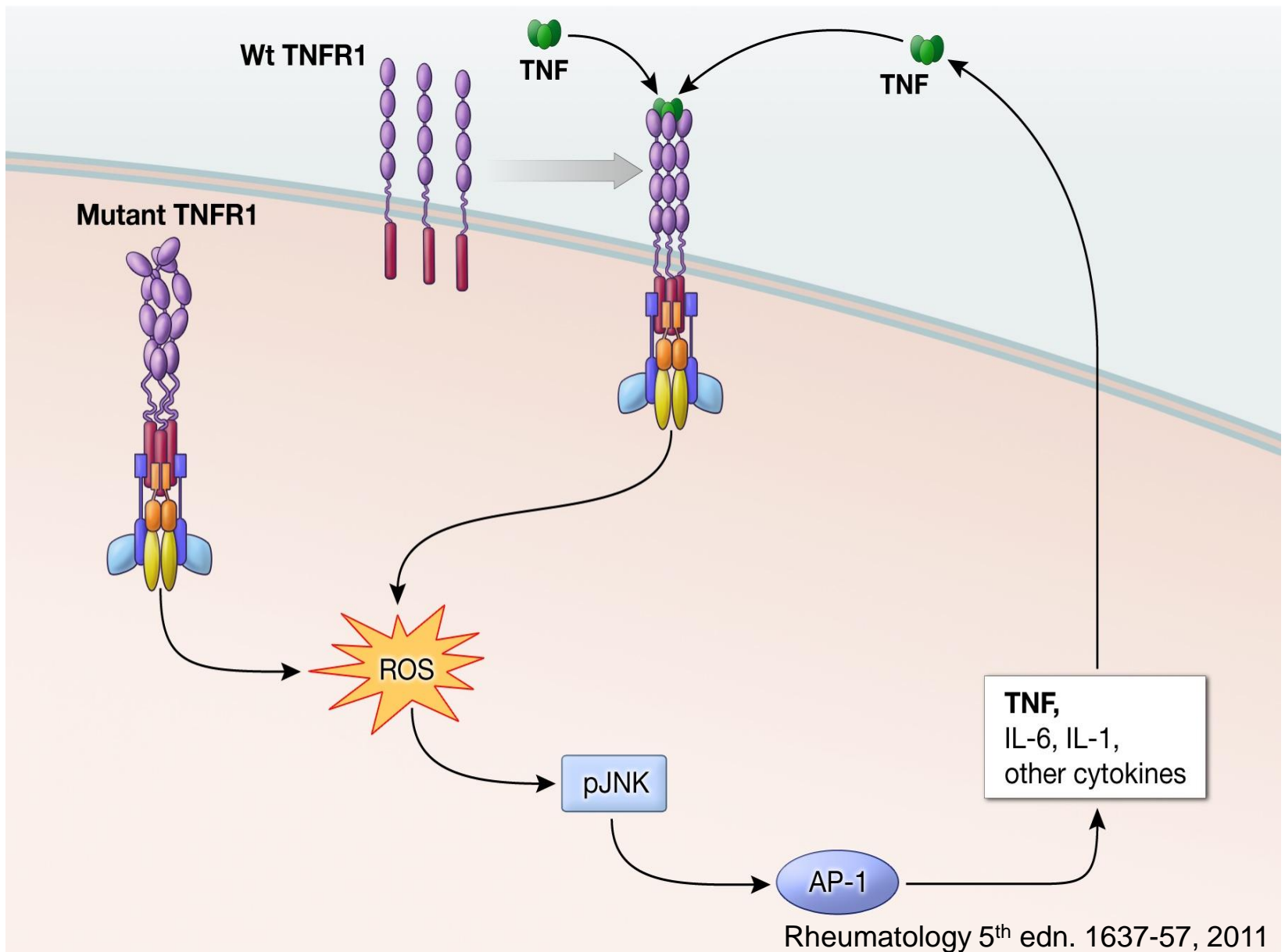


# IL-1 $\beta$ Activation Disorders





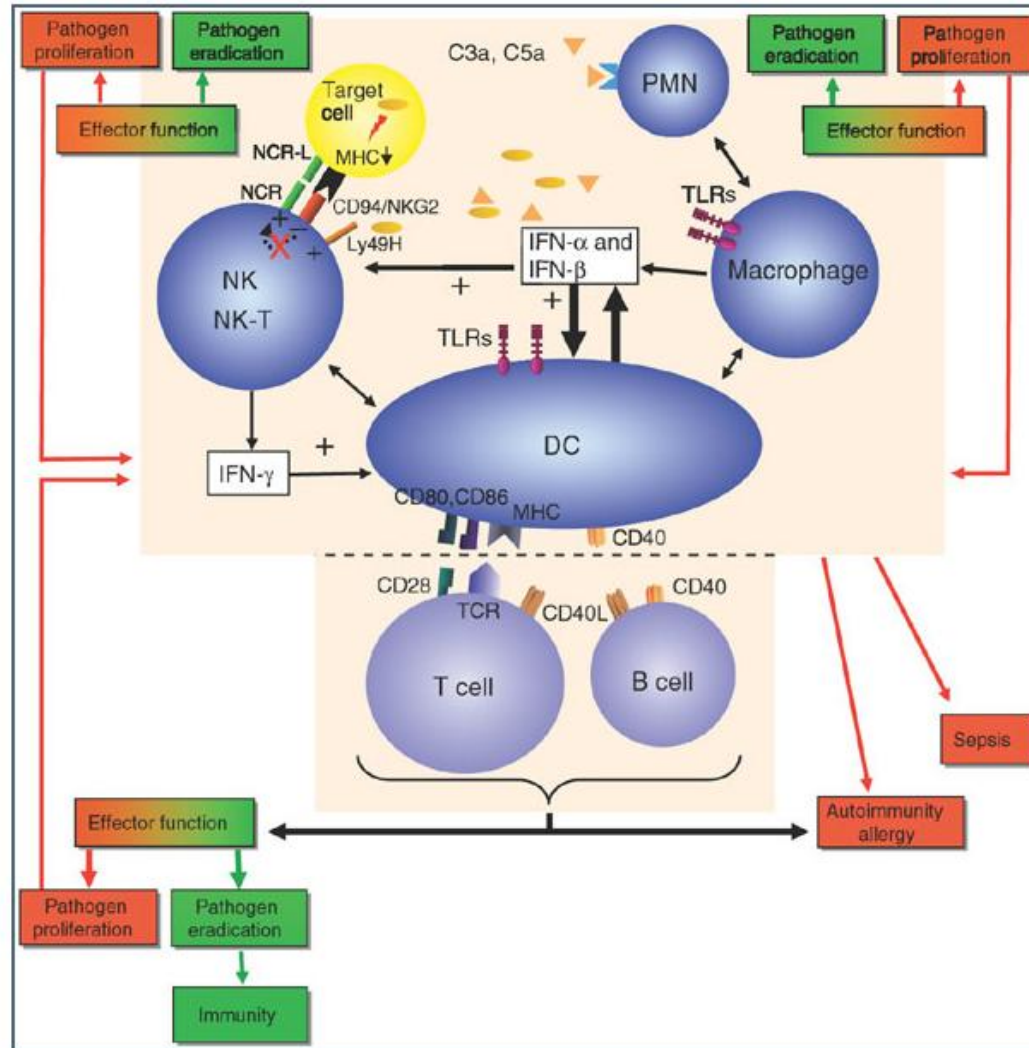
# Protein-Misfolding in TRAPS



**Table 1. Clinical Classification of Selected Autoinflammatory Diseases**

Disease	Gene (Protein)	Proposed Mechanism*
<b>Hereditary Recurrent Fevers</b>		
Familial Mediterranean fever (FMF)	<i>MEFV</i> (pyrin)	Increased inflammasome activation
TNF receptor-associated periodic syndrome (TRAPS)	<i>TNFRSF1A</i> (TNFR1)	Protein misfolding
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)	<i>MVK</i> (mevalonate kinase)	Increased inflammasome activation
Familial cold autoinflammatory syndrome (FCAS)	<i>NLRP3/CIAS1</i> (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
Muckle-Wells syndrome (MWS)	<i>NLRP3/CIAS1</i> (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
Neonatal-onset multisystem inflammatory disease (NOMID)	<i>NLRP3/CIAS1</i> (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
<b>Idiopathic Febrile Syndromes</b>		
Systemic onset juvenile idiopathic arthritis (SoJIA)	Complex	Unknown
Adult-onset Still's disease	Complex	Unknown
Schnitzler syndrome	Sporadic?	Increased inflammasome activation
<b>Pyogenic Disorders</b>		
Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA)	<i>PSTPIP1/CD2BP1</i> (PSTPIP1/CD2BP1)	Abnormal PSTPIP1 binding to pyrin causing increased IL-1 $\beta$ activation
<b>Granulomatous Diseases</b>		
Chronic granulomatous synovitis with uveitis and cranial neuropathy (Blau syndrome)	<i>NOD2/CARD15</i> (NOD2/CARD15)	NF- $\kappa$ B activation disorder
Crohn's disease	Complex ( <i>NOD2</i> , <i>ATG16L1</i> , <i>IRGM</i> )	NF- $\kappa$ B activation disorder
<b>Autoinflammatory Disorders of Skin and Bone</b>		
Deficiency in IL-1 receptor antagonist (DIRA)	<i>IL1RN</i> (IL-1Ra)	Absence of negative regulator of IL-1 $\alpha$ and IL-1 $\beta$
Majeed syndrome	<i>LPIN2</i> (Lipin-2)	Unknown
Chronic recurrent multifocal osteomyelitis (CRMO)	Complex	Unknown
Synovitis acne pustulosis hyperostosis osteitis (SAPHO)	Complex	Unknown
<b>Metabolic Disorders</b>		
Gout (monosodium urate deposition)	Complex ( <i>SLC2A9/GLUT9</i> , <i>ABCG2</i> )	Crystal-induced inflammasome activation
Pseudogout (calcium pyrophosphate dihydrate deposition)	Complex	Crystal-induced inflammasome activation
Type 2 diabetes mellitus	Complex	Hyperglycemia-induced inflammasome activation
<b>Complement Disorders</b>		
Atypical hemolytic-uremic syndrome (aHUS)	<i>CFH</i> (complement factor H), <i>MCP</i> (CD46), <i>CFI</i> (complement factor I), <i>CFB</i> (complement factor B)	Abnormal regulation of C3b
Age-related macular degeneration	Complex, <i>CFH</i>	Impaired inactivation of C3b
<b>Vasculitis</b>		
Behçet's disease	Complex	Unknown
<b>Macrophage Activation Syndromes</b>		
Familial hemophagocytic lymphohistiocytosis (HLH)	<i>UNC13D</i> (Munc13-4), <i>PRF1</i> (perforin 1), <i>STX11</i> (syntaxin 11)	Impaired efficacy of cytotoxic T lymphocytes with compensatory macrophage activation
Secondary HLH	Complex	Unknown
<b>Storage Diseases</b>		
Gaucher's disease	<i>GBA</i> (acid $\beta$ -glucosidase)	Unknown
Atherosclerosis?	Complex	Unknown
<b>Fibrosing Diseases</b>		
Asbestosis/silicosis	Complex	Particle-induced inflammasome activation

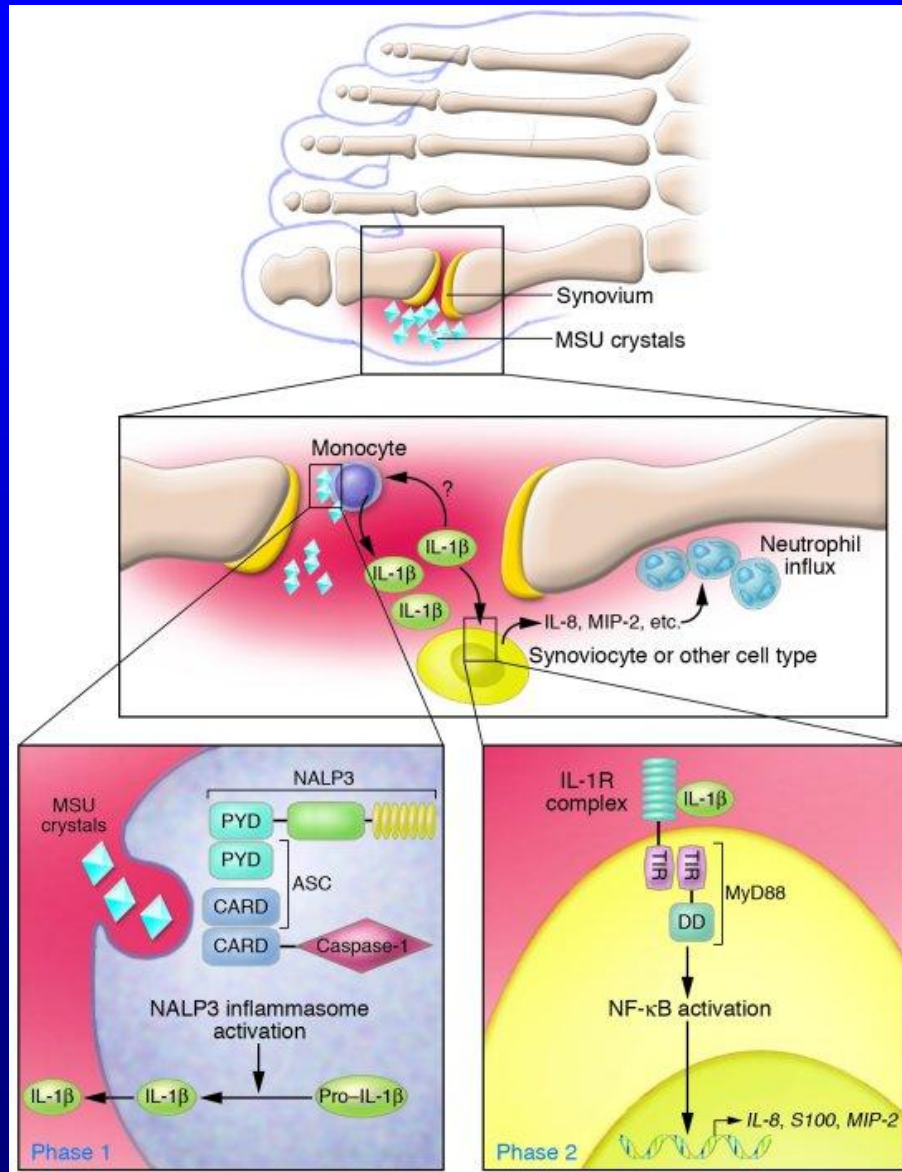
# Adaptive and Innate Immunity



**Table 1. Clinical Classification of Selected Autoinflammatory Diseases**

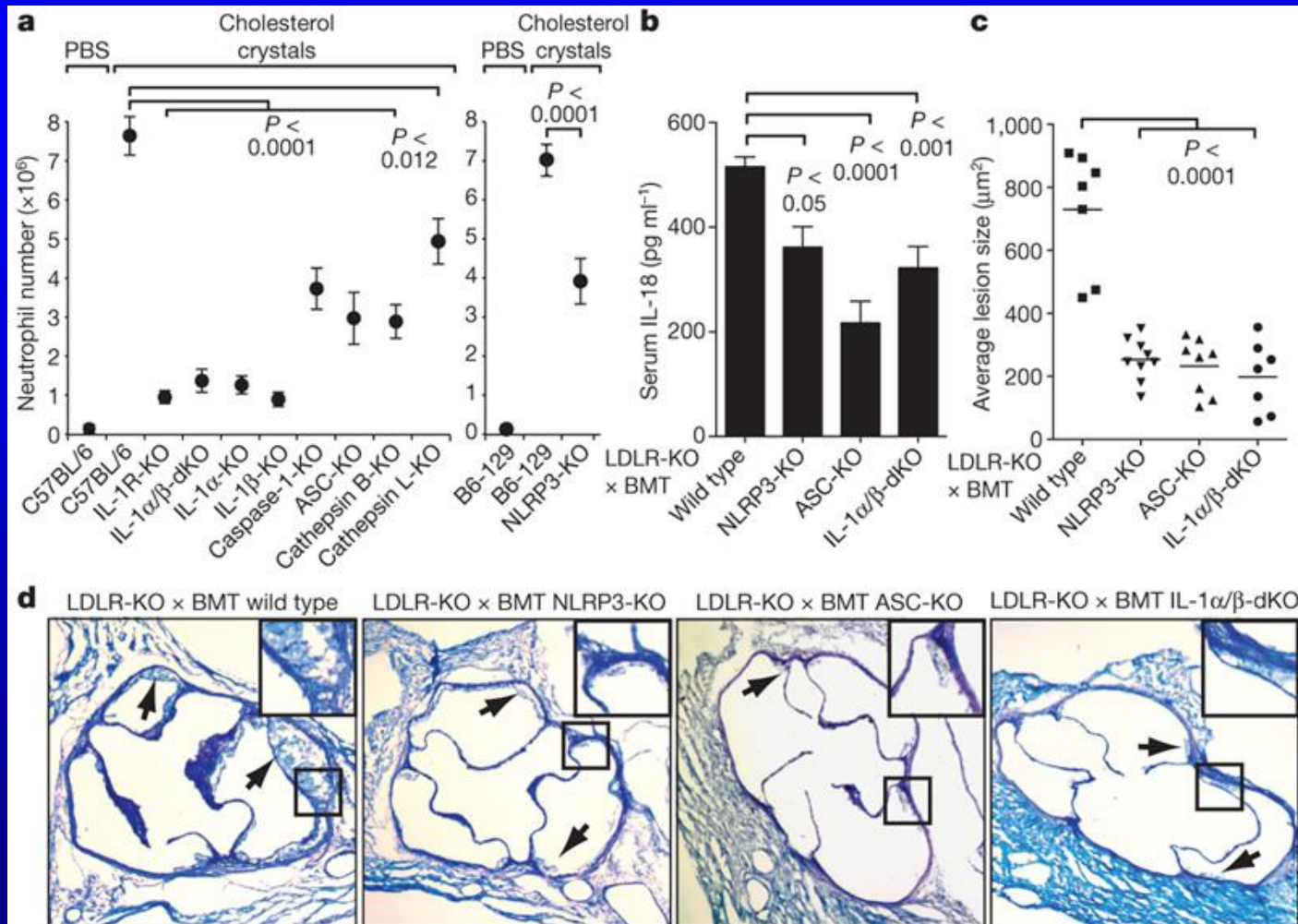
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Adult-onset Still's disease	Complex	Unknown
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Crohn's disease	Complex ( <i>NOD2</i> , <i>ATG16L1</i> , <i>IRGM</i> )	NF- $\kappa$ B activation disorder
<b>Autoinflammatory Disorders of Skin and Bone</b>		
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Majeed syndrome	<i>LPIN2</i> (Lipin-2)	Unknown
Chronic recurrent multifocal osteomyelitis (CRMO)	Complex	Unknown
Synovitis acne pustulosis hyperostosis osteitis (SAPHO)	Complex	Unknown
<b>Metabolic Disorders</b>		
Gout (monosodium urate deposition)	Complex ( <i>SLC2A9/GLUT9</i> , <i>ABCG2</i> )	Crystal-induced inflammasome activation
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Type 2 diabetes mellitus	Complex	Hyperglycemia-induced inflammasome activation
<b>Complement Disorders</b>		
Atypical hemolytic-uremic syndrome (aHUS)	<i>CFH</i> (complement factor H), <i>MCP</i> (CD46), <i>CFI</i> (complement factor I), <i>CFB</i> (complement factor B)	Abnormal regulation of C3b
Age-related macular degeneration	Complex, <i>CFH</i>	Impaired inactivation of C3b
<b>Vasculitis</b>		
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Familial hemophagocytic lymphohistiocytosis (HLH)	<i>UNC13D</i> (Munc13-4), <i>PRF1</i> (perforin 1), <i>STX11</i> (syntaxin 11)	Impaired efficacy of cytotoxic T lymphocytes with compensatory macrophage activation
Secondary HLH	Complex	Unknown
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Atherosclerosis?	Complex	Unknown
<b>Fibrosing Diseases</b>		
Asbestosis/silicosis	Complex	Particle-induced inflammasome activation

# Gout as an Autoinflammatory Disease



Martinon and Glimcher *JCI*  
116:2073-2075, 2006

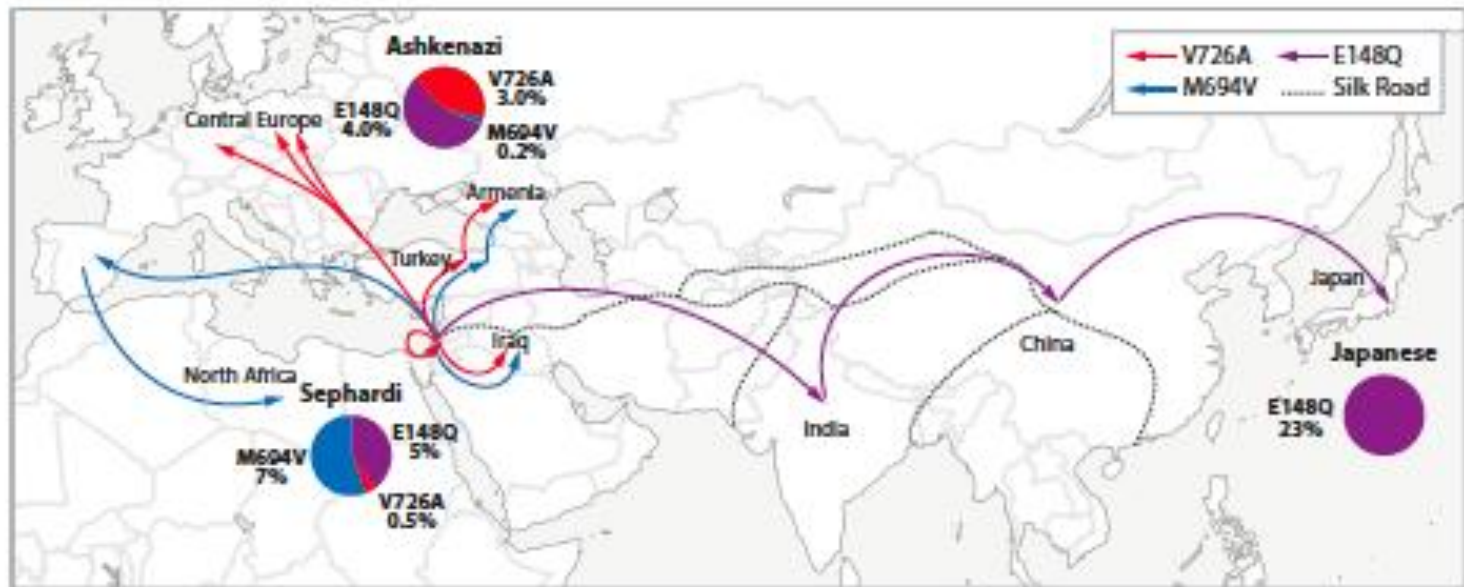
# Atherosclerosis as an Autoinflammatory Disease



Duewell *et al.* *Nature* 464:1357-1361, 2010

# MEFV Mutations: The Case for Selection

a



b

Predicted structure of the pyrin B30.2/SPRY domain



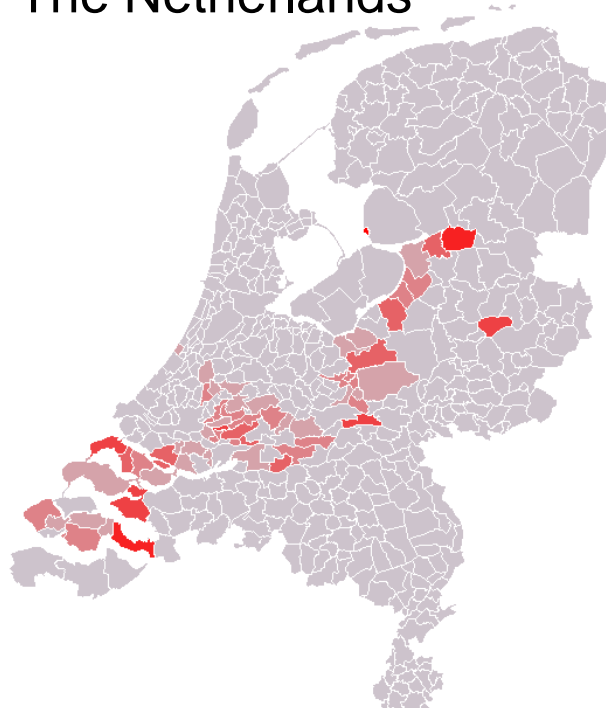
# Frequency of the mutation in the founder population

	<b>p.N52Kfs25 c.156-157delCA</b>	<b>p. E77X c.229G&gt;T</b>	<b>p.Q54X c.160C&gt;T</b>	<b>175kB deletion</b>
<b><i>Caucasian Controls (NY)</i></b>	Neg in 364 DNA samples	Neg in 364 DNA samples	Neg in 364 DNA samples	Neg in 364 DNA samples
<b><i>Population of origin</i></b>	2:555 DNA samples	0:351 DNA samples	Not done	3:119 DNA samples

Newfoundland 0.4%



The Netherlands



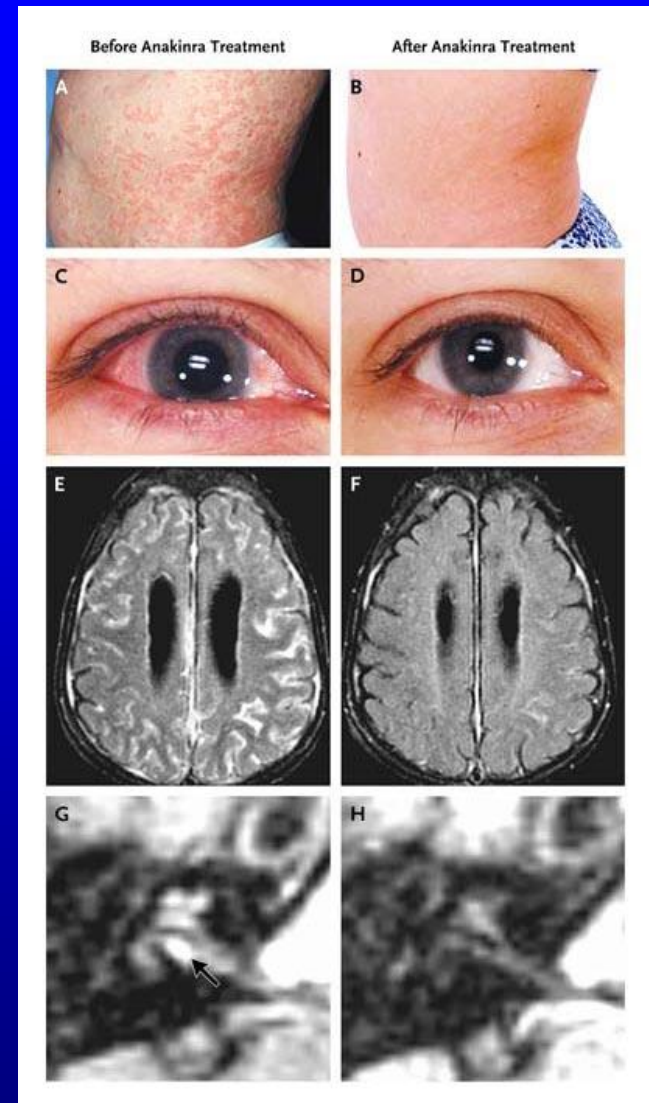
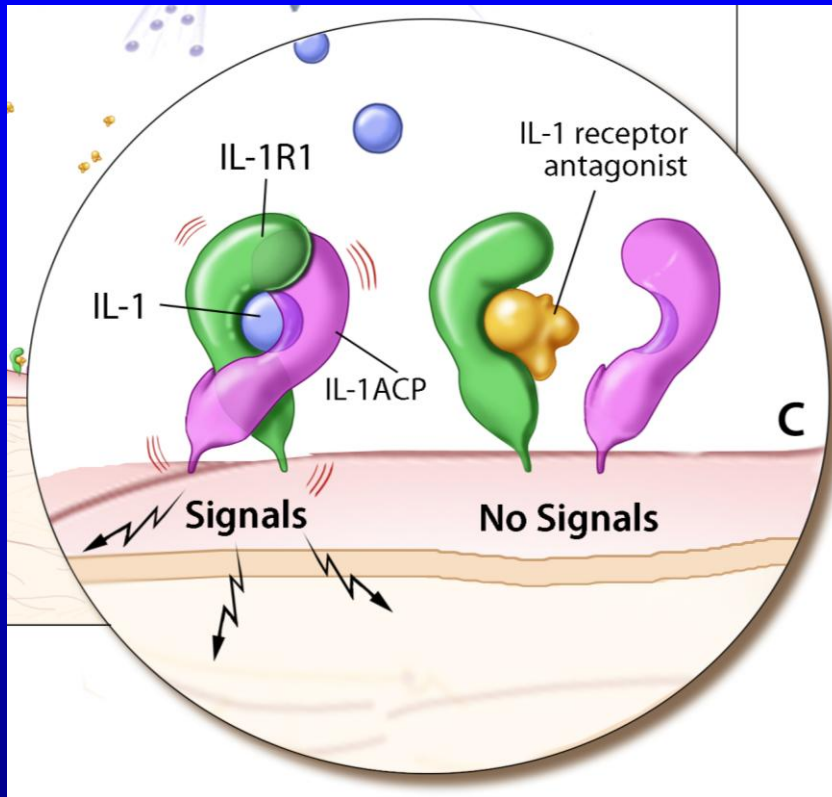
Puerto Rico 2.6%







# Treatment of 18 NOMID Patients with the IL-1 Receptor Antagonist Anakinra



# Anakinra Treatment of DIRA



Age 9 months,  
before therapy

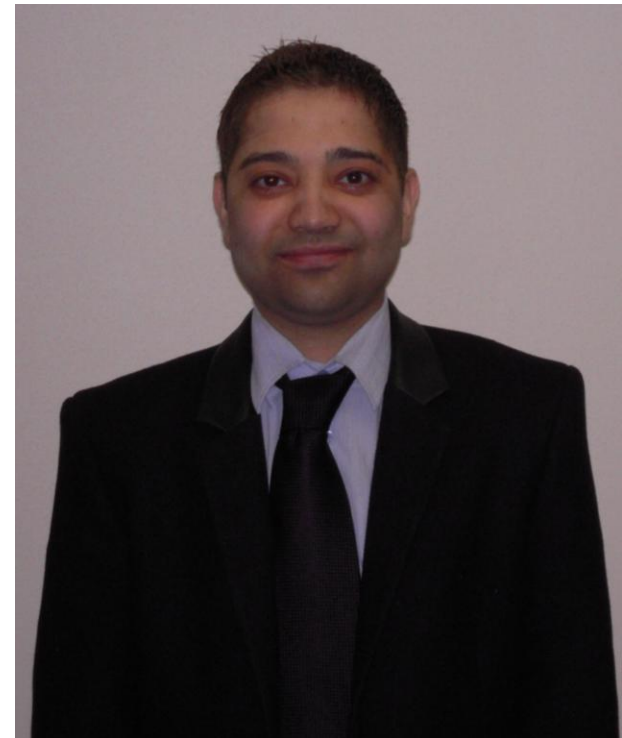
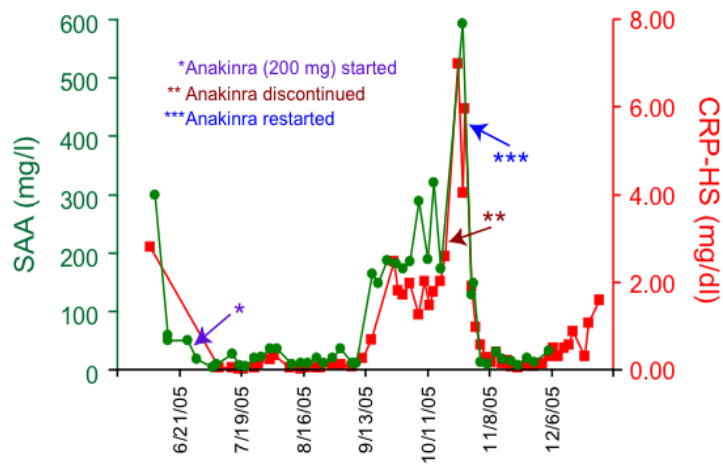
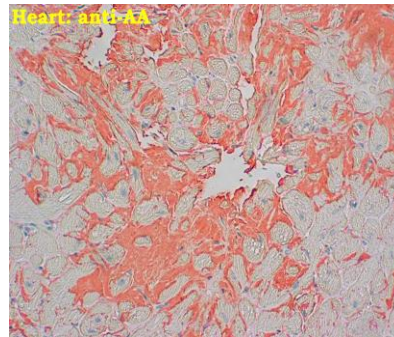
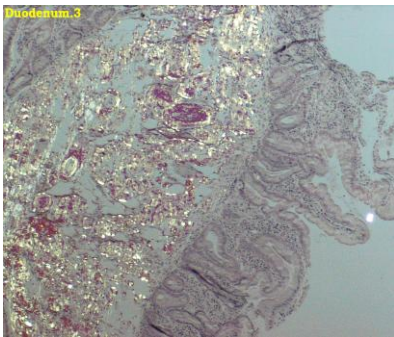
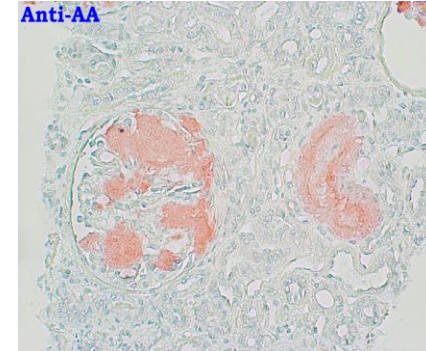
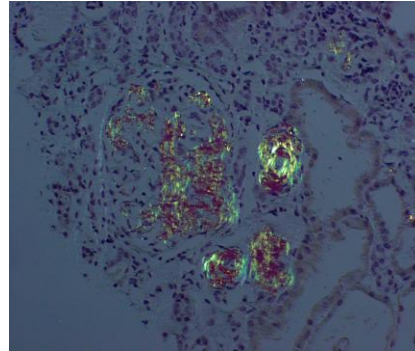
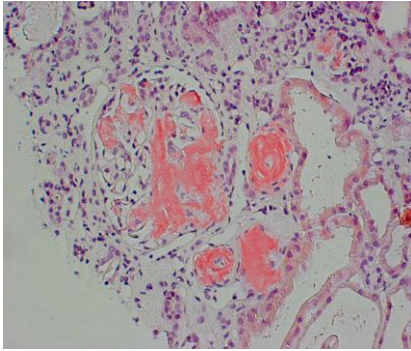


3 days post  
treatment initiation

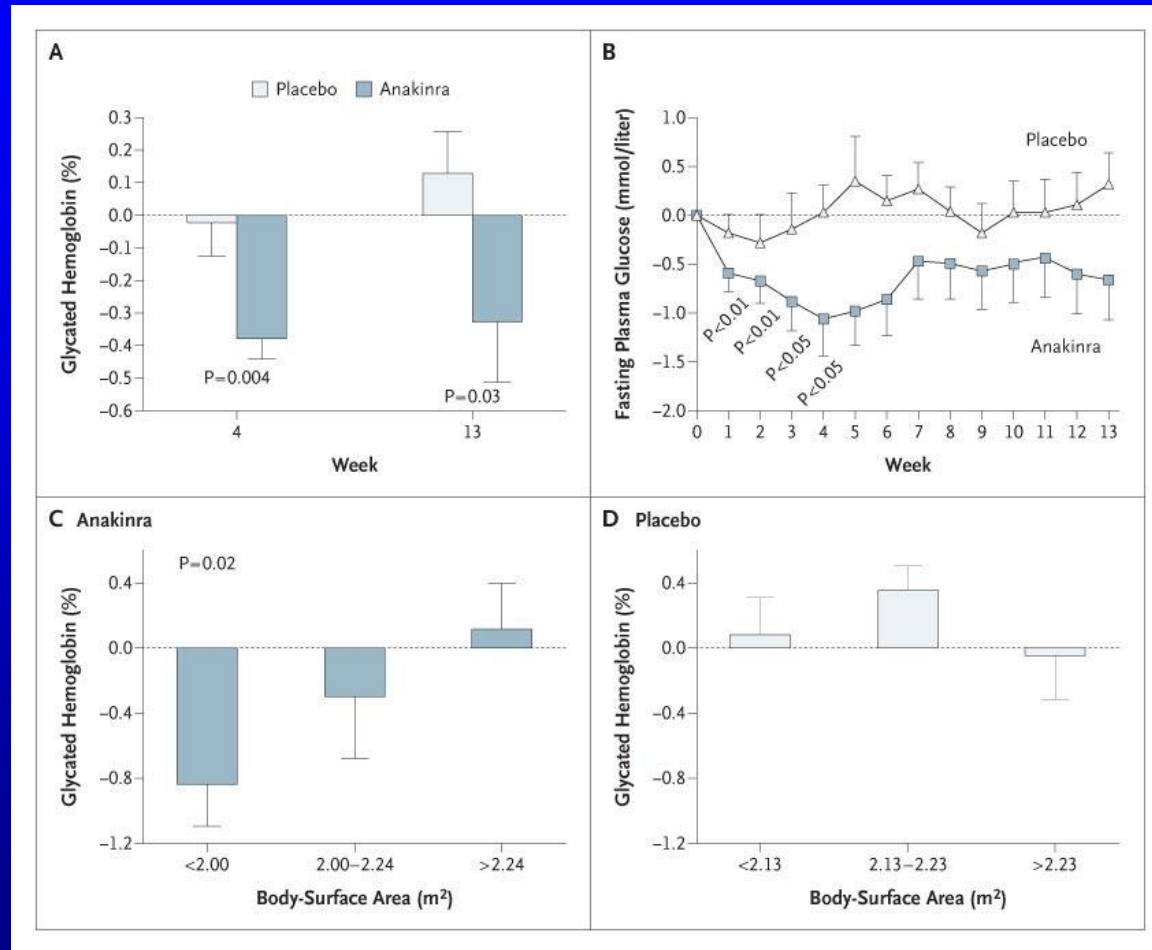


7 days post  
treatment initiation

# IL-1 Inhibition in FMF Amyloidosis



# Type 2 Diabetes Mellitus as an Autoinflammatory Disease



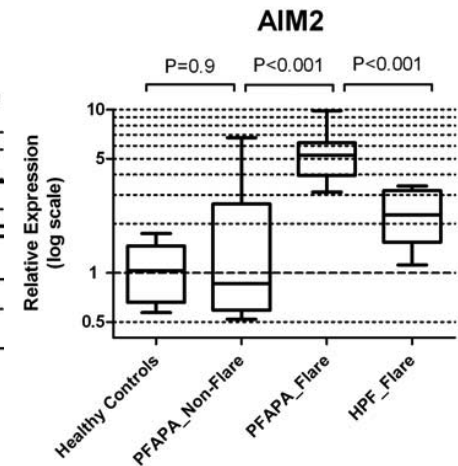
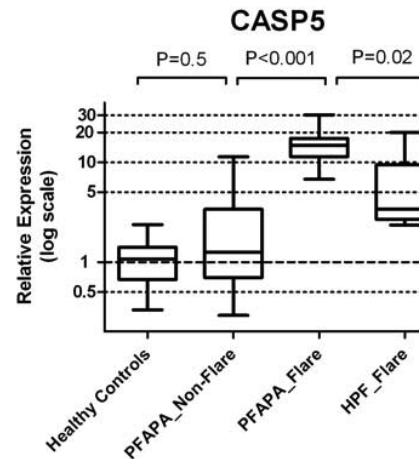
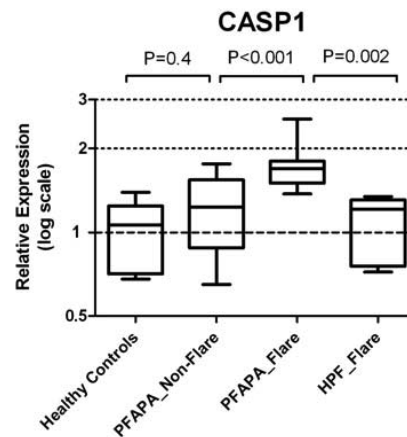
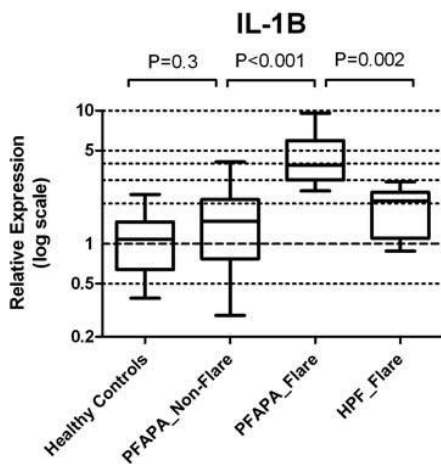
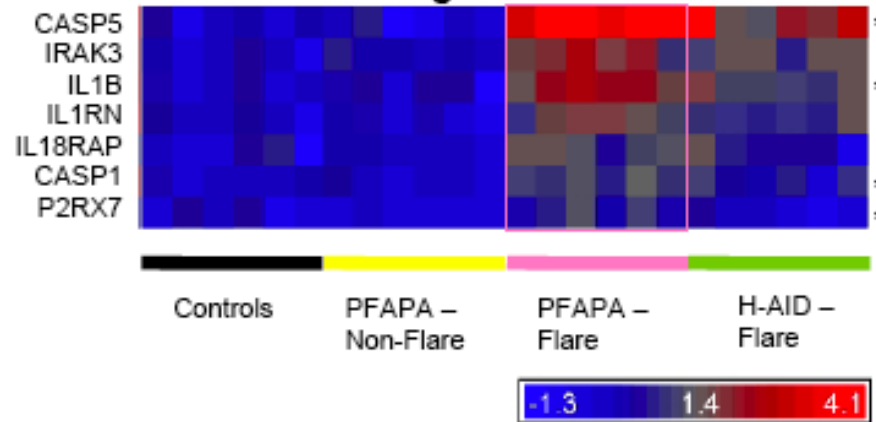
Larsen CM et al. *N Engl J Med* 356:1517-1526, 2007



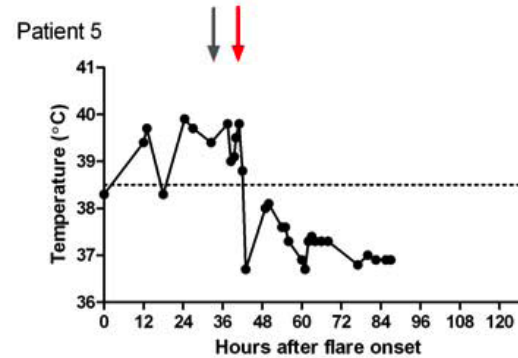
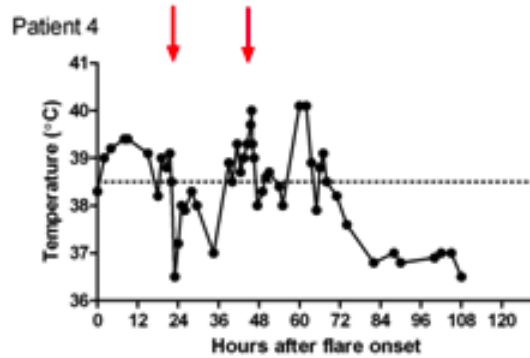
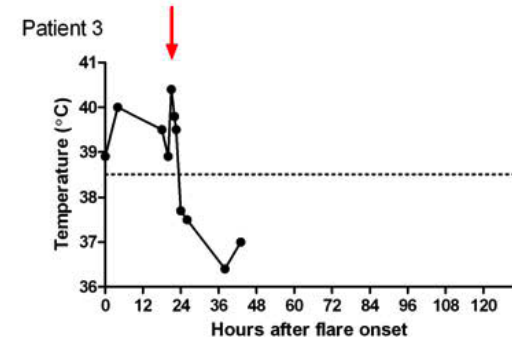
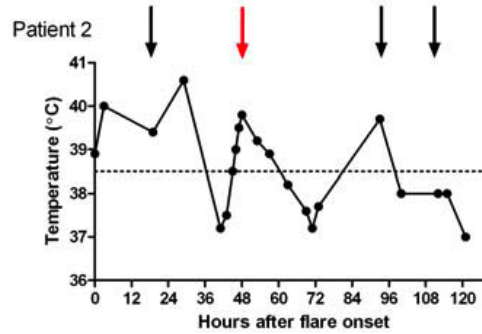
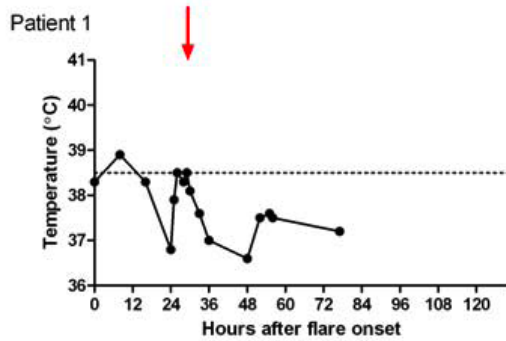
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# An Inflammasome Signature in PFAPA Flares

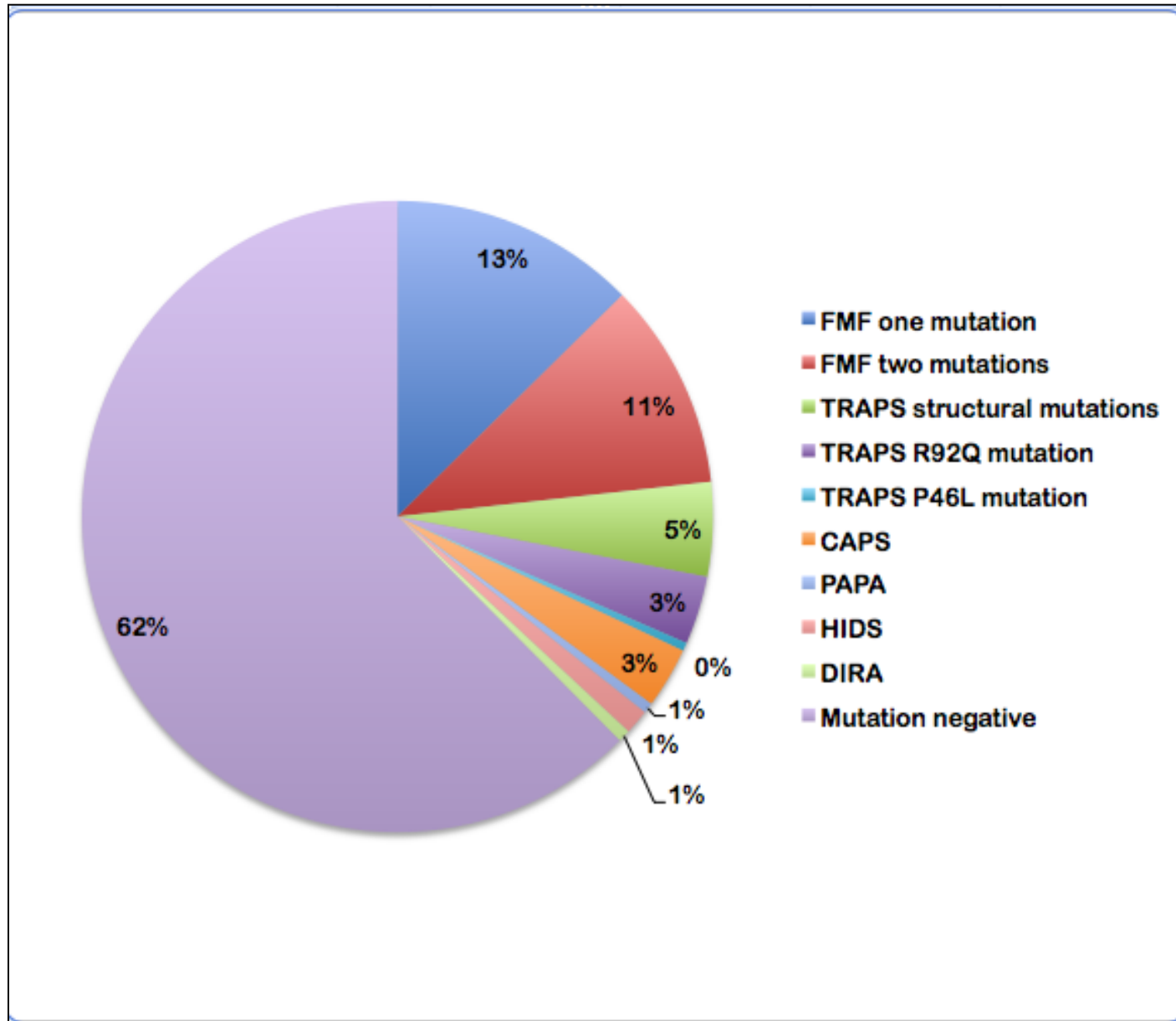
## IL-1 $\beta$ - and inflammasome - associated genes



# Anakinra in PFAPA



# The NIH Autoinflammatory Cohort





# NIH Intramural Research Program



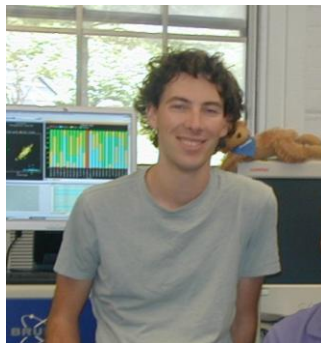
Ivona Aksentijevich



Raphaela  
Goldbach-Mansky



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Elaine Remmers

# NHGRI Inflammatory Disease Section, 2010



“It’s a genome world . . . .”

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