From Gene to Treatment in Rare Inflammatory Disease: Importance of Families

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Disclosures

- *Consultant/Speaker for Novartis pharmaceuticals*

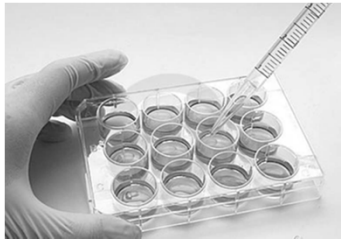
Translational Approach

Patients / Families

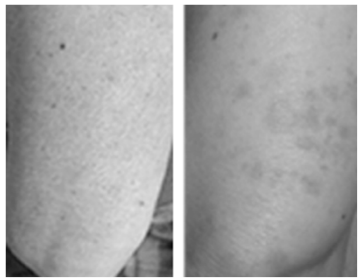
Disease Characterization

Genetic Studies

In vitro or Ex vivo studies



In vivo studies

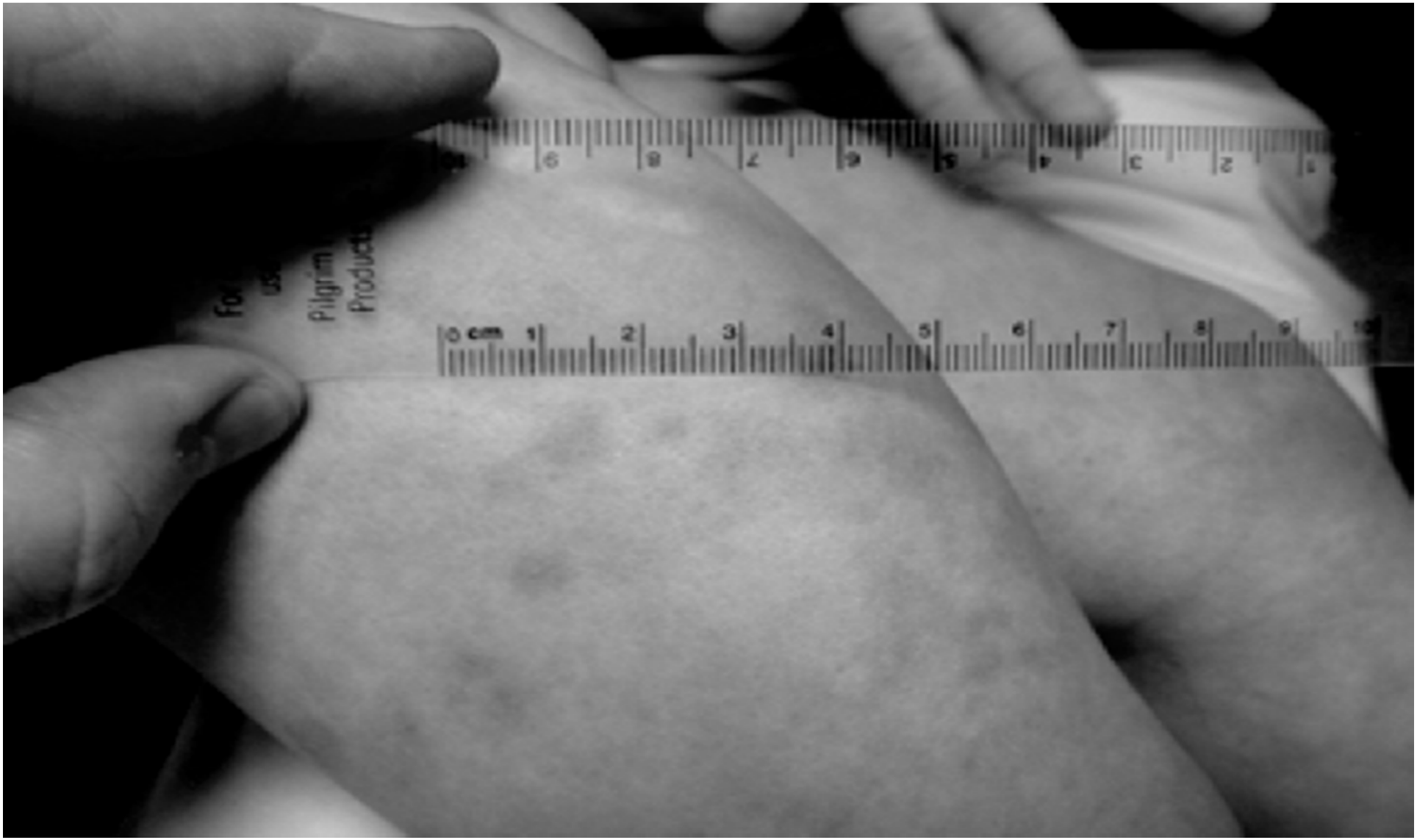


Therapeutic Studies

Outline

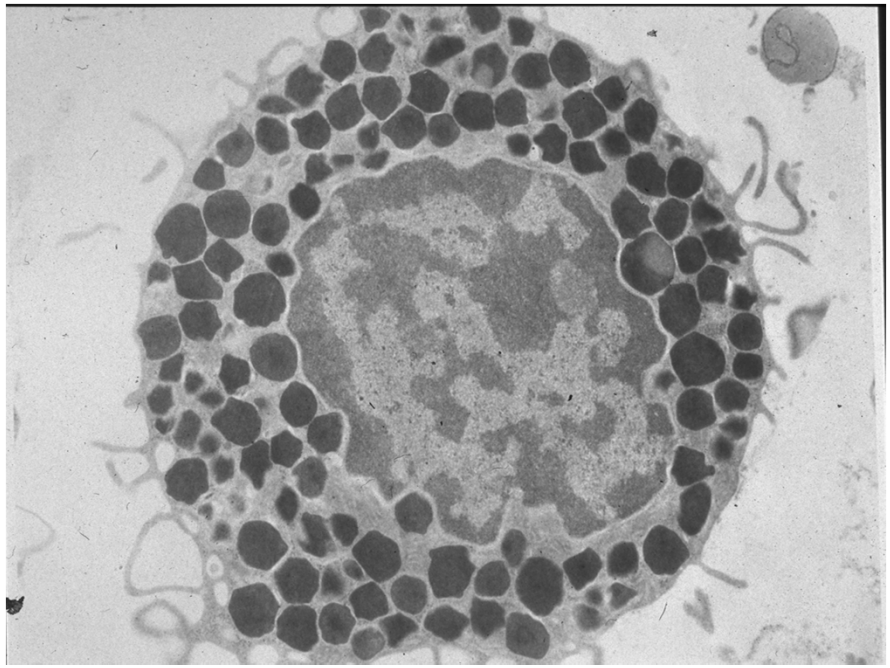
- A patient with cold induced rash
- Proven methods of gene identification
- Gene to Disease mechanisms
- Disease mechanisms to therapy

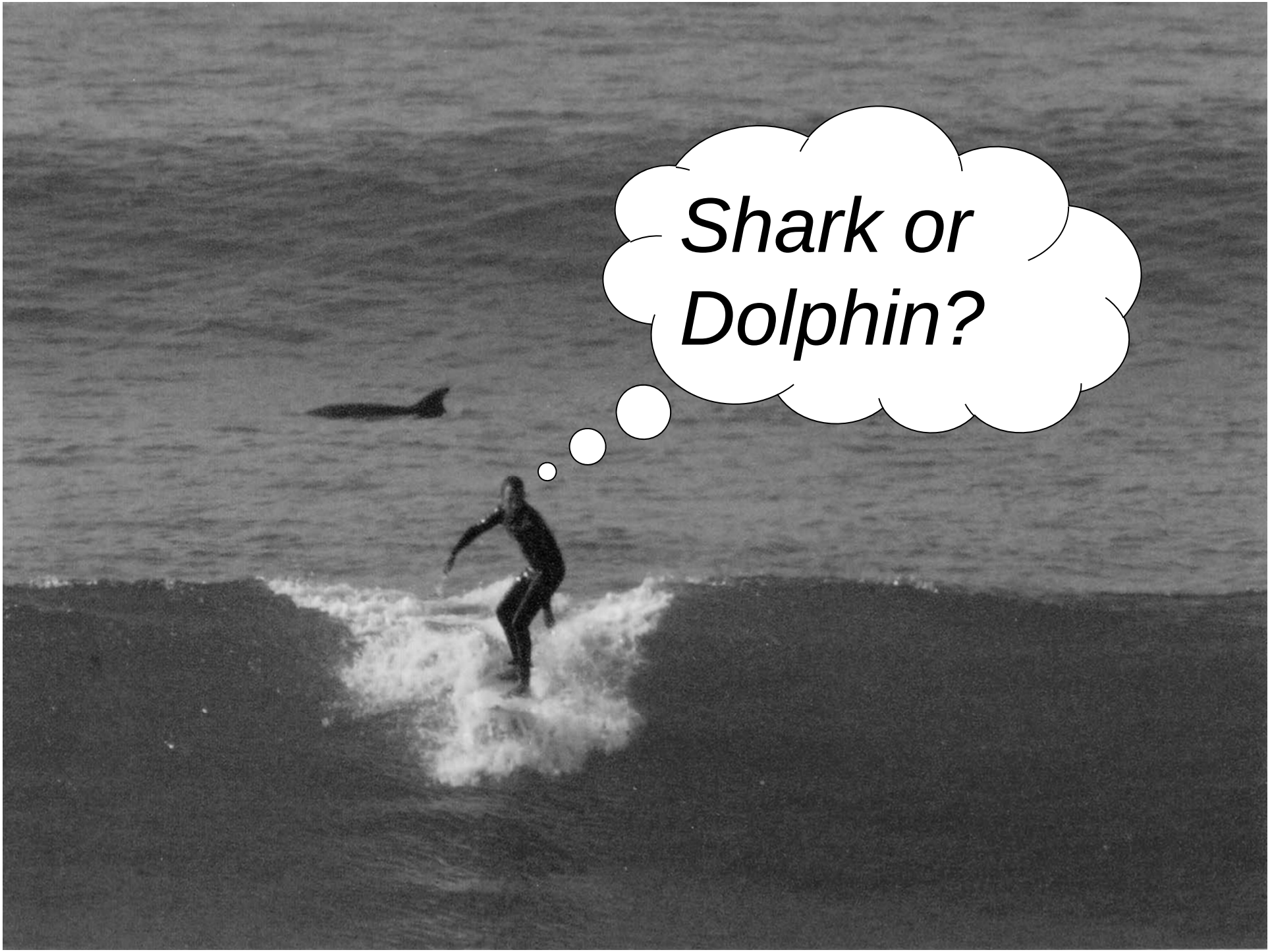
3 y/o girl with rash after cold exposure



Cold Urticaria?

- Acute hives with direct cold exposure
- Usually presents in adolescents or adults
- May present with systemic anaphylaxis
- Involvement of histamine and mast cells




Shark or
Dolphin?

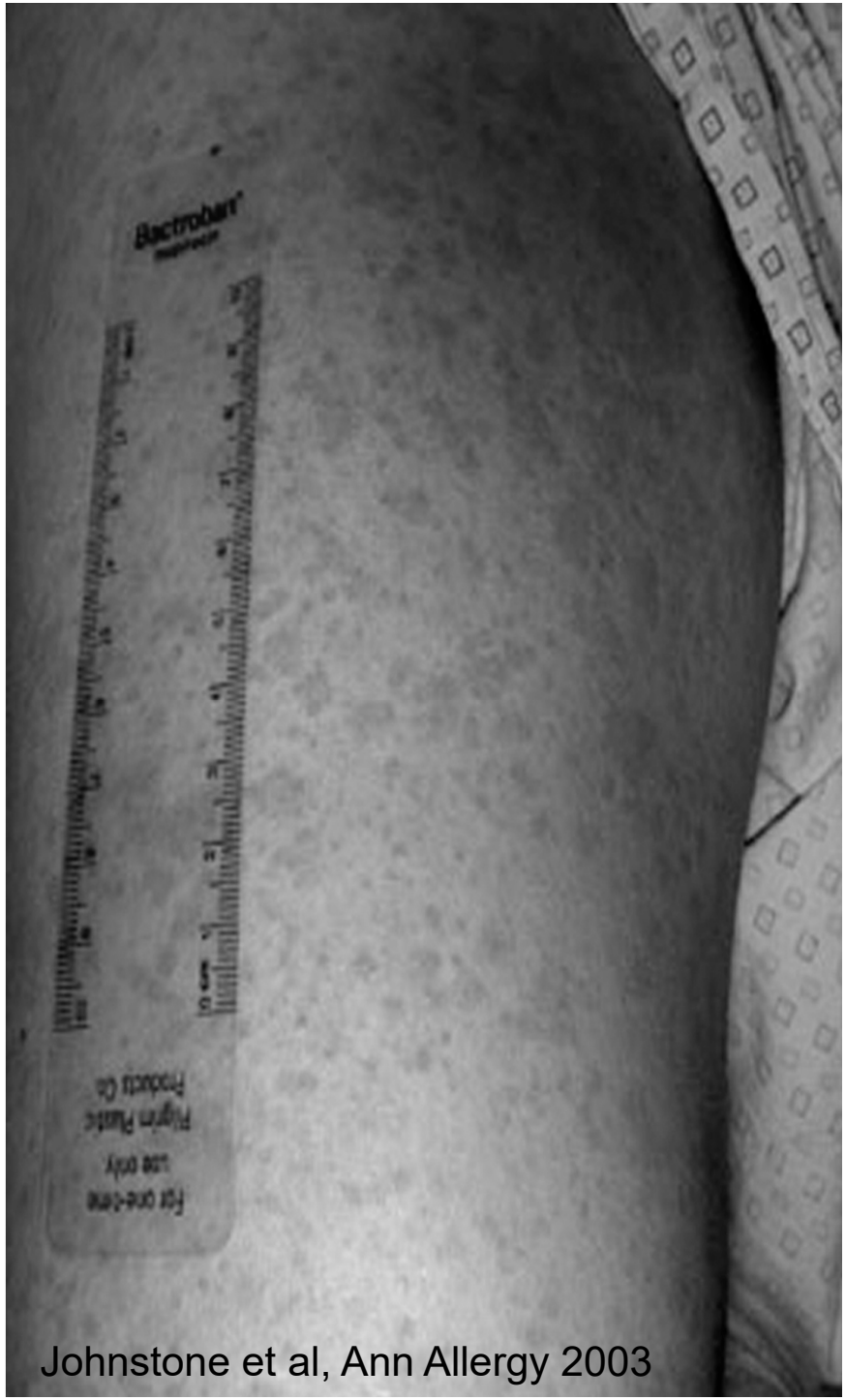
It's NOT cold urticaria

- Rash develops hours after generalized cold exposure
- Associated symptoms include fever, joint pain/swelling and eye redness/pain
- Antihistamines don't work
- Age of onset at birth
- Significant family history

Rash was present at birth

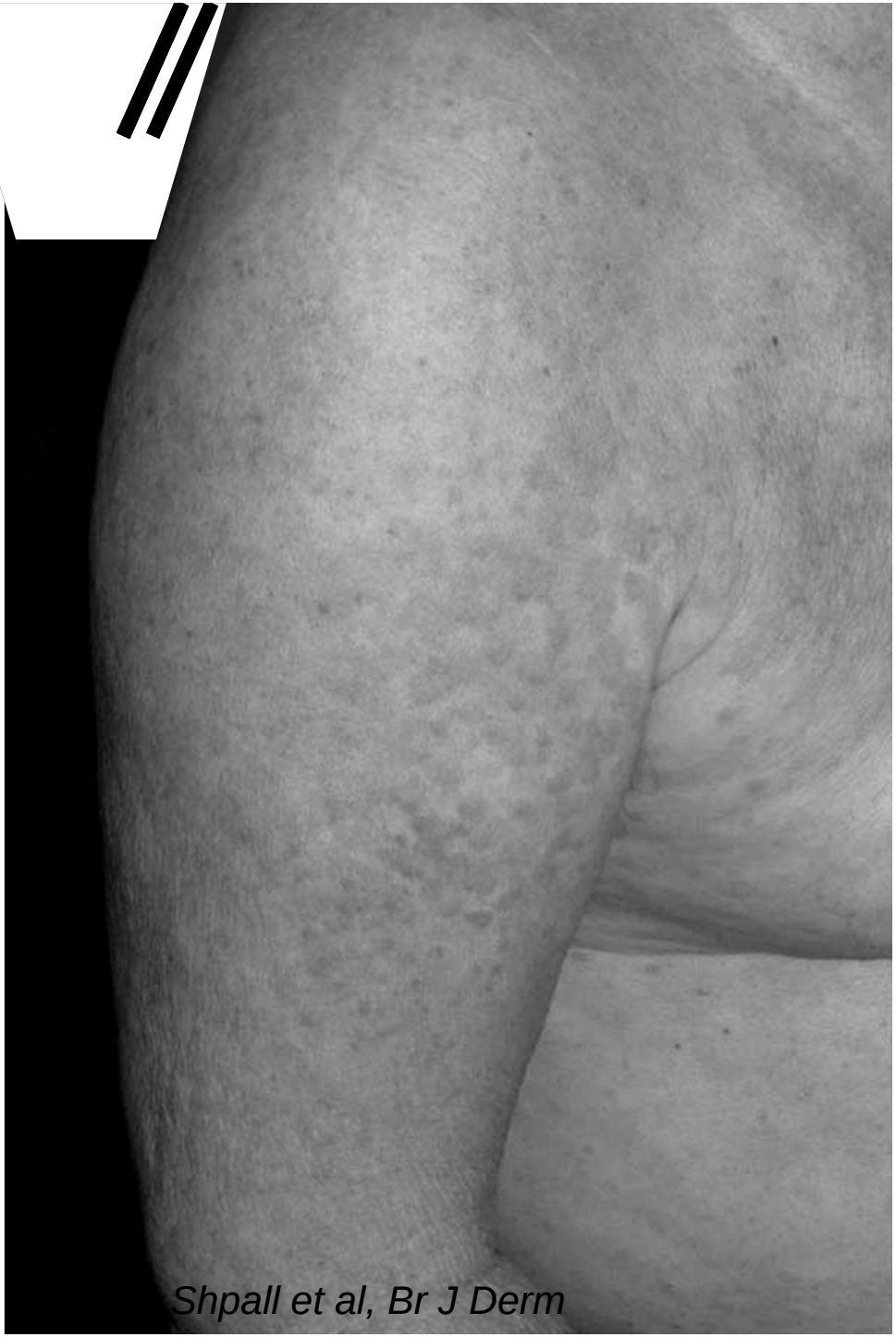
C. Fikkert, M.D.

32 year old mother with same history

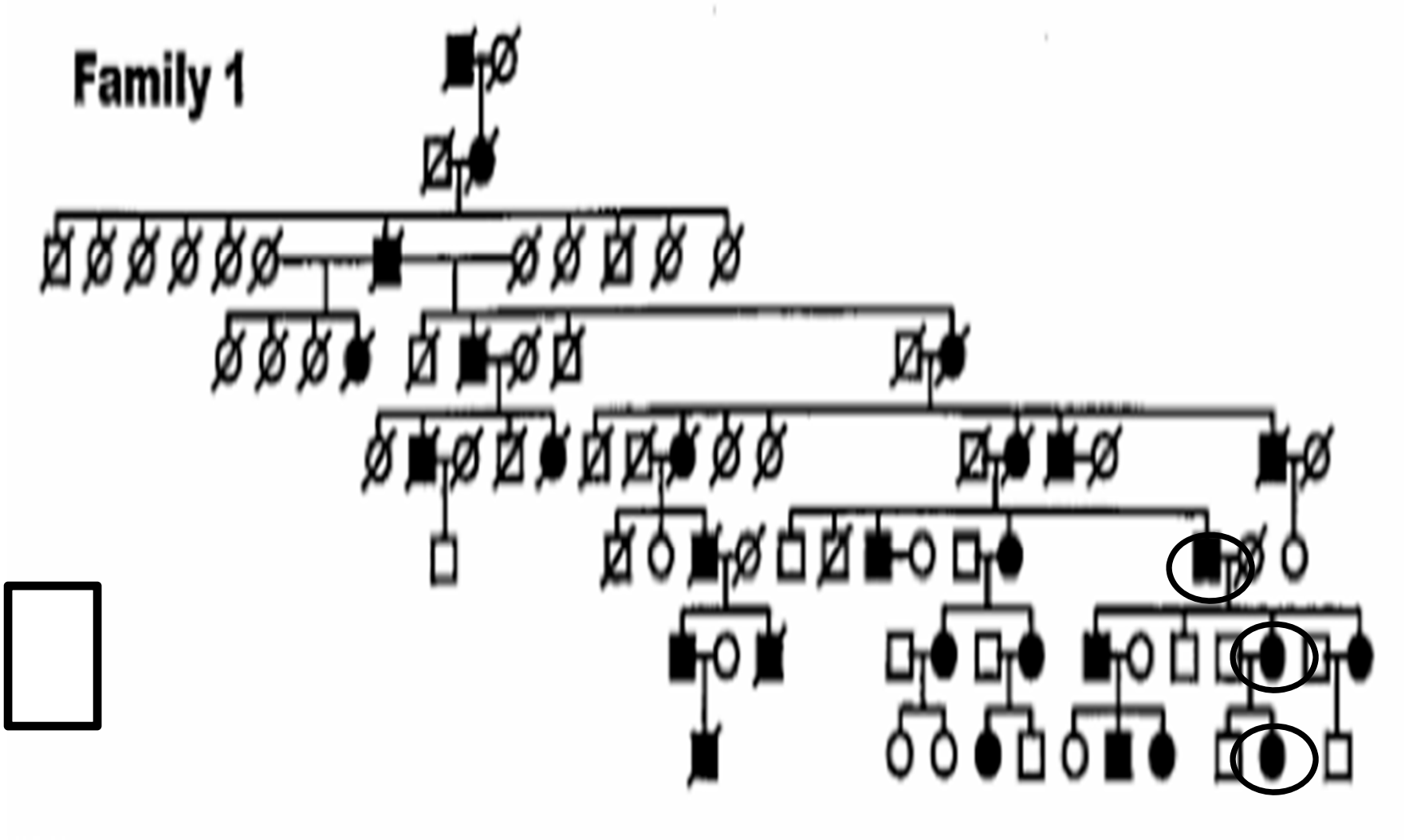


Johnstone et al, Ann Allergy 2003

66 year old grandfather with same rash



Family History



Hereditary Fever Disorders
Autoinflammatory Syndromes

- **Familial Mediterranean fever (FMF)**
- **Hyper IgD syndrome (HIDS)**
- **TNF Receptor Assoc. Periodic Syndrome (TRAPS)**

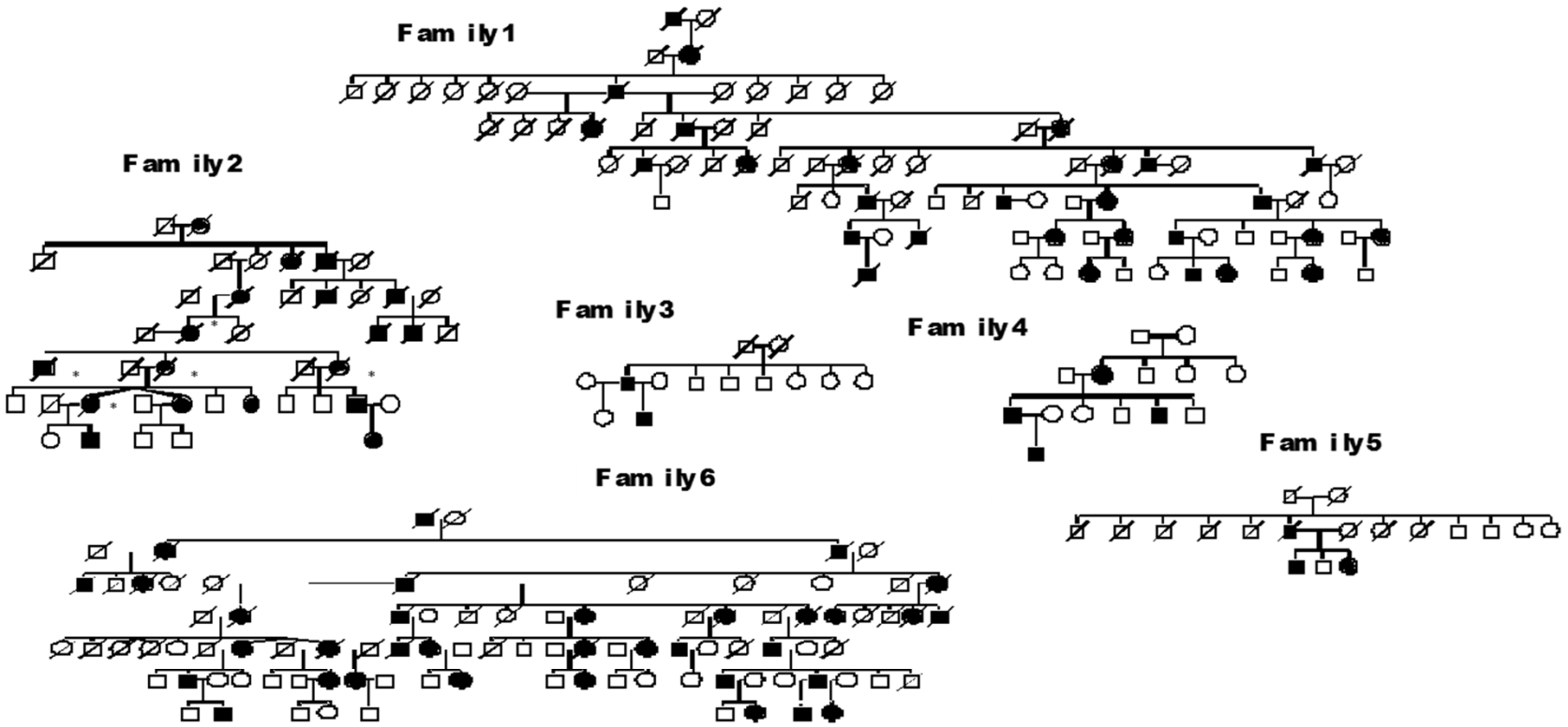
All are characterized by recurrent episodes of fever, rash, and joint pain


Hoffman Syndrome
Familial Cold Autoinflammatory Syndrome

Autoinflammatory Diseases Genetics

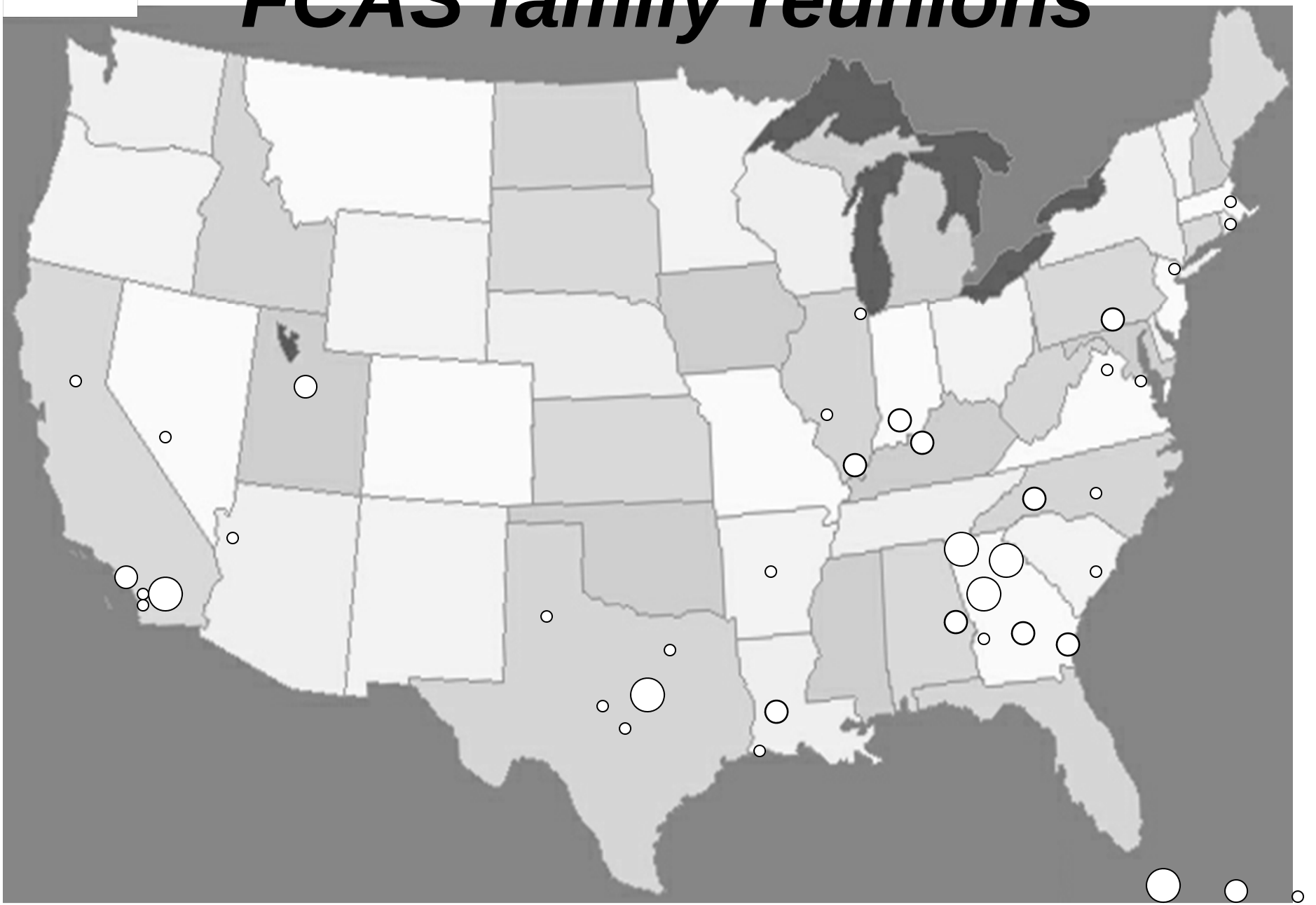
- **Gene for Familial Mediterranean Fever (FMF) was discovered in 1997**
  - **MEFV - Pyrin**
- **Gene for Hyper IgD syndrome (HIDS) was discovered in 1999**
  - **MVK - Mevalonate Kinase**
- **Gene for TNF receptor associated periodic syndrome (TRAPS) was discovered in 1999**
  - **TNFSRIA - TNF Receptor p55**
- **Gene for Familial Cold Autoinflammatory Syndrome ?**

FCAS Pedigrees



Hoffman et al, JACI 2001

FCAS family reunions



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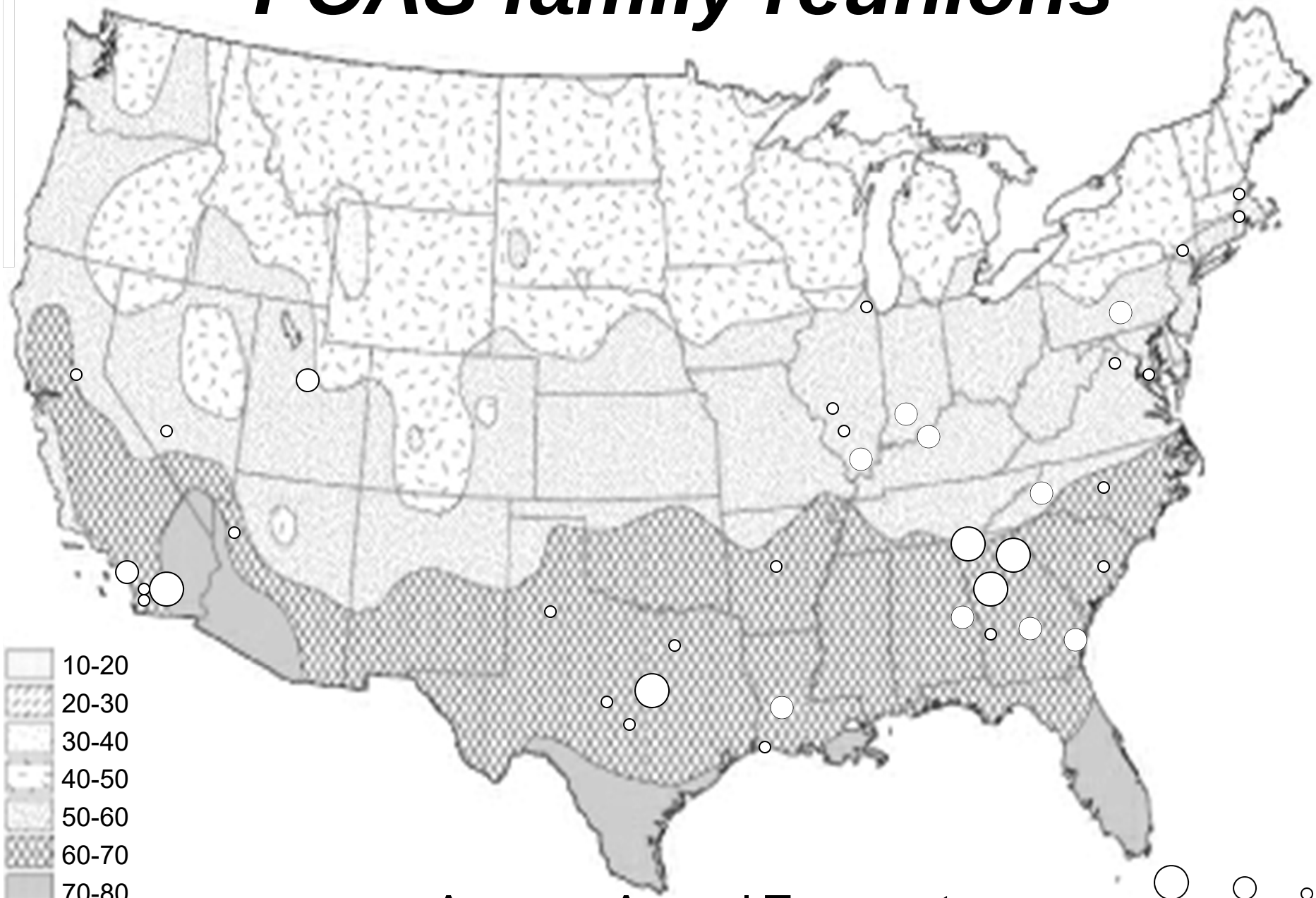
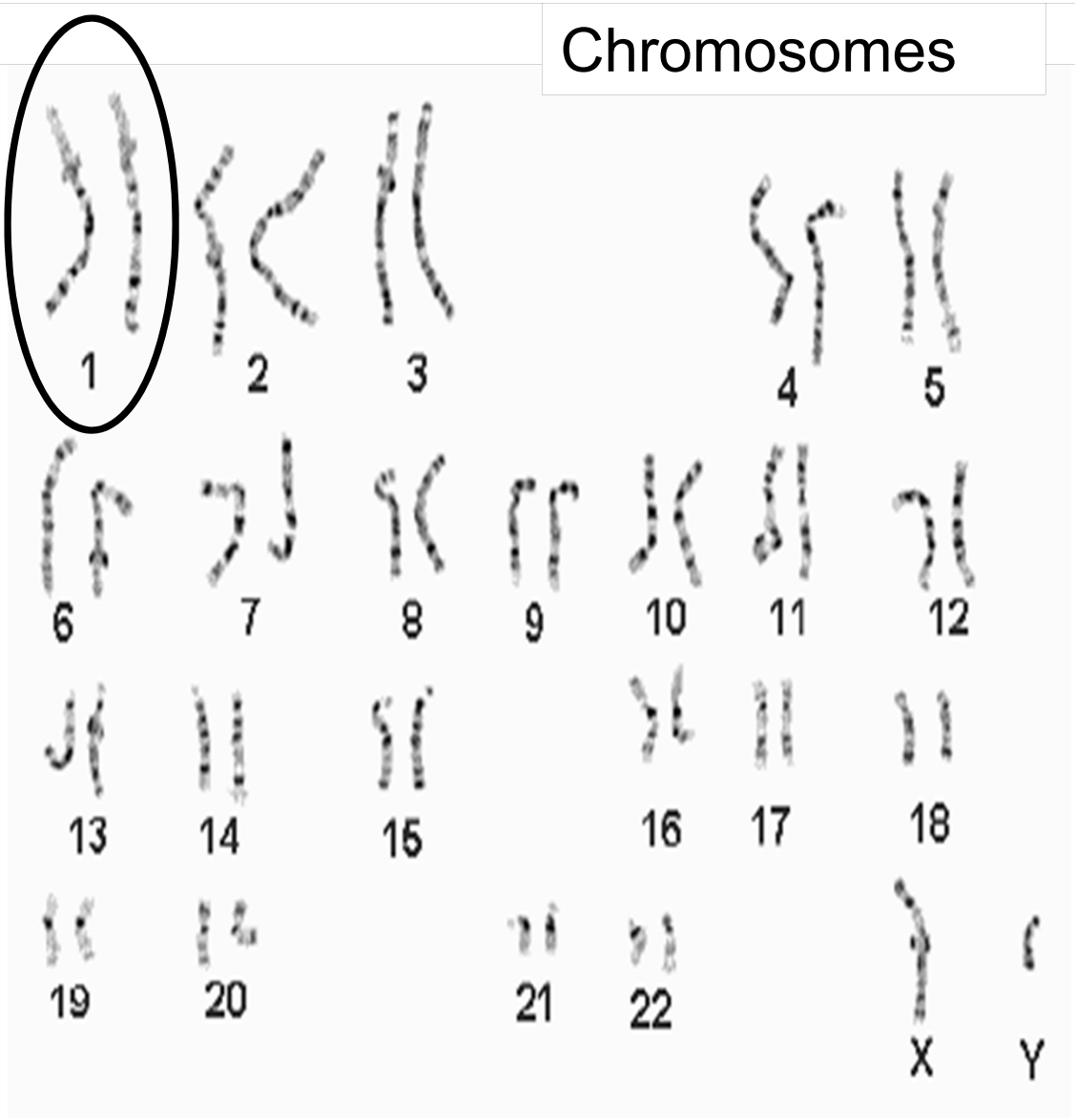
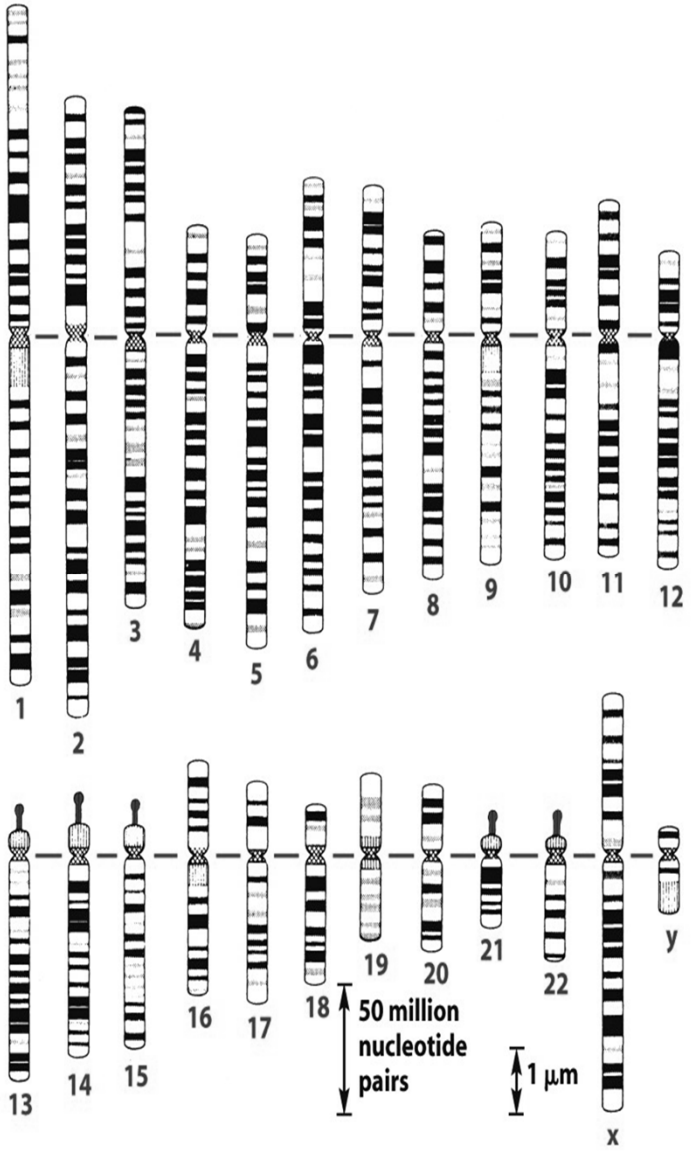


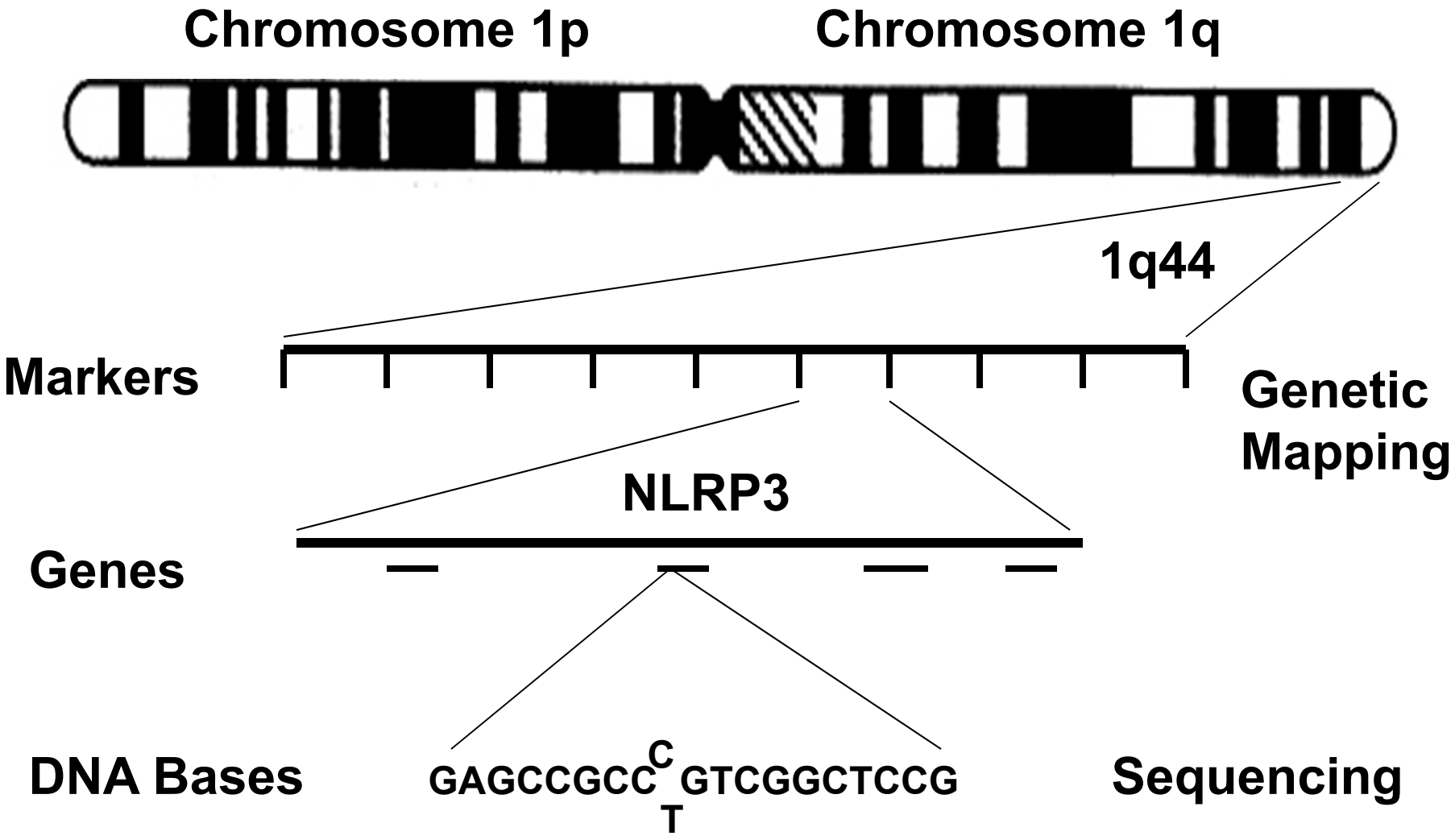
Human Genome

Chromosomes





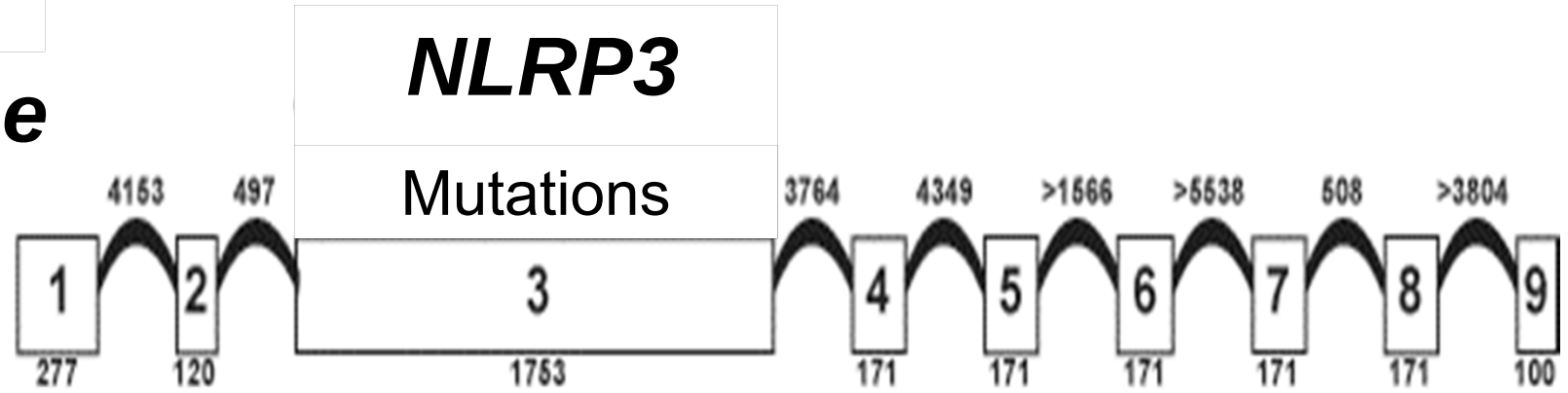
Positional Cloning



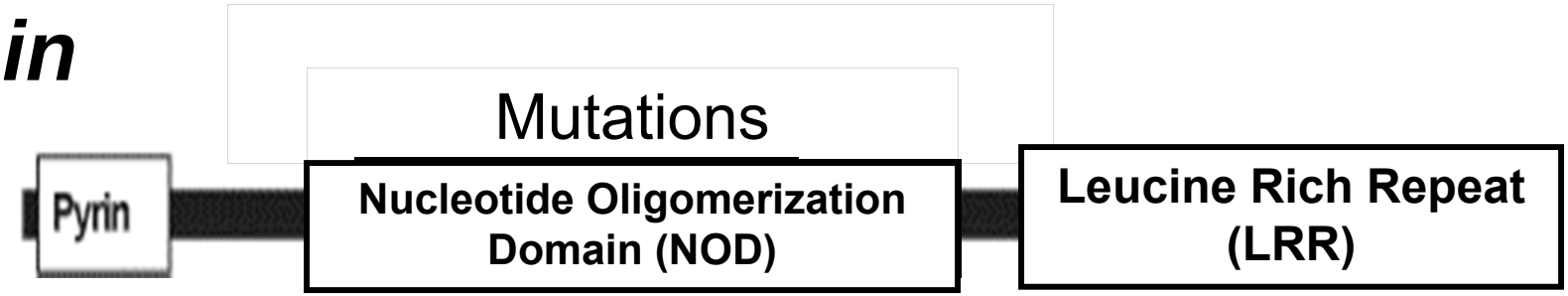
Heterozygous *NLRP3* mutations in FCAS patients

Gene and Protein Structure

Gene



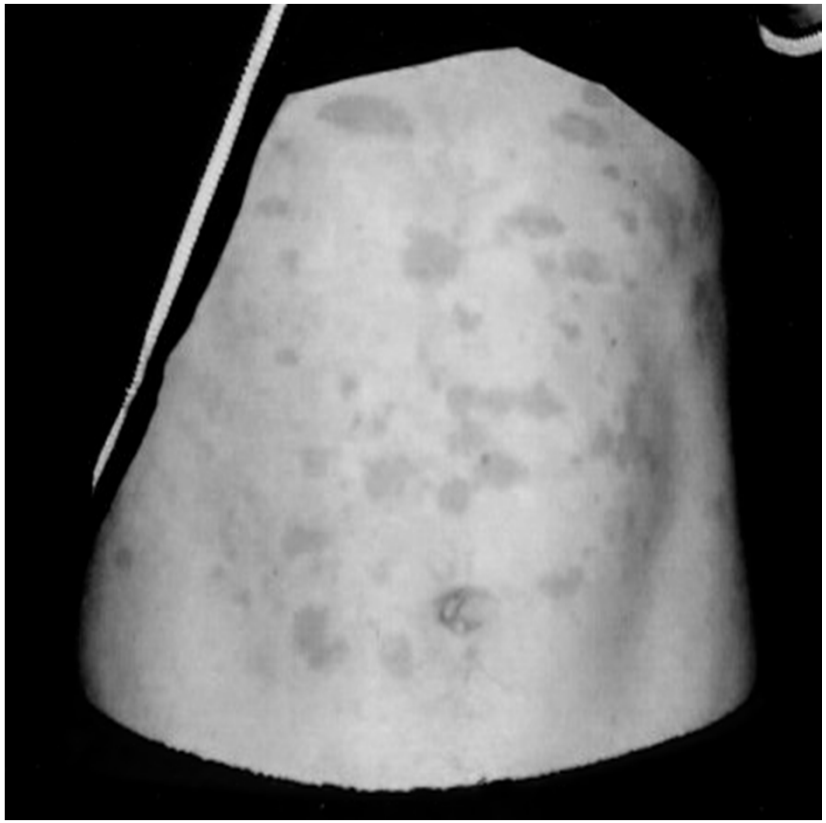
Protein



Cryopyrin

Hoffman et al, Nature Genetics 2001

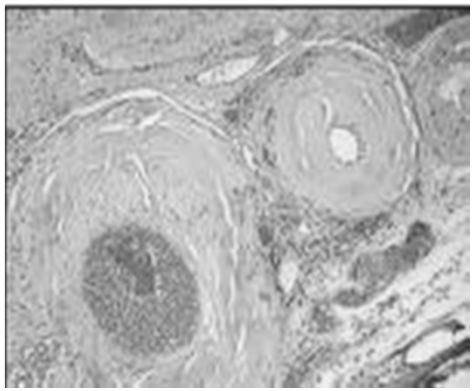
Muckle Wells Syndome

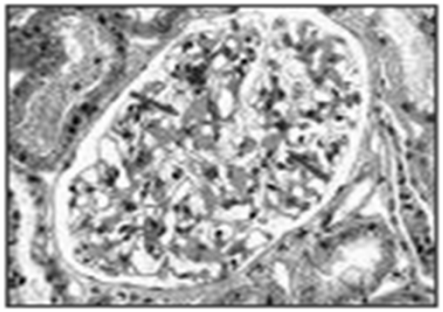


Fever episodes with urticaria like rash and joint symptoms

Progressive neuro-sensory hearing loss

AA Amyloidosis





Neonatal Onset Multisystem Inflammatory Disorder (NOMID)

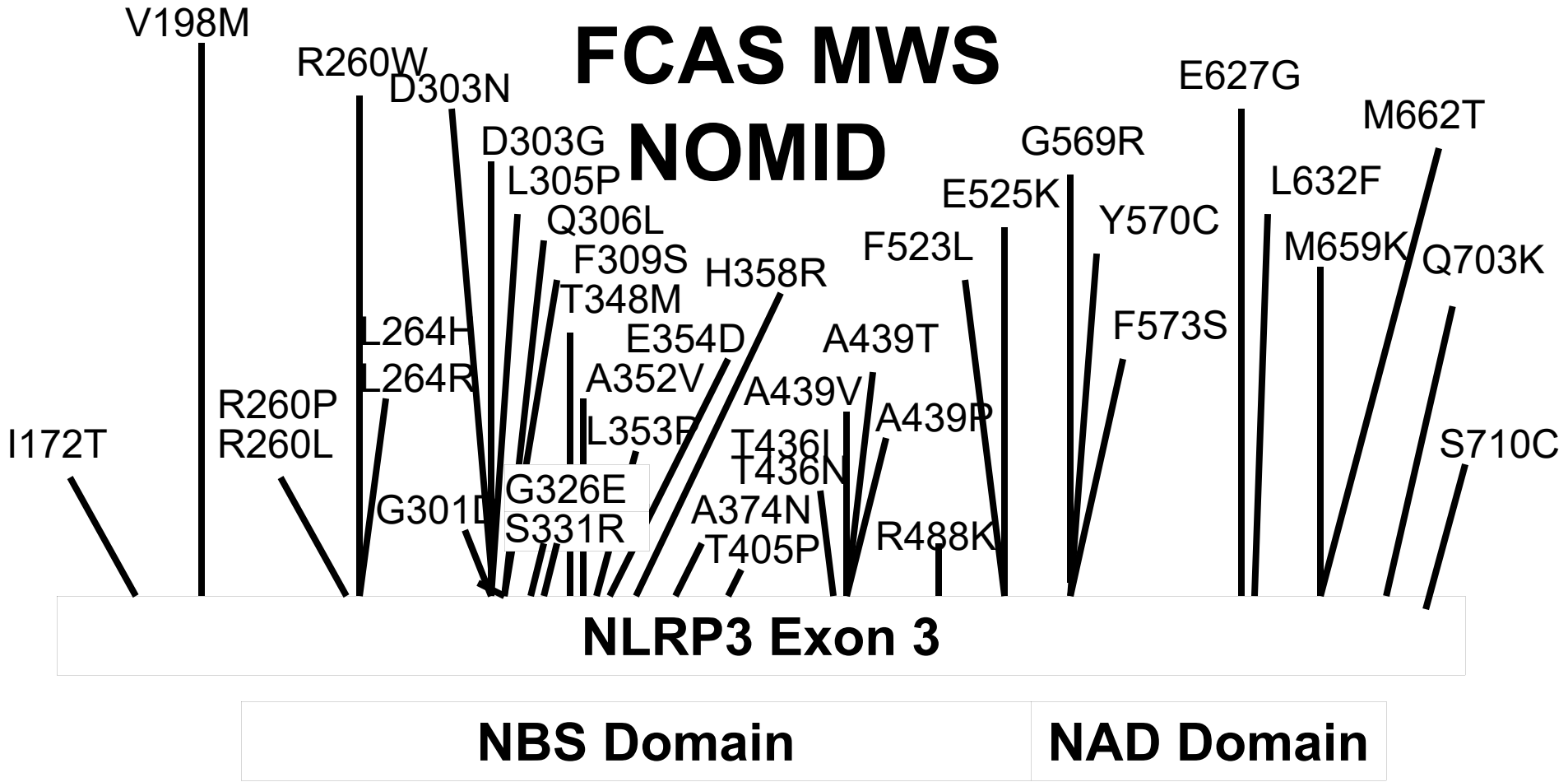
Chronic fever, pain, and urticaria-like rash

Hearing loss, and other CNS inflammation

Dysmorphic features and enlarged tibial epiphysis

Courtesy of R Goldbach-Mansky

NLRP3 Mutations/Variants - >90



Variants *in healthy controls, but also in atypical patients*

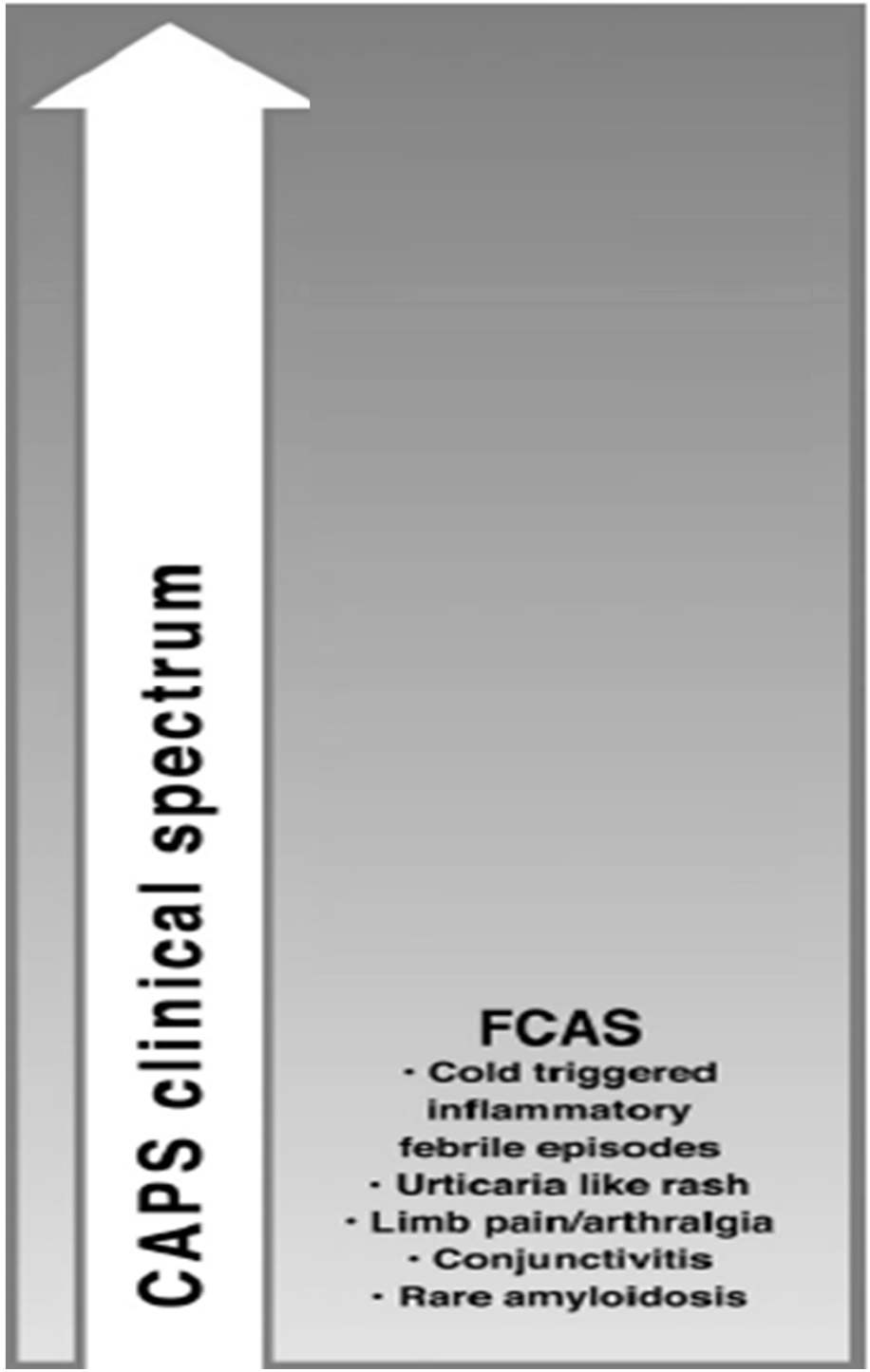
Cryopyrin

Mutation negative patients – most somatic mosaics

Infevers – Touitou et al

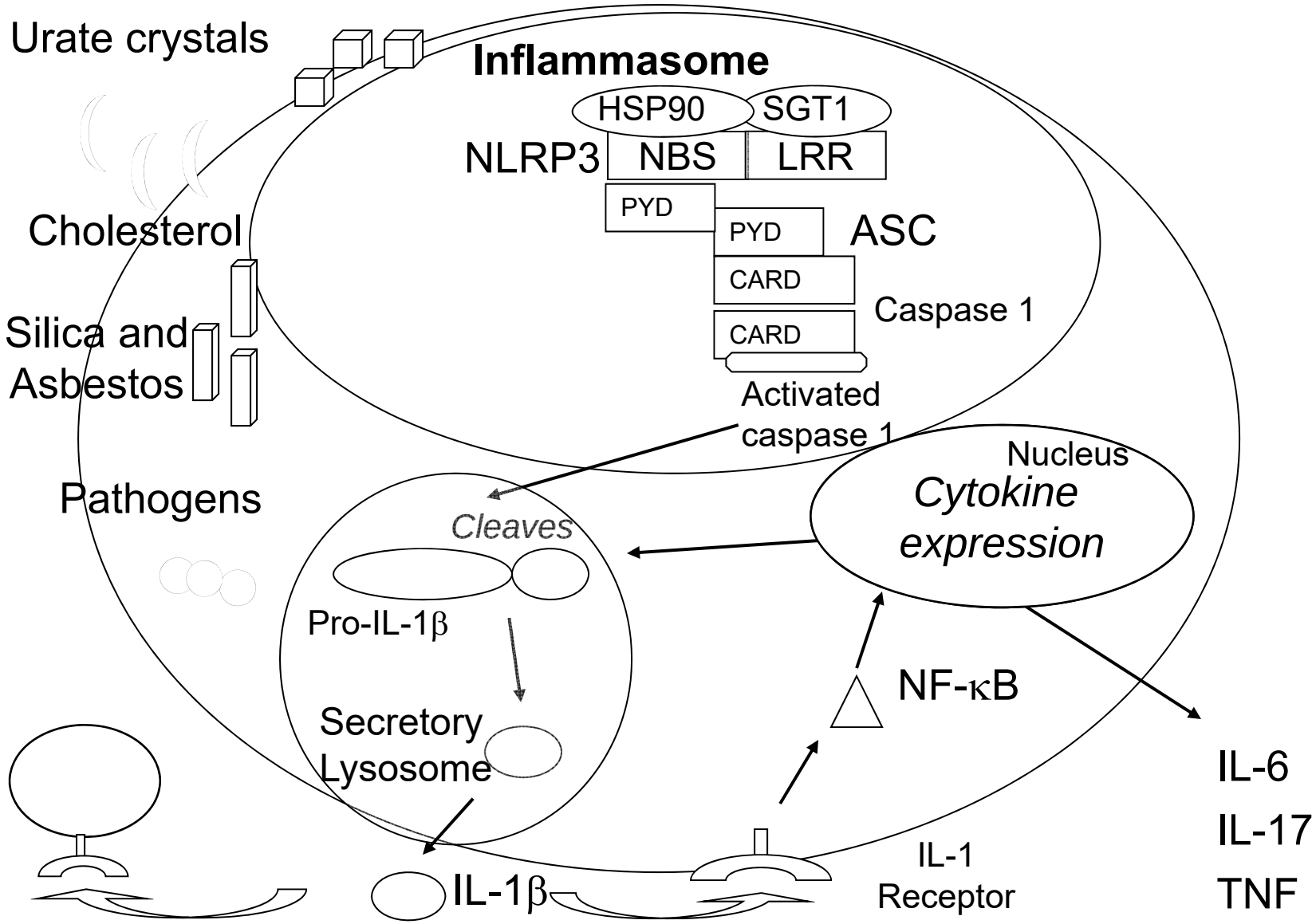
Diseases associated with NLRP3 mutations

- Cryopyrinopathies or CAPS - Cryopyrin associated periodic syndromes



Monocyte
Macrophage

NLRP3 Inflammasome



Diseases of the Inflammasome

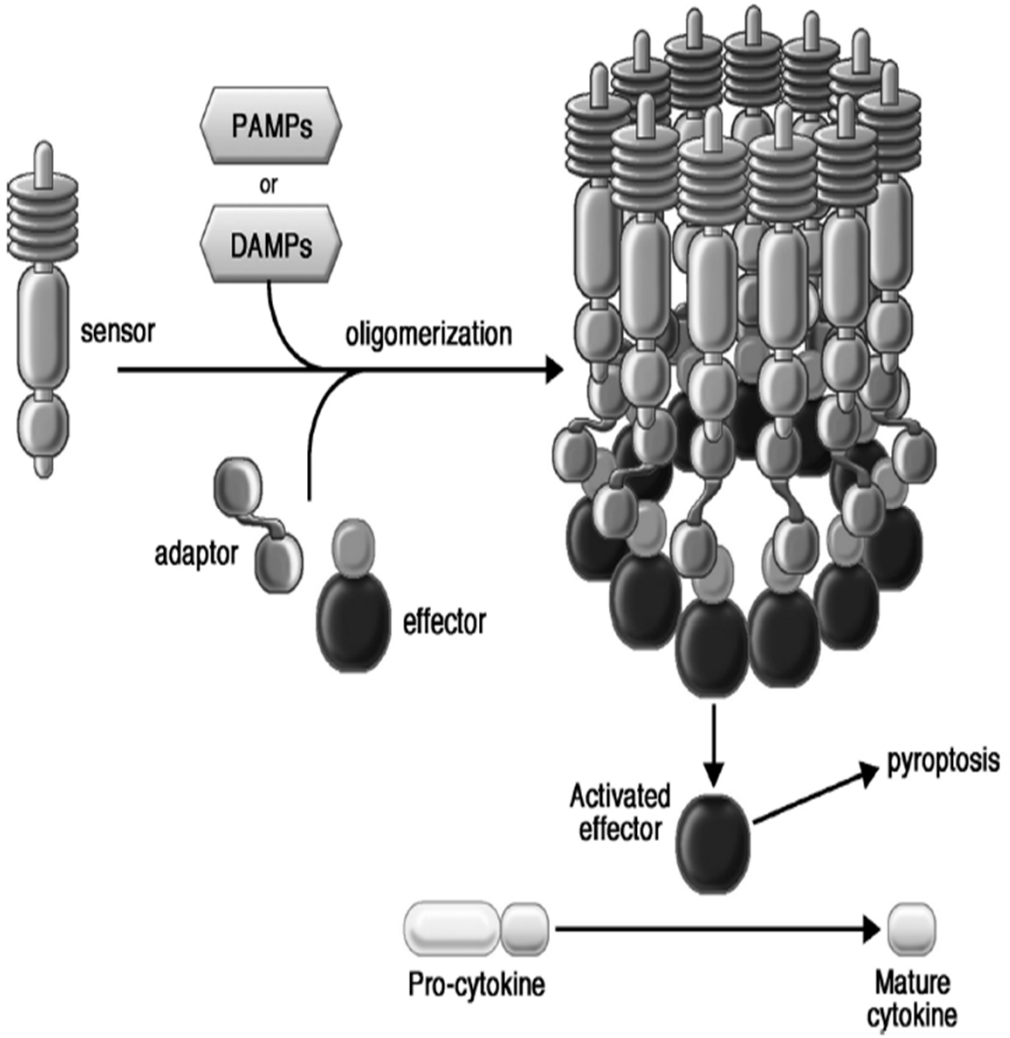
Gout

Pseudogout

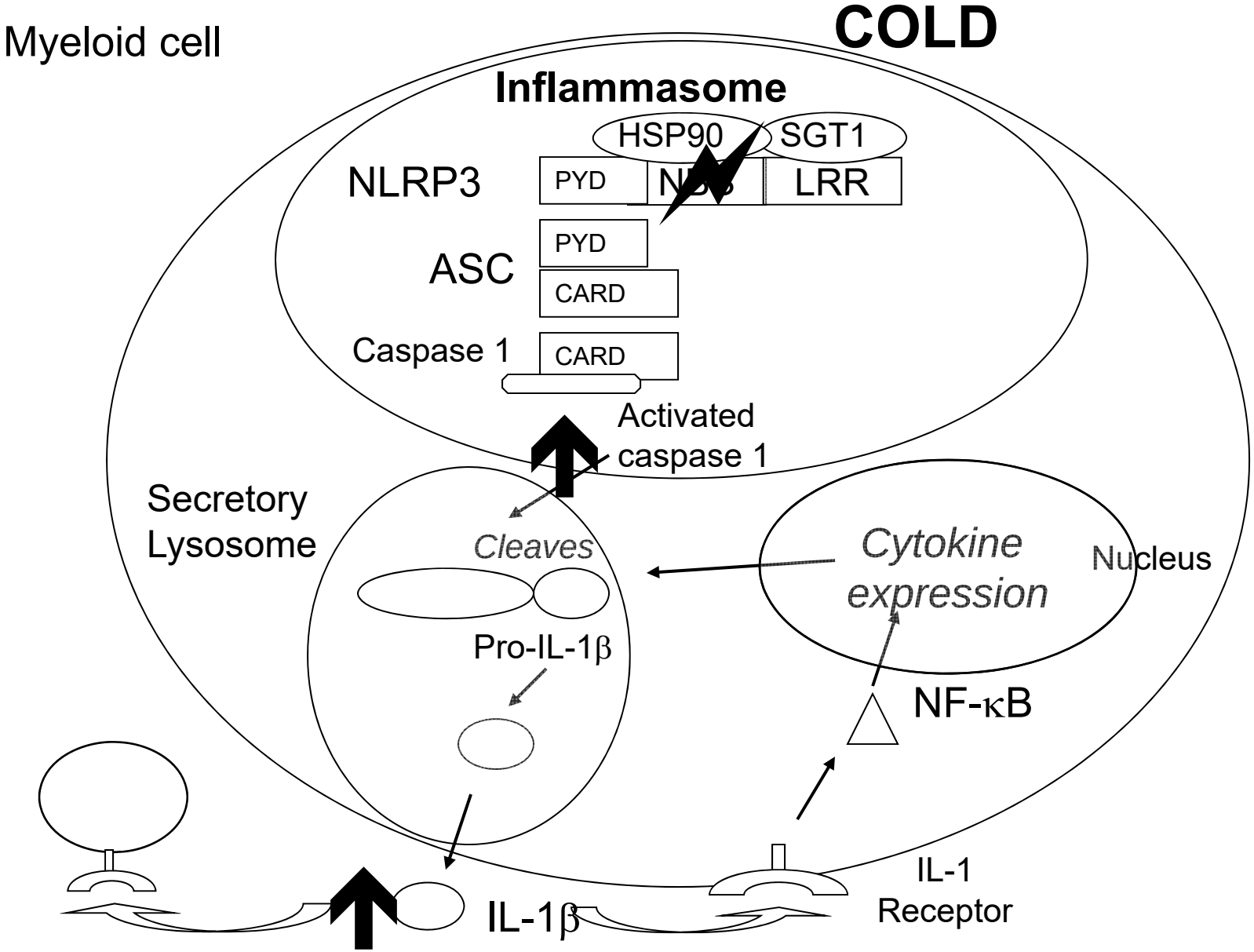
Asbestosis

Silicosis

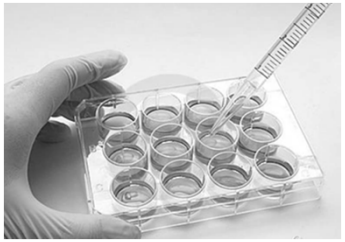
Atherosclerosis



NLRP3 Inflammasome and CAPS

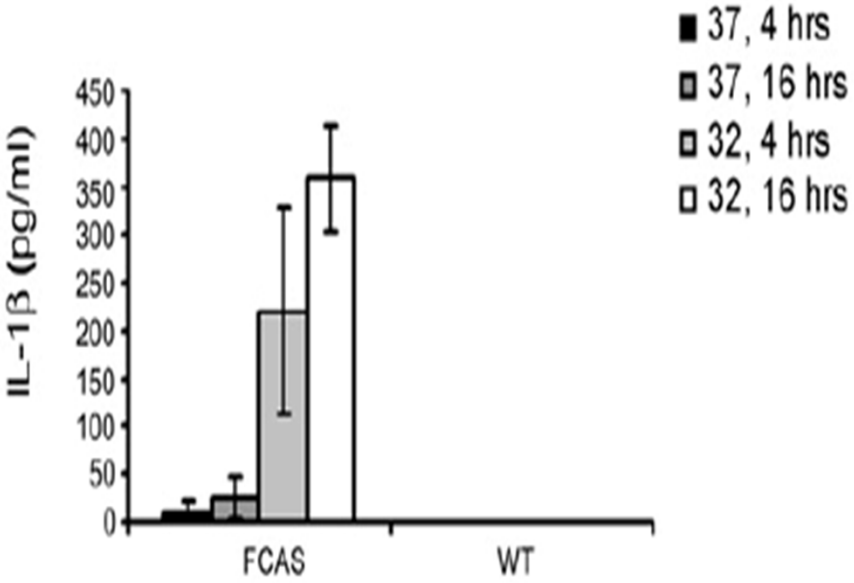


Agostini et al, Immunity 2004



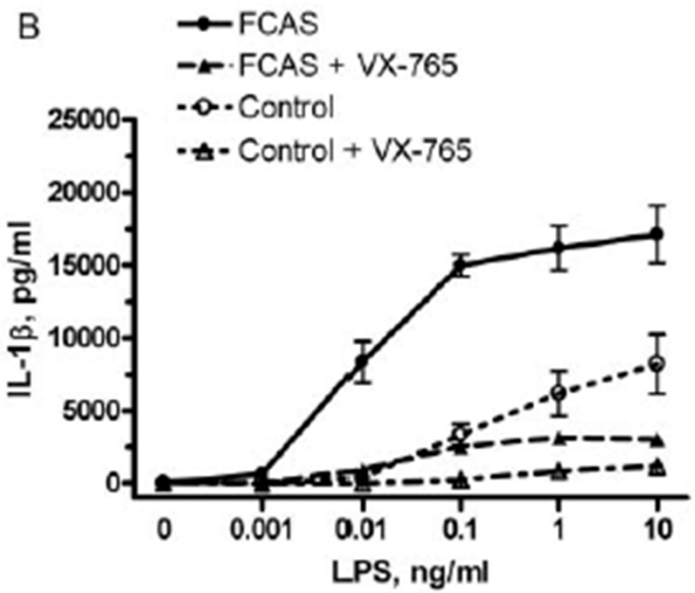
CAPS Blood studies

COLD

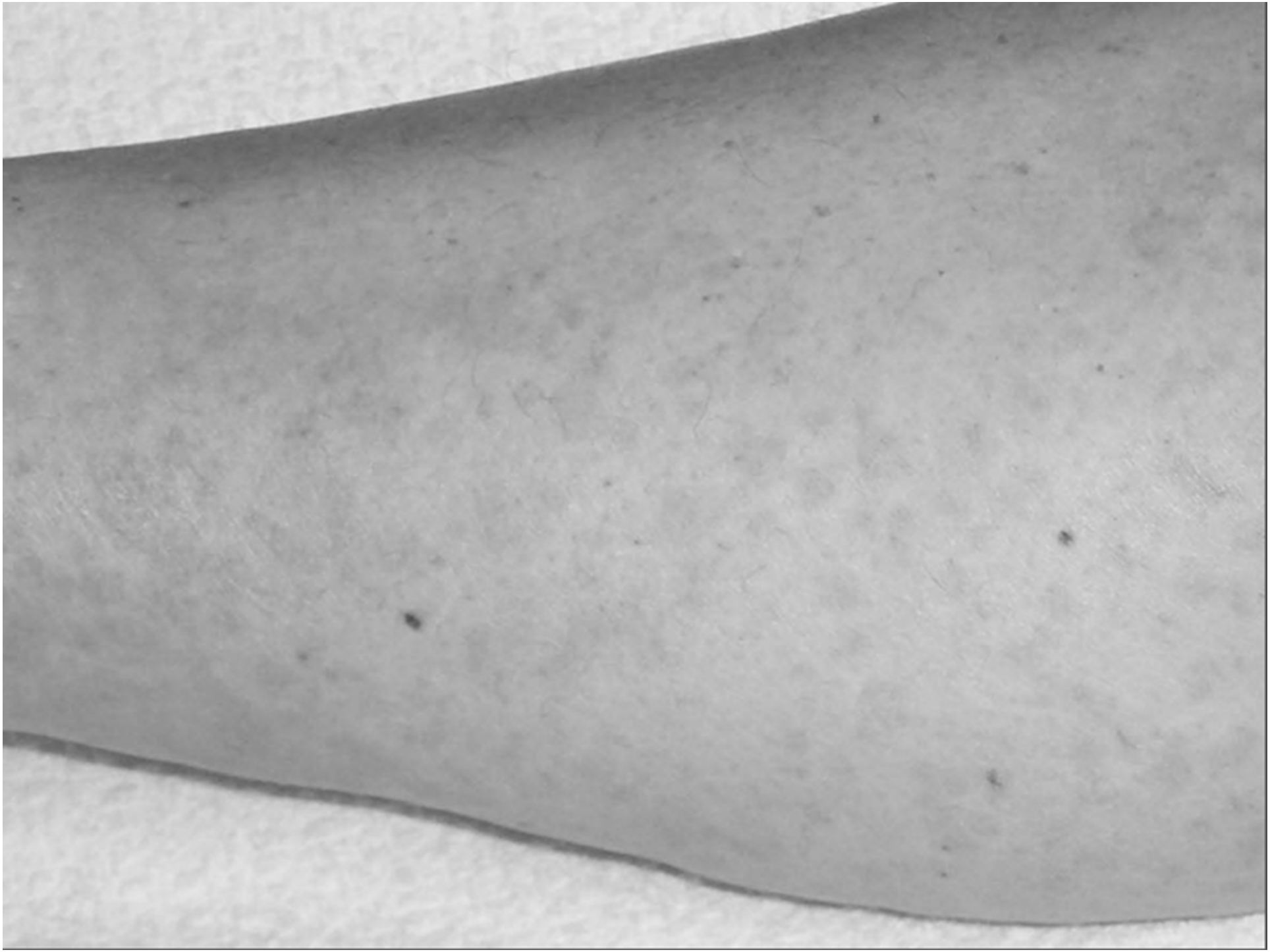


Hoffman et al JACI 2007

Bacterial Toxin



Stack et al JI 2005

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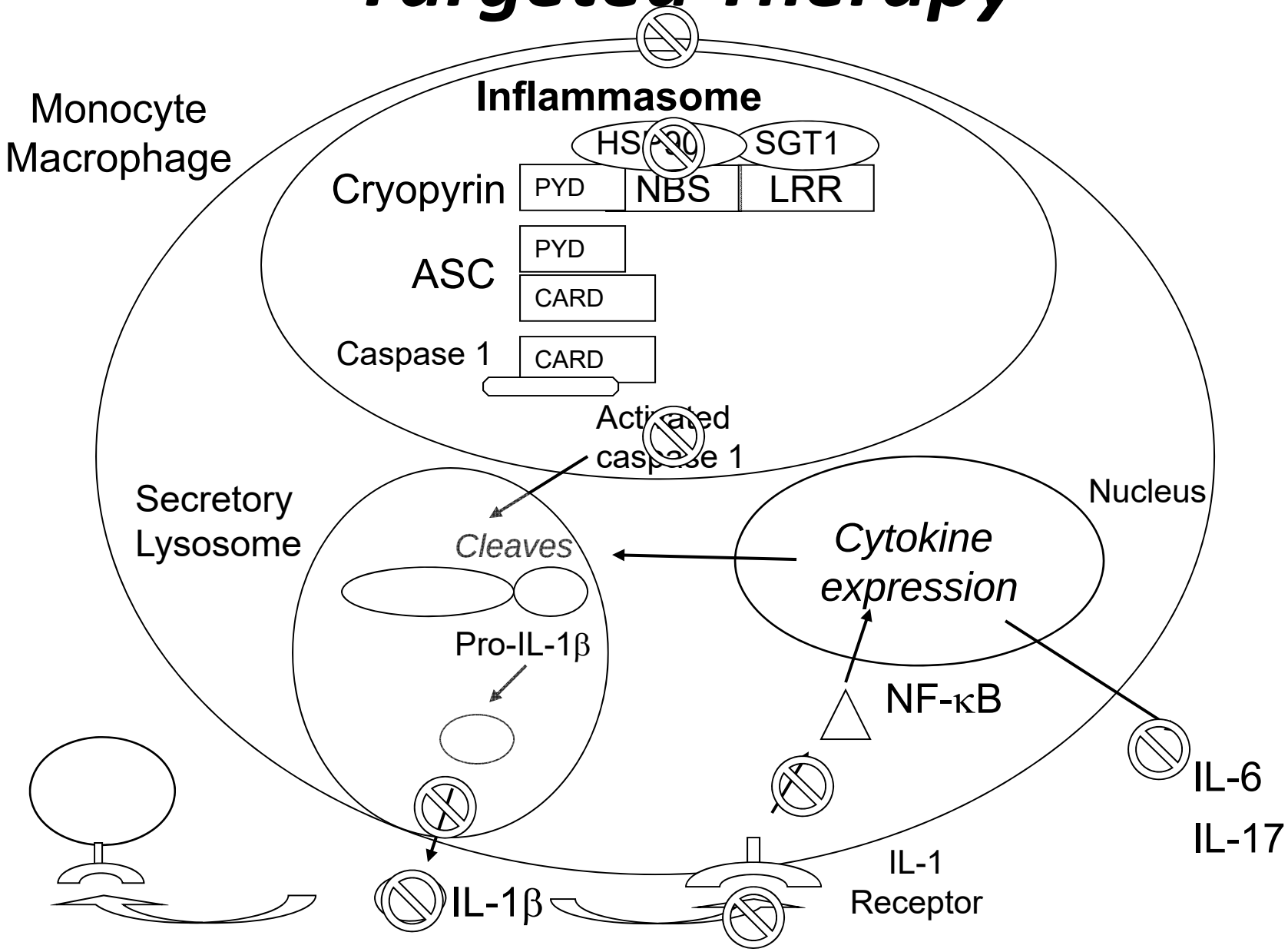
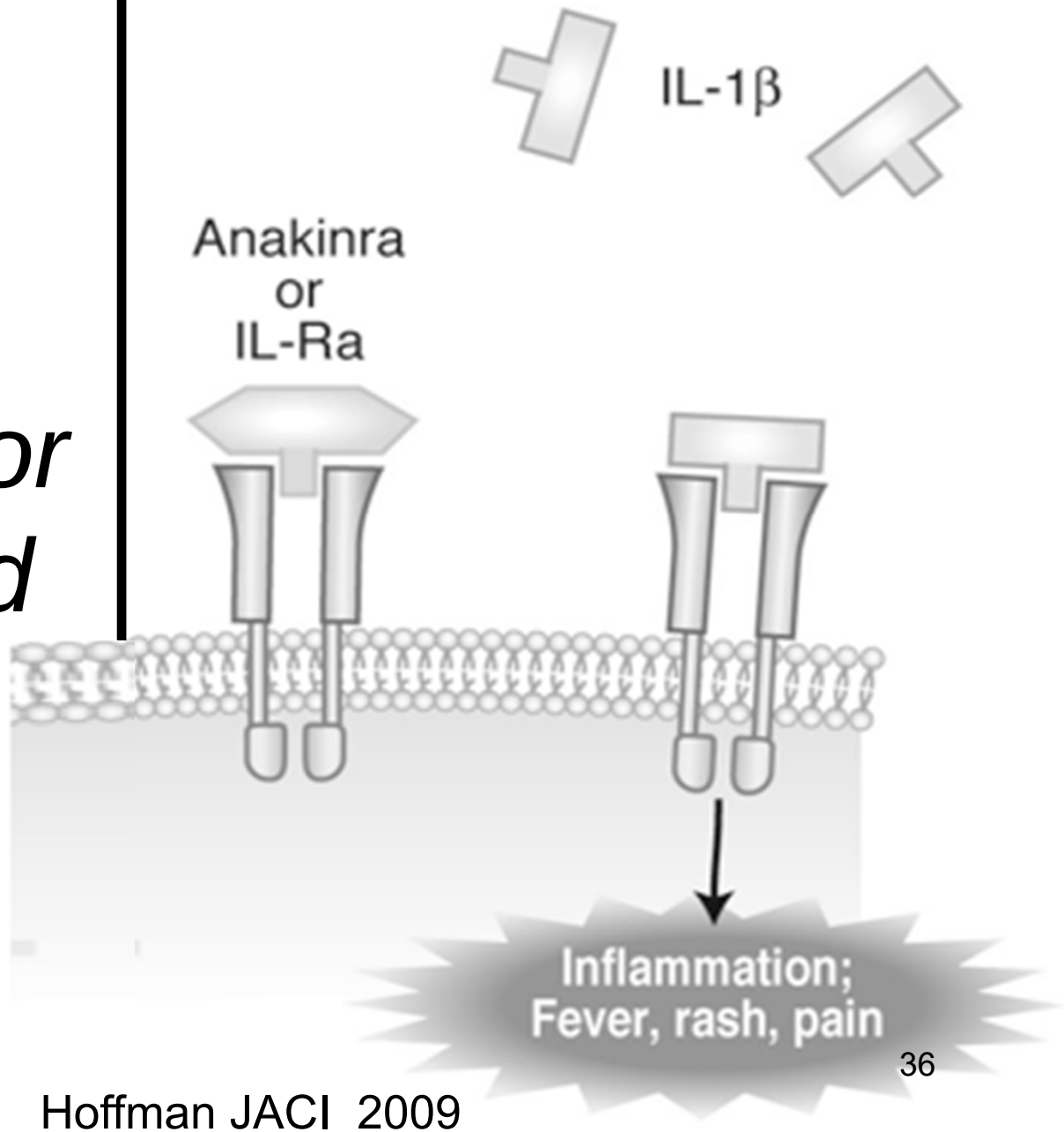
Targeted Therapy



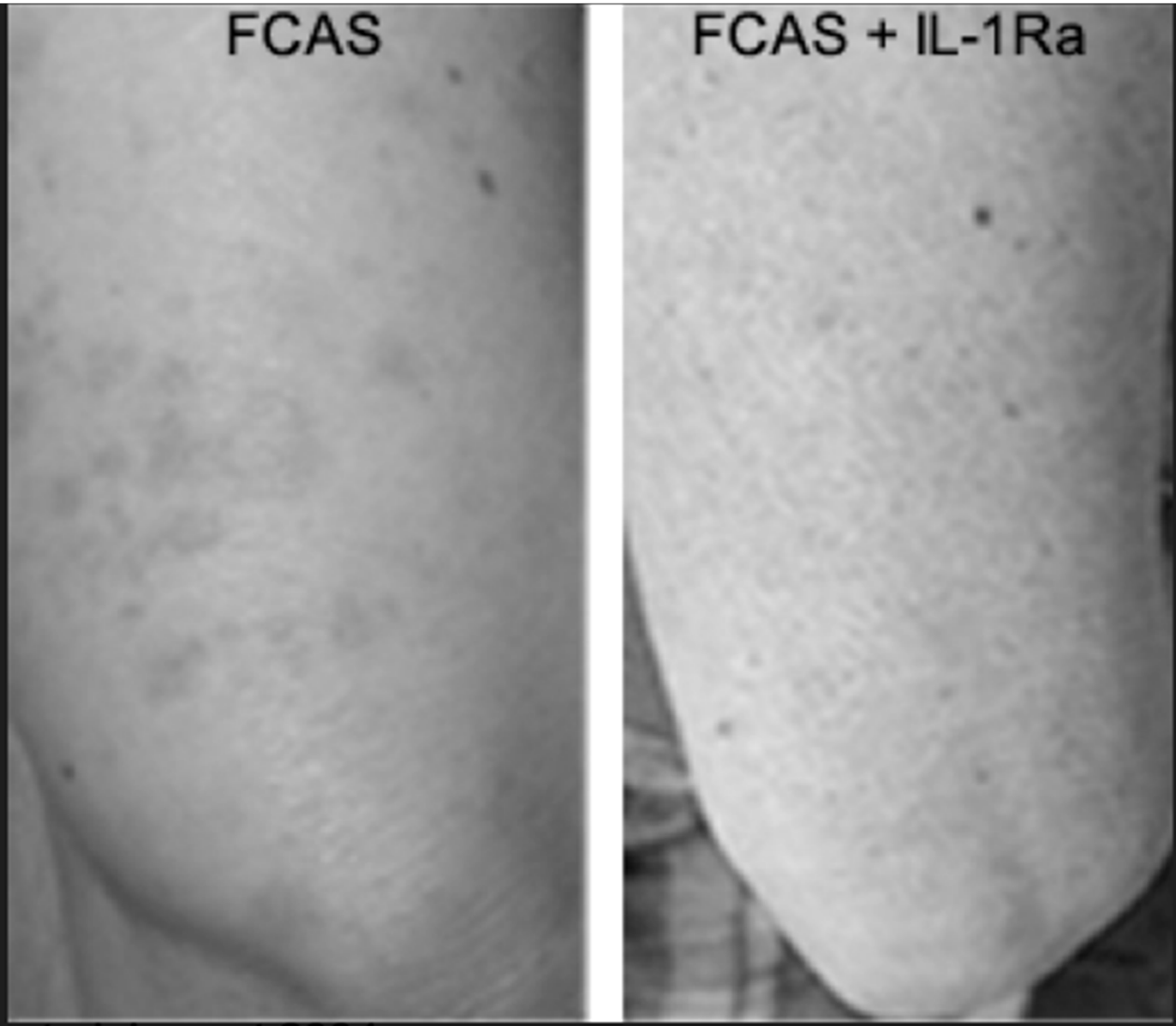
Anakinra (IL-1Ra)

Approved for Rheumatoid Arthritis in 2001



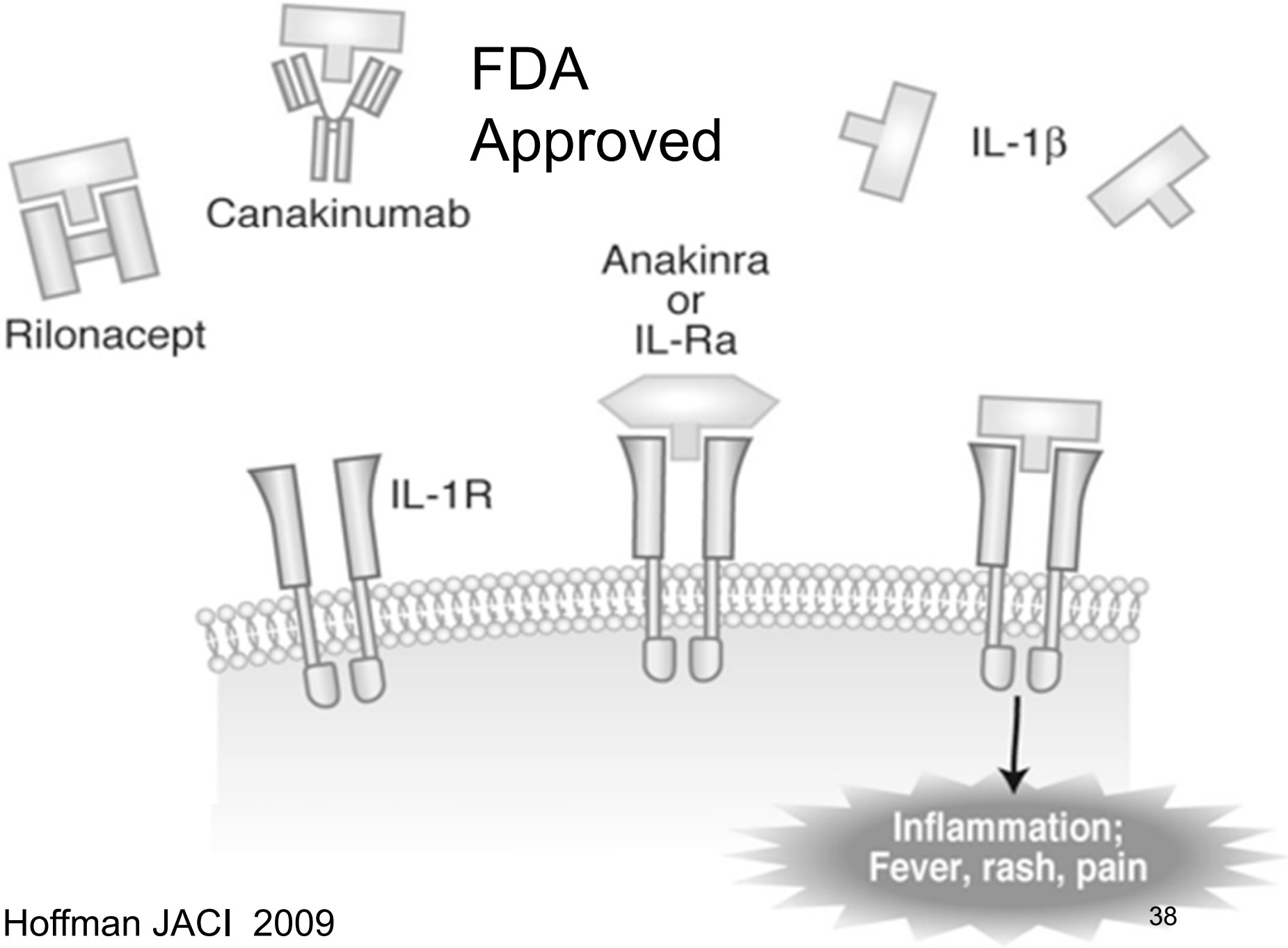
Hoffman JACI 2009

Skin following cold challenge



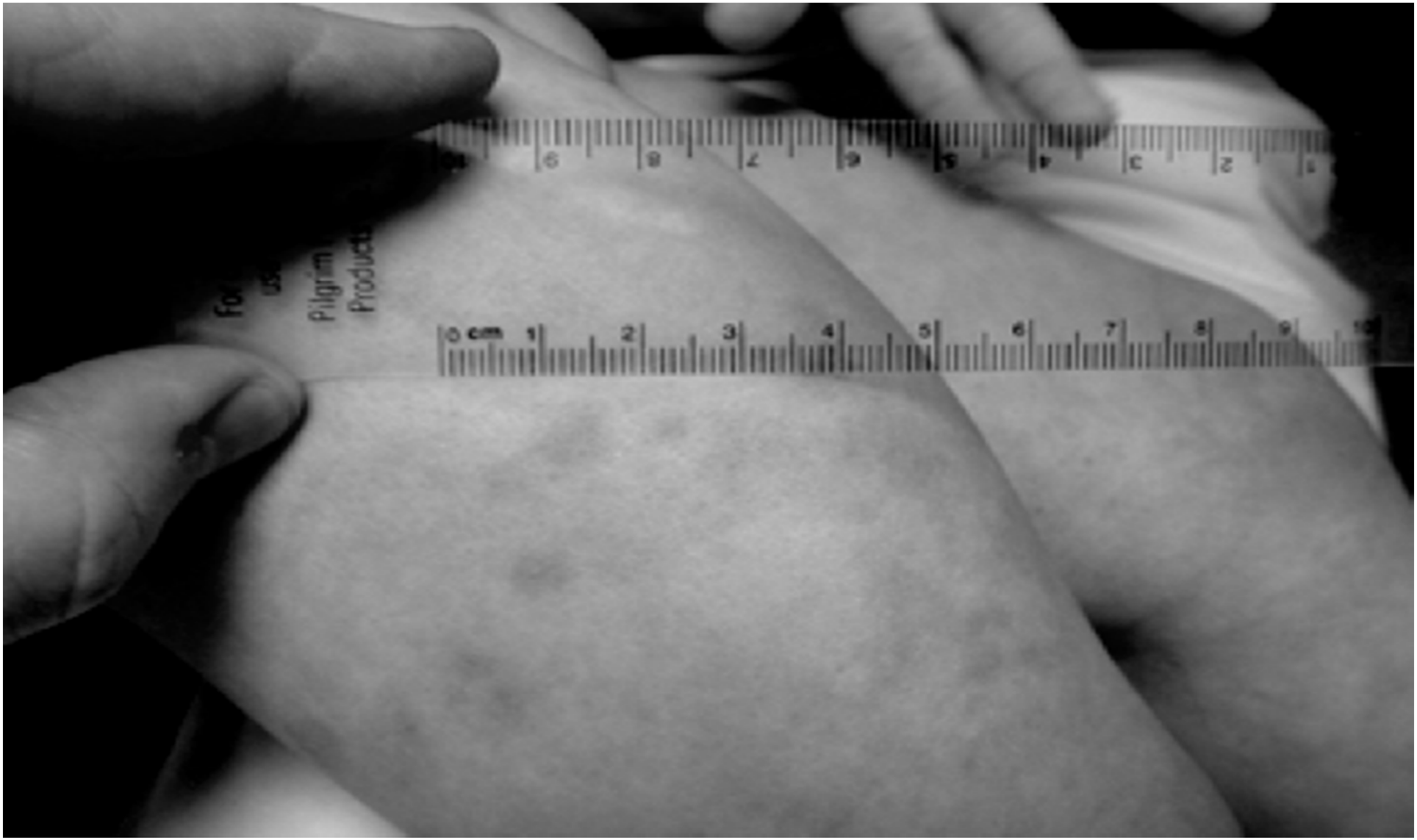
Hoffman et al, Lancet 2004

FDA Approved



Hoffman JACI 2009

3 y/o girl with rash after cold exposure



Translational Success

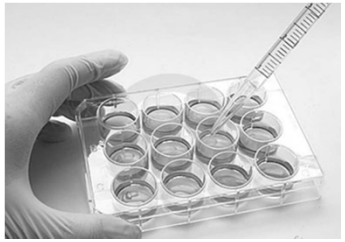
Therapeutic Studies

Patients / Families

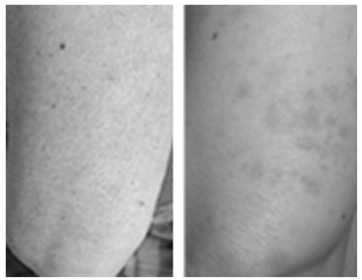
Disease Characterization

Genetic Studies

In vitro or Ex vivo studies



In vivo studies



IL-1 Targeted Therapy Issues

Safety - Infections

- Gram positive pathogens
- Increased upper respiratory infections

Costs

Anakinra	*$ 25,000/year*
Rilonacept	*$250,000/year*
Canakinumab	*$110,000/year*

Summary

- **FCAS is a rare autoinflammatory diseases caused by mutations in the *NLRP3* gene resulting in dysregulated IL-1β release**
- **IL-1 targeted therapy has shown proven efficacy in FCAS and other diseases**
- **Studying rare diseases has challenges and advantages**
- **Family involvement is crucial in all steps of the process**


Questions?