Immune Deficiency Foundation

Lunch & Learn: Hyper IgE/Job Syndrome

October 19th, 2022


IDF MISSION
Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education and research.
Immune Deficiency Foundation

HOUSEKEEPING

- Attendees will not have access to their microphone or webcam throughout the event.
- To see the full slides, you can adjust the settings on the speaker view panel on the top of the Zoom screen and select "side-by-side" in the dropdown option.
- Please submit all questions for the presenter via the Q&A box

DISCLAIMER

Immune Deficiency (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.

IDF Website: www.primaryimmune.org

Chapter 20

Hyper IgE Syndromes (HIES): STAT3 Loss of Function, DOCK8 Deficiency and Others

Alexandra Freeman, MD, National Institutes of Health, Bethesda, Maryland, USA

Jennifer Heimall, MD, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Hyper IgE Syndromes (HIES) are rare forms of primary immunodeficiency diseases (PI) characterized by recurrent eczema, skin abscesses, lung infections, eosinophilia (high numbers of eosinophils in the blood), and high serum levels of immunoglobulin E (IgE). Although initially described as two forms, with autosomal dominant (AD) and autosomal recessive (AR) inheritance, we now recognize that these are two distinct diseases caused by different genetic causes, with the two most common being from harmful mutations in STAT3 causing loss of function (STAT3-LOF) and DOCK8. These diseases share overlapping clinical and laboratory features; however, they also exhibit distinct clinical symptoms, disease courses, and outcomes. In addition, several other genetic variants have since been described to present with similar symptoms.

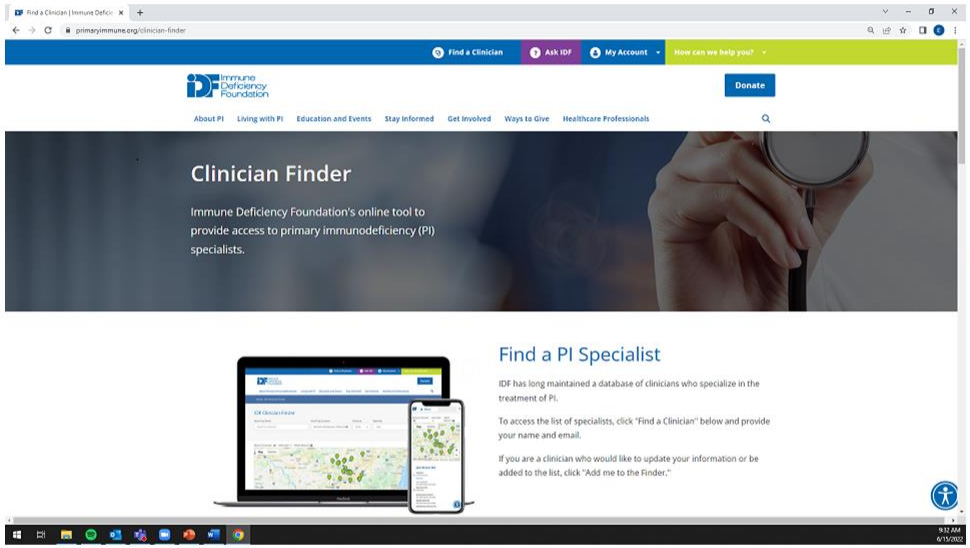
History

STAT3-LOF was described first as Job Syndrome in 1966 in two girls with many episodes of pneumonia, eczema-like rashes, and recurrent skin boils. These boils were remarkable for their lack of surrounding warmth, redness or tenderness, and were so called cold abscesses. In 1972, the syndrome was refined and clarified upon. It found similar infectious problems in two boys who also had a distinctive facial appearance and extremely elevated IgE levels. Following this report, elevated IgE was found in the two girls from the initial report, showing that Job Syndrome and Buckley Syndrome represented the same condition. In 2007, a heterozygous mutation in the gene encoding the transcription factor STAT3 was found to underlie most cases of AD-HIES. In 2009 mutations and deletions in the DOCK8 gene were found to underlie many patients with similar symptoms inherited in an AR fashion.

Clinical Presentation

STAT3 Deficiency

STAT3 Deficiency is associated with heterozygous loss of function mutations in the transcription factor STAT3. This is the more common form of HIES in the U.S. It commonly presents with skin findings including newborn rash, eczema, and recurrent staphylococcal skin abscesses as well as ear, sinus, and lung infections. The lung infections often result in cavitary lesions in the lungs (pneumatoceles). Other common infections in STAT3 deficiency include mucocutaneous candidiasis (Candida fungus on mucous membranes and/or skin), manifesting typically as thrush, vaginal candidiasis or candidal nail infection (onychomycosis), and recurrent shingles outbreaks. Additional findings include connective tissue and skeletal abnormalities, such as a typical facial appearance, hyper-extensibility of joints, retained primary teeth, recurrent bone fractures with minimal trauma, and



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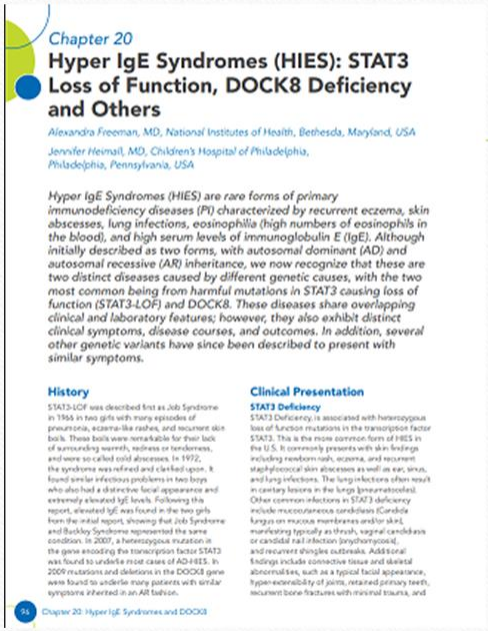
To view all Hyper IgE Resources and Materials, visit:

https://primaryimmune.org/about-primary-immunodeficiencies/specific-disease-types/hyper-ige-syndrome



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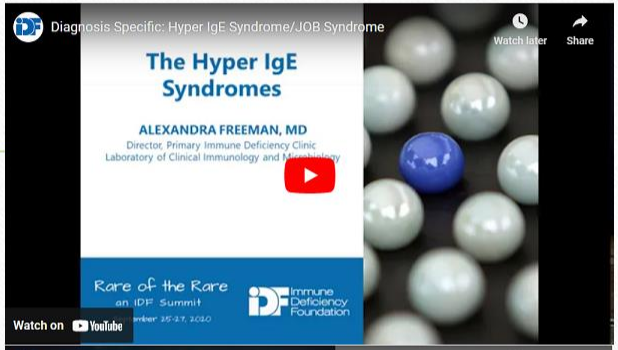

Reel Stories

Immune Deficiency Foundation

PI COMMUNITY SERVICES

- Monthly Lunch & Learns- medical experts present on various diagnosis-specific topics
- Get Connected Groups: share experiences, receive information, and gain support
- IDF Forums
- Ask IDF
- Annual PI Conference

To view a list of all upcoming IDF events, visit: https://community.primaryimmune.org/s/events?language=en_US

WELCOME!

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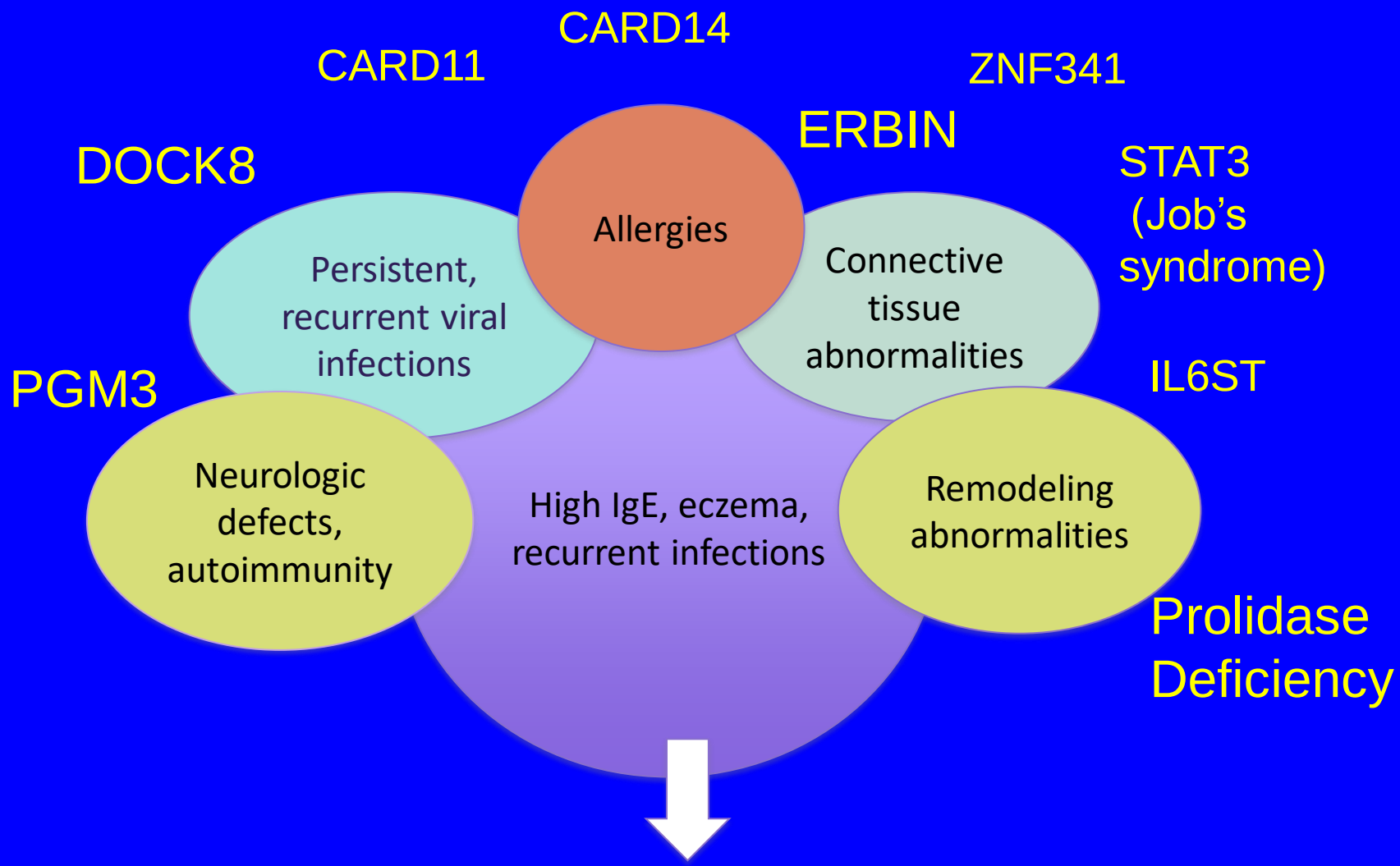
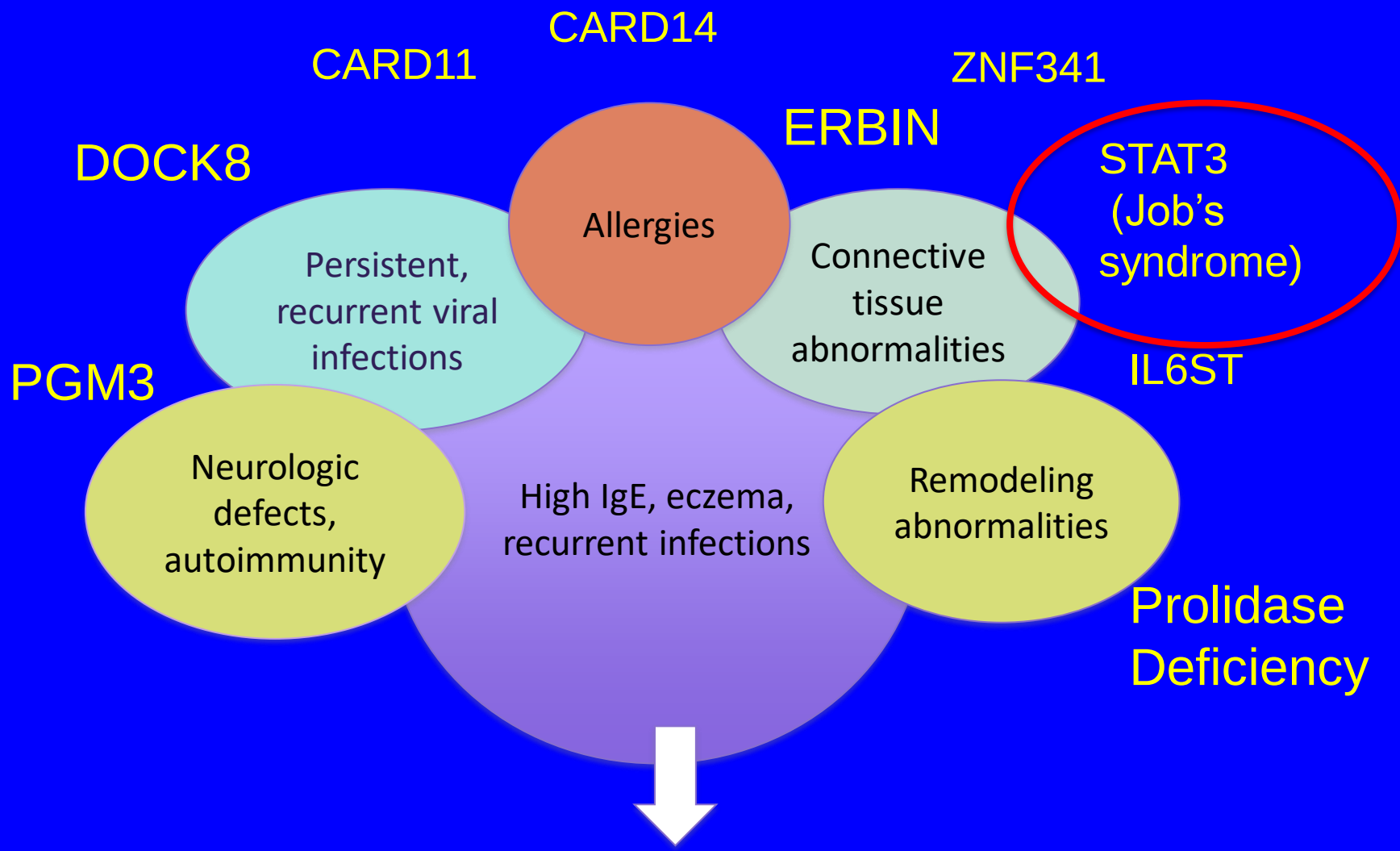
Pediatric Infectious Diseases Clinician
Director, Primary Immune Deficiency Clinic
National Institute of Allergy and Infectious Diseases
National Institutes of Health

The Hyper IgE Syndromes

Alexandra Freeman MD
Director, Primary Immune Deficiency Clinic
Laboratory of Clinical Immunology and Microbiology
National Institute of Allergy and Infectious Diseases, NIH



Hyper IgE syndromes: Each distinct disease

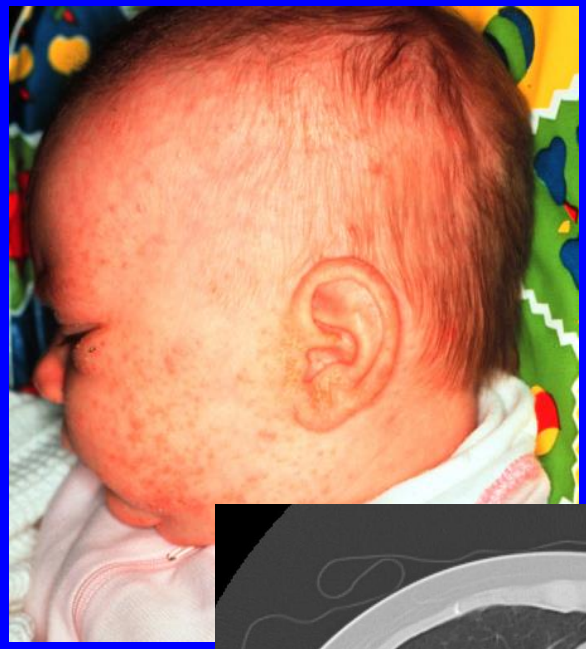


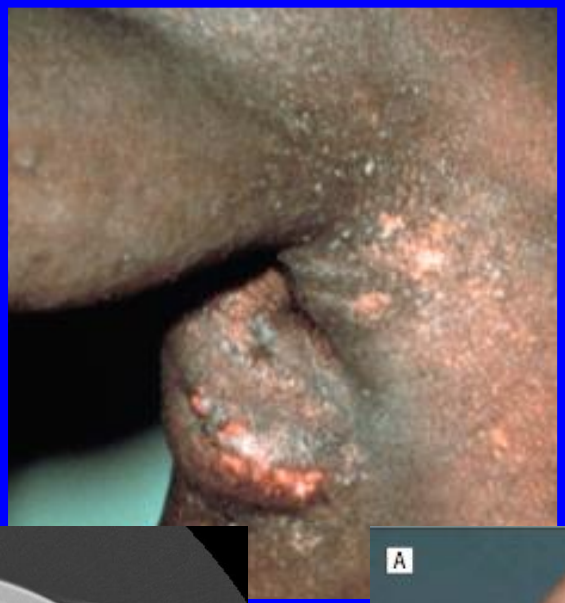
Hyper IgE syndromes: Each distinct disease

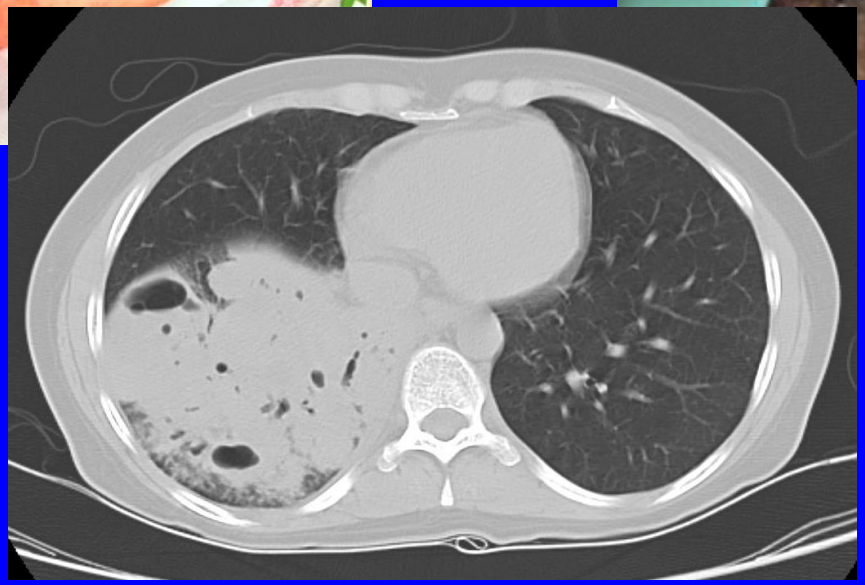
STAT3 deficient Hyper IgE Syndrome (Autosomal dominant HIES; Job's syndrome)

"So Satan went forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown."

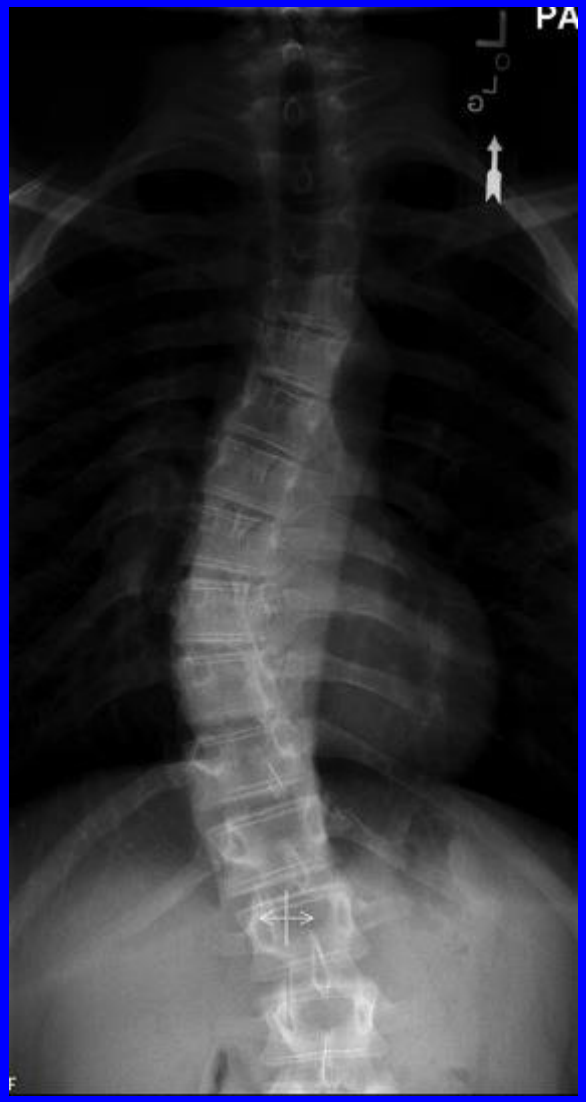
Staphylococcus aureus and *Candida* epithelial infections in STAT3 DN

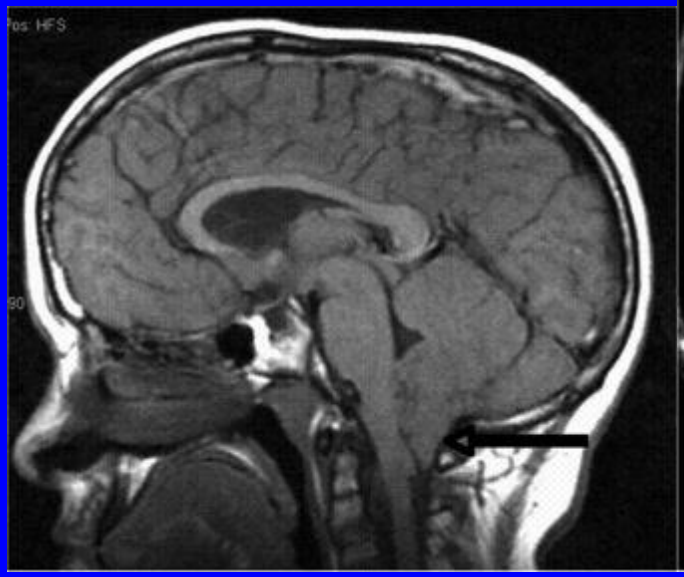


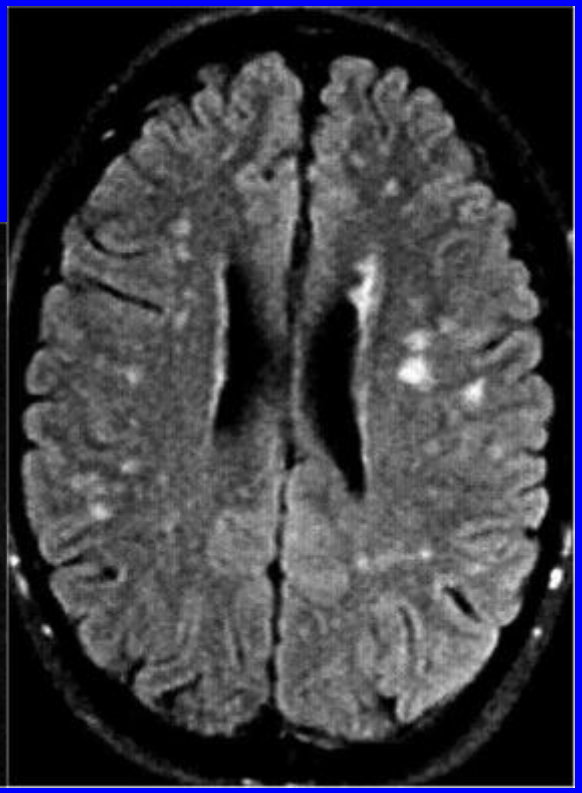


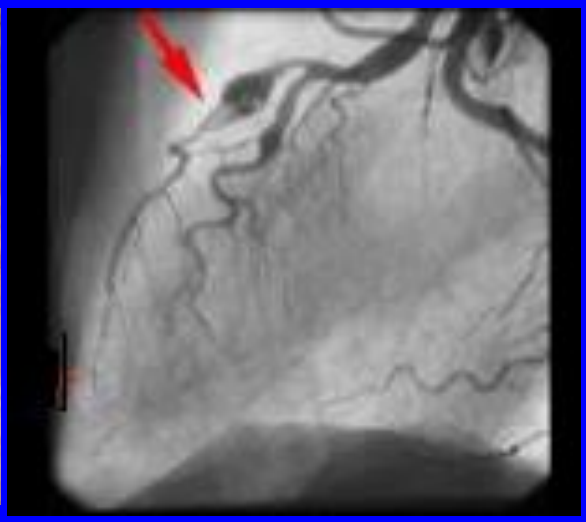


Skeletal, joint, dental, vascular abnormalities



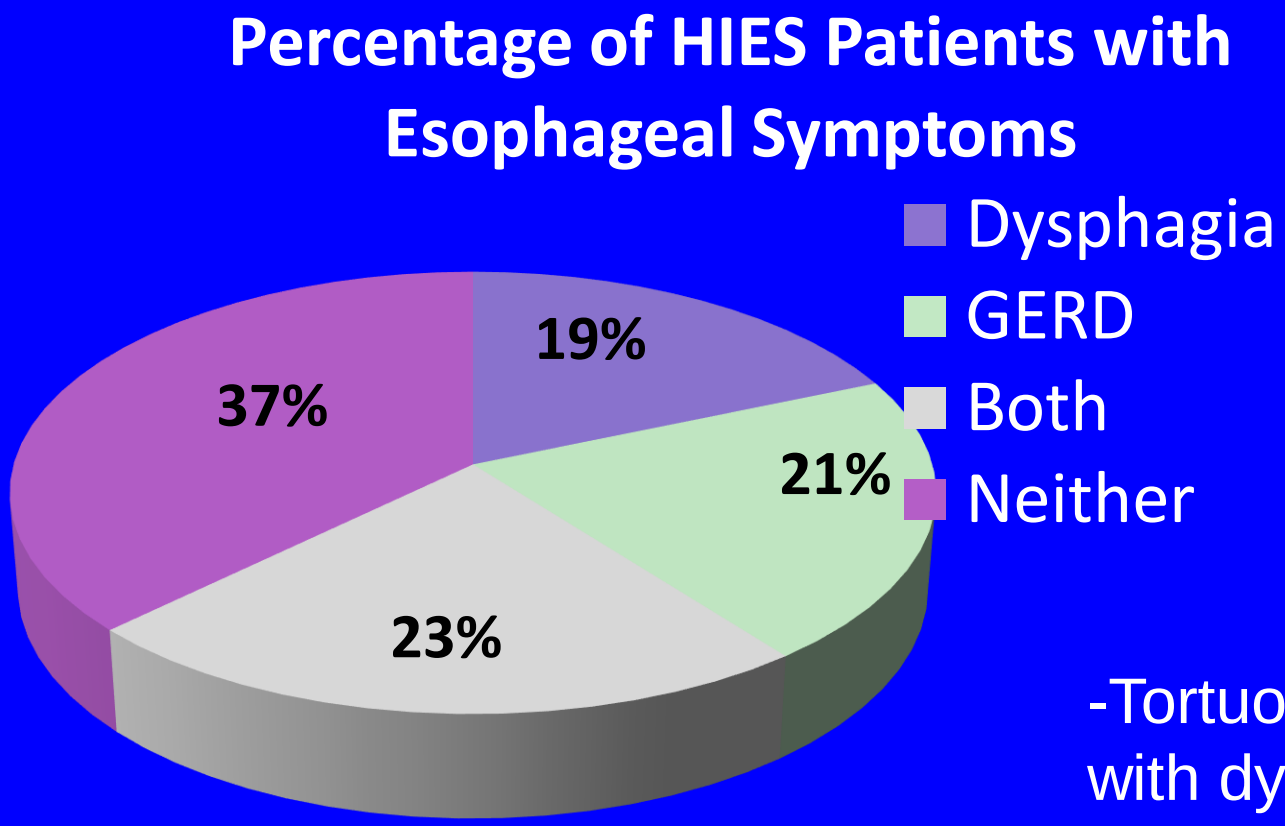






Characteristic facial appearance

GI dysfunction



-Tortuous esophagus with dysmotility
-Colon and cecum perforations
-Diverticulitis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

STAT3 Mutations in the Hyper-IgE Syndrome

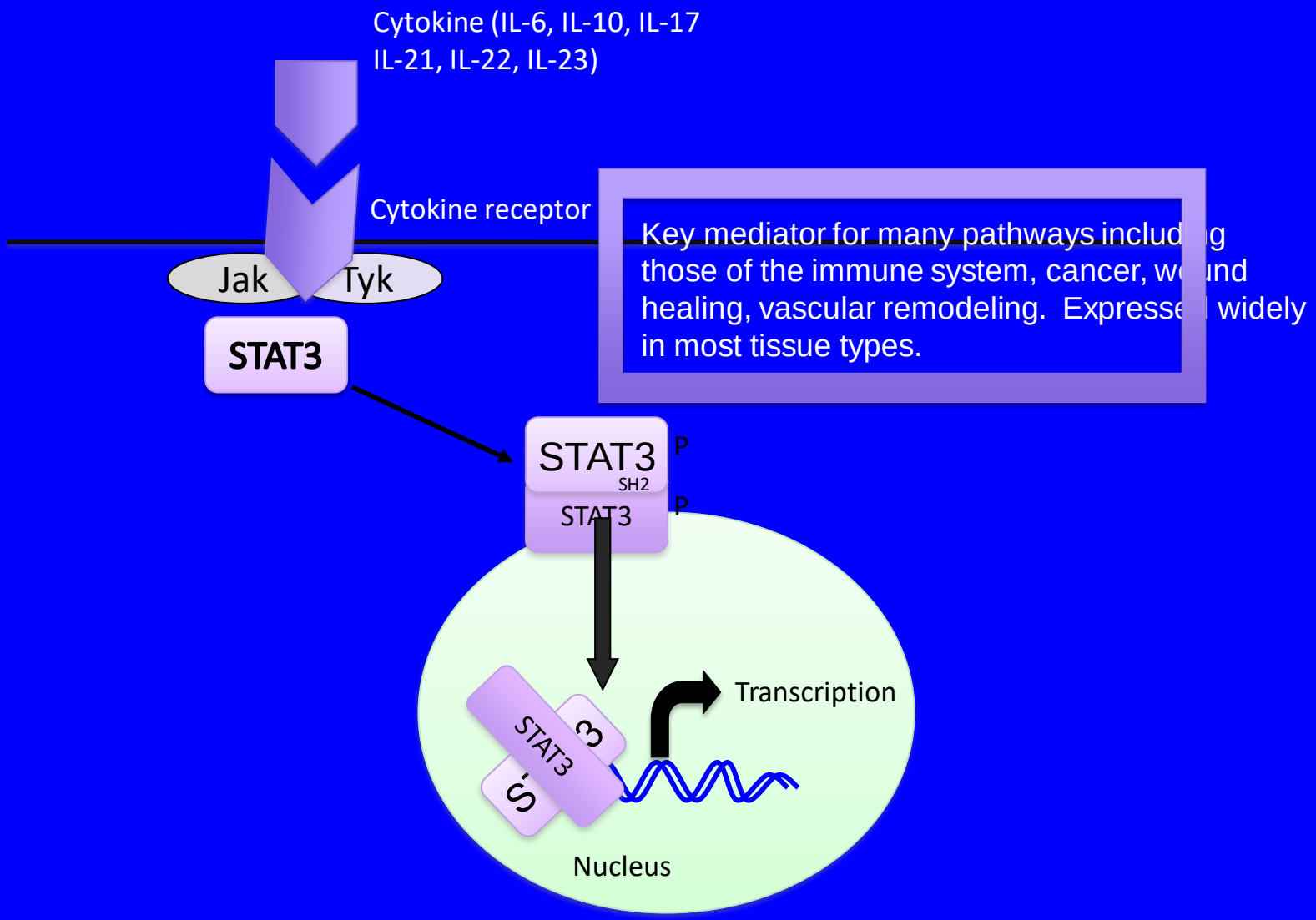
Steven M. Holland, M.D., Frank R. DeLeo, Ph.D., Houda Z. Elloumi, Ph.D., Amy P. Hsu, B.A., Gulbu Uzel, M.D., Nina Brodsky, B.S., Alexandra F. Freeman, M.D., Andrew Demidowich, B.A., Joie Davis, A.P.R.N., Maria L. Turner, M.D., Victoria L. Anderson, C.R.N.P., Dirk N. Darnell, M.A., Pamela A. Welch, B.S.N., Douglas B. Kuhns, Ph.D., David M. Frucht, M.D., Harry L. Malech, M.D., John I. Gallin, M.D., Scott D. Kobayashi, Ph.D., Adeline R. Whitney, B.A., Jovanka M. Voyich, Ph.D., James M. Musser, M.D., Ph.D., Cristina Woellner, M.Sc., Alejandro A. Schäffer, Ph.D., Jennifer M. Puck, M.D., and Bodo Grimbacher, M.D.

Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome

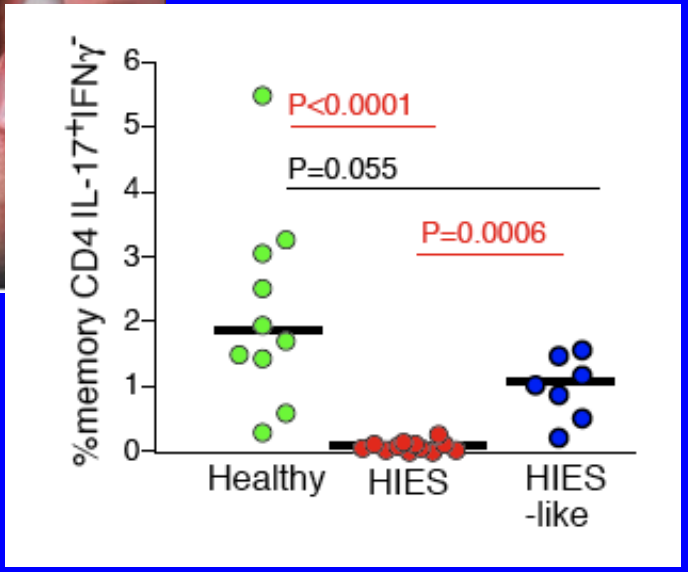
Yoshiyuki Minegishi[1], Masako Saito[1], Shigeru Tsuchiya[2], Ikuya Tsuge[3], Hidetoshi Takada[4], Toshiro Hara[4], Nobuaki Kawamura[5], Tadashi Ariga[5], Srdjan Pasic[6], Oliver Stojkovic[7], Ayse Metin[8] & Hajime Karasuyama[1]

nature

2007


Cytokine (IL-6, IL-10, IL-17
IL-21, IL-22, IL-23)
Cytokine receptor
Jak
Tyk
STAT3
Key mediator for many pathways including those of the immune system, cancer, wound healing, vascular remodeling. Expressed widely in most tissue types.
STAT3
SH2
P
STAT3
P
Transcription
STAT3
Nucleus

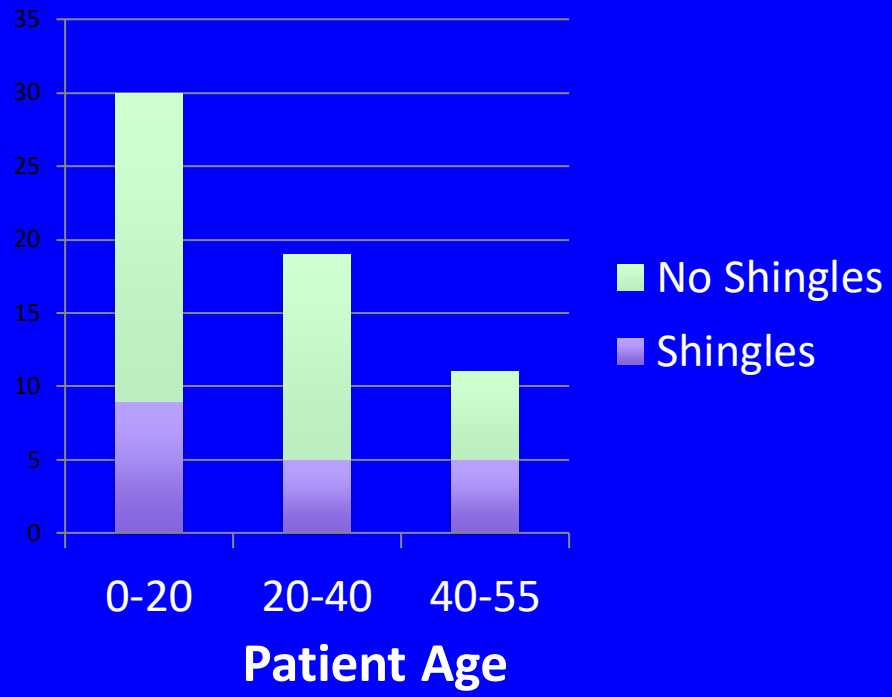
Epithelial/mucosal infection susceptibility: Lack of Th17 cells



Milner et al, Nature, 2008

Decreased memory T and B Cells

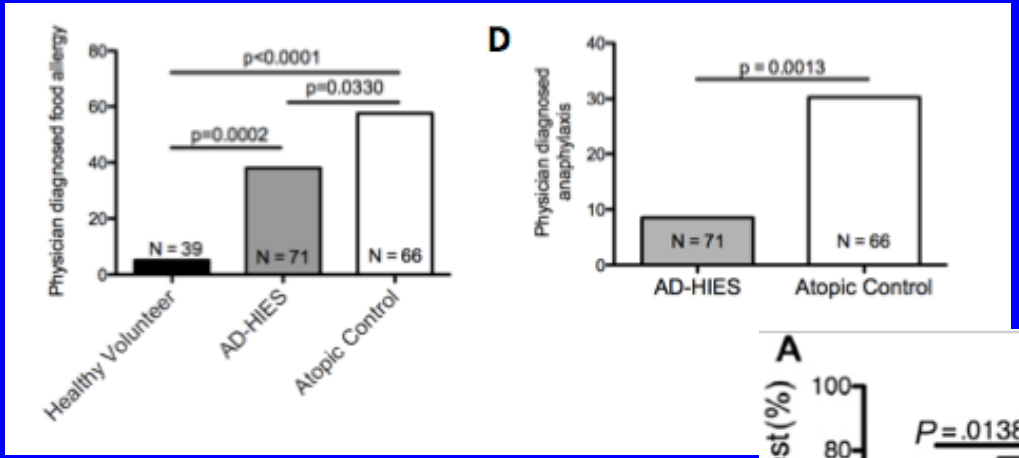
Zoster reactivation is increased in HIES patients and occurs at young ages



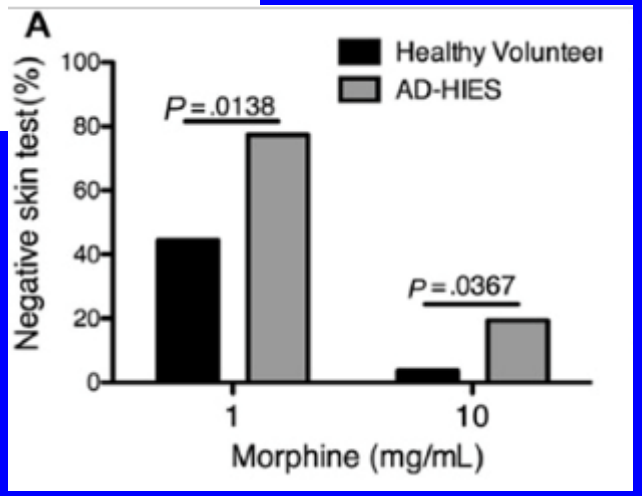
Minimum lifetime prevalence 19/60=31.7%

Siegel et al, Immunity 2011

AD-HIES with less food allergy and anaphylaxis

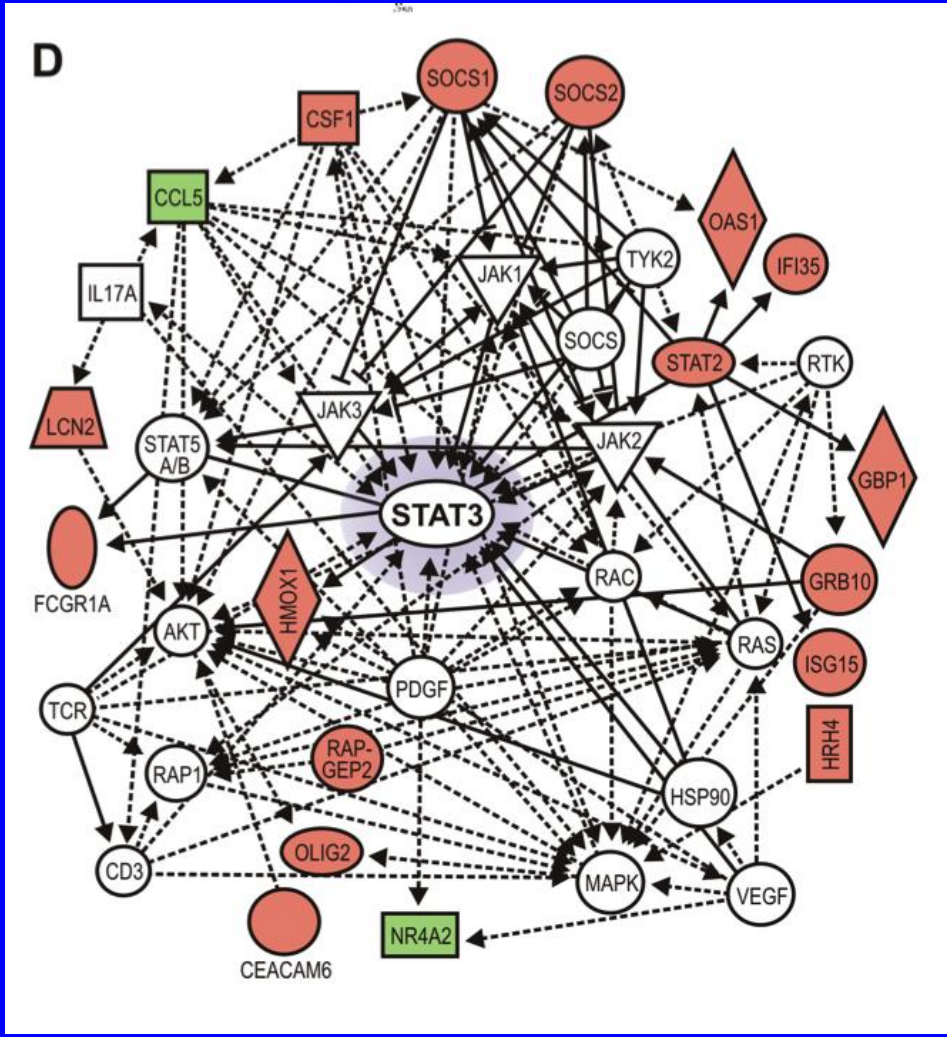


Similar levels of IgE

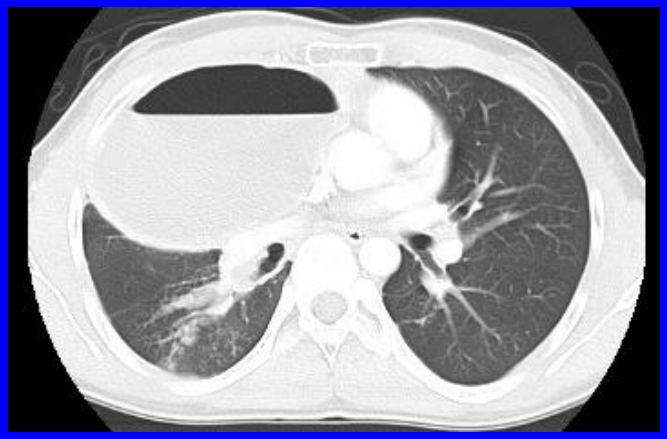


Less mast cell reactivity

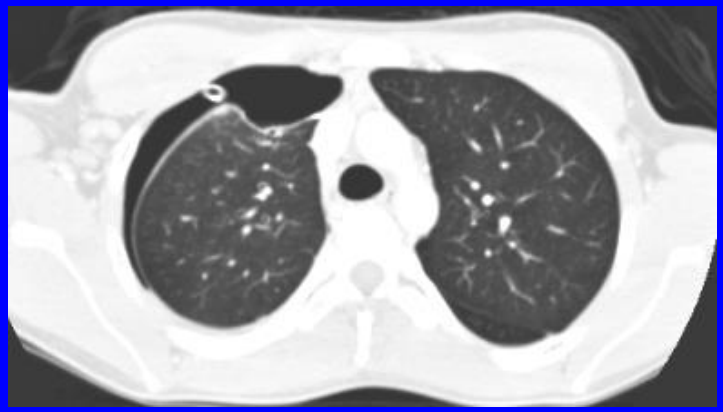
STAT3 is expressed widely and involved in many pathways making understanding the diverse clinical features difficult

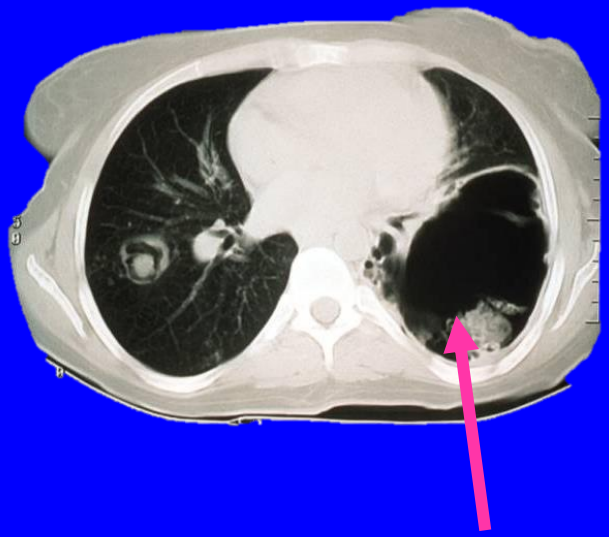


AD-HIES abnormal tissue remodeling



Bronchopleural fistulae

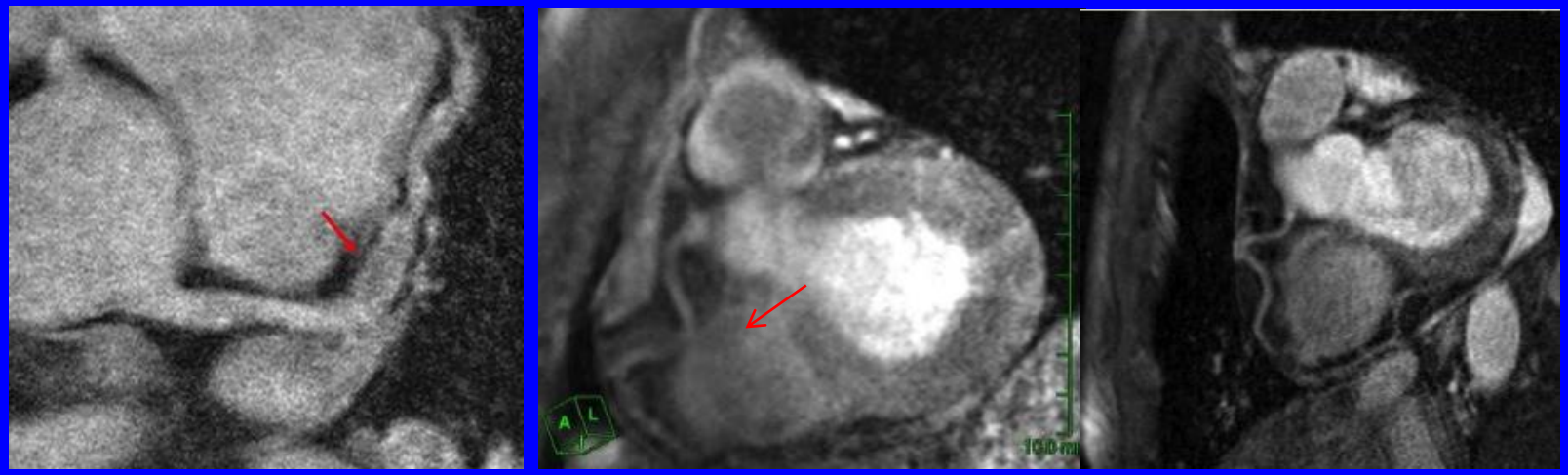




Pneumatocoele with aspergilloma

Freeman et al, J of Clin Immunology 2013

Middle sized arterial aneurysm



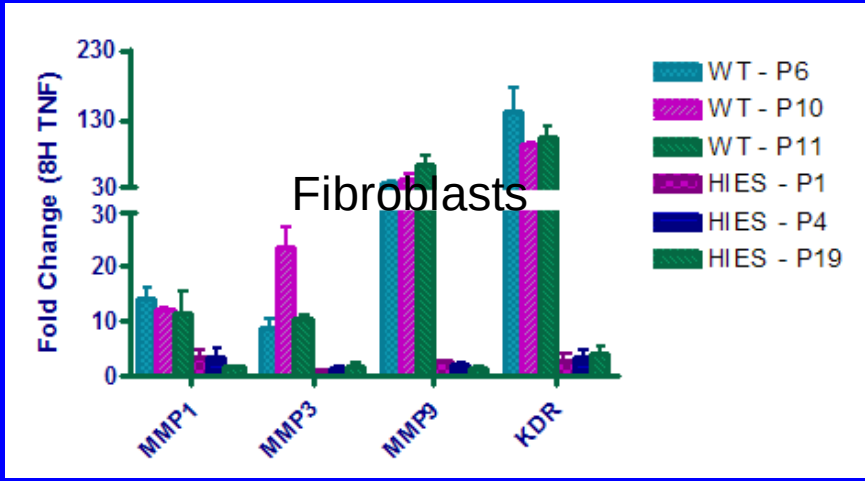
Left anterior descending artery dilation and aneurysm, and RCA Tortuosity

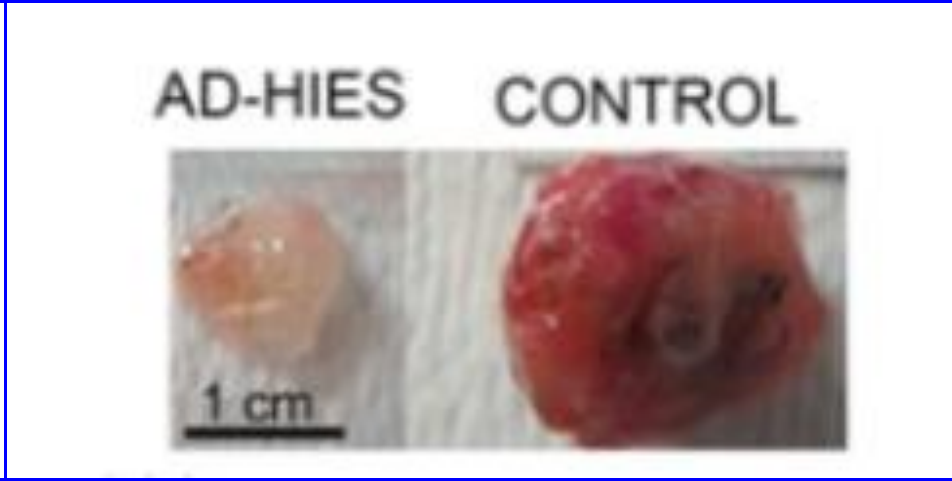
We screen coronary and brain middle size arteries by MRA or CT to try and prevent complications

Disordered Tissue Remodeling

Collaboration with Manfred Boehm NHLBI and lab, and Ian Myles, NIAID

- STAT3 important for angiogenesis (new blood vessel growth) and tissue remodeling

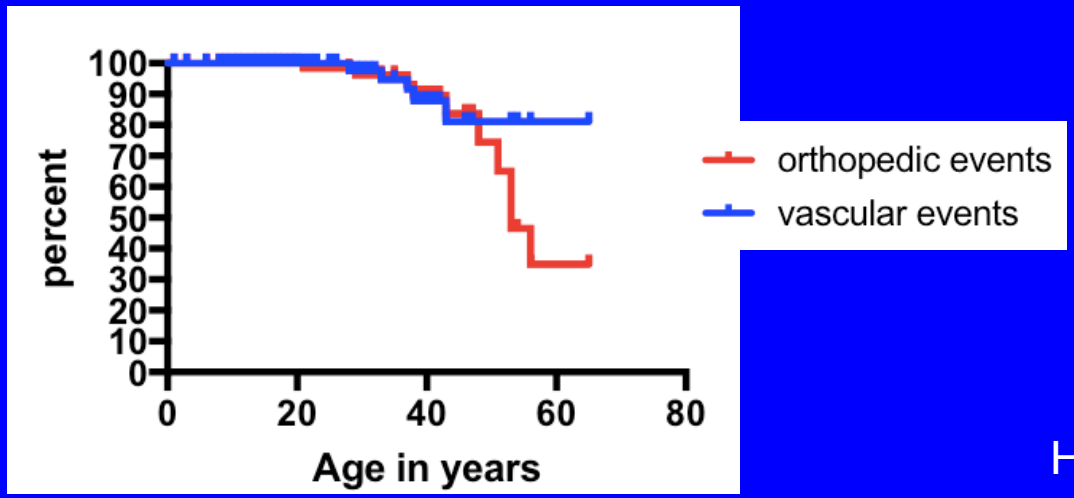


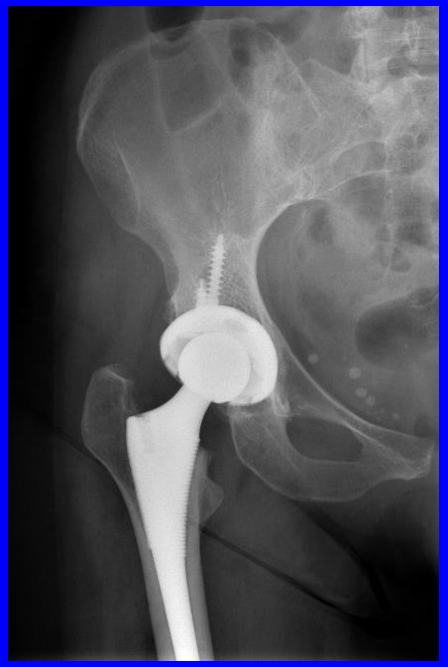


iPSC Teratomas

Evolving Prognosis

Improving long term survival
Early diagnosis changing natural history
But need to figure out the vascular and orthopedic issues





Hip Replacement in a 55 year old

Diagnosis of HIES

- Genetic testing with compatible symptoms
  - STAT3- BOTH infections/eczema plus connective tissue (such as flexible joints) or bone issues
- HIES scoring system- was used more before STAT3 testing was widely available
- Whole exome sequencing or panel can identify the other Hyper IgE syndromes as well.

Approach to Care

- Supportive with suppressive antimicrobials
  - TMP/SMX (Bactrim) typically, antifungals
  - Travel plans- antifungals if going to Southwest US!
- Antiseptics (i.e.dilute bleach baths, chlorhexidine, swimming in chlorinated water) to control eczema, reduce *S. aureus* colonization
- Consideration of dupilumab for eczema
- Consideration of IgG supplementation: IVIG or SCIG
- Bone and dental health: Vitamin D levels
- Low suspicion of infection
- Consideration of bone marrow transplant

Dupilumab

- Monoclonal antibody approved for use in eczema (above 6 months), moderate to severe asthma (6 years and up), eosinophilic esophagitis (12 years and up), sinusitis with polyps
  - Mostly used in HIES for eczema
- Injection (comes as pre-filled injection with pen) that is given subcutaneously every 2 weeks. Can be given at home- let warm to room temp before giving.
- Side effects- main one are injection site pain and conjunctivitis (pink eye)
- Can cause transient increase in eosinophils in the blood, and decreases IgE.

What is the role for HSCT?

Bone Marrow Transplantation (2000) 25, 1303–1305

www.nature.com/bmt

Case report

Bone marrow transplantation does not correct the hyper IgE syndrome

AR Gennery, TJ Flood, M Abinun and AJ Cant

Department of Paediatric Immunology, Newcastle General Hospital, Newcastle upon Tyne, UK

J Allergy Clin Immunol. 2010 Aug;126(2):392-4. doi: 10.1016/j.jaci.2010.05.005. Epub 2010 Jul 2.

Successful long-term immunologic reconstitution by allogeneic hematopoietic stem cell transplantation cures patients with autosomal dominant hyper-IgE syndrome.

Goussetis E, Peristeri I, Kitra V, Traeger-Synodinos J, Theodosaki M, Psarra K, Kanariou M, Tzortzatou-Stathopoulou F, Petrakou E, Fylaktou I, Kanavakis E, Graphakos S.

General Approach to Transplant

- Choose who is the best donor
  - HLA (white blood cell typing) matched sibling, matched unrelated donor, haplo-identical donor
- General tune up to be in best health possible
- Typically about one week of chemotherapy to clear out one's own bone marrow from progenitors of white blood cells, red blood cells, platelets.
- Infusion of bone marrow or stem cells from donor
- Wait with lots of supportive care for the new cells to grow

HSCT Pros/Cons

- Pro: Eczema and infection susceptibility should be cured or close to cured
  - Exception- if bronchiectasis or pneumatocele is present, the lung disease will hopefully stabilize and improve but infections may occur still.
- Cons: Increased infection risk around HSCT (closely monitored)
  - Graft versus host disease
  - Potential infertility (discuss possible options in advance)

What is the role for HSCT in STAT3 HIES?

- Seems to make sense in some cases
  - four pediatric patients transplanted at NIH- all at worse end of spectrum
  - About 25 patients transplanted worldwide?
  - Some great outcomes being reported
- But for HIES from STAT3, not everything will be corrected
  - Will the infection phenotype be improved? Probably
  - Will the bone phenotype be improved? Maybe
  - Will the vascular phenotype be improved? Maybe not
  - Lung healing if there a post- transplant pneumonia? Unknown

COVID-19 in STAT3 HIES

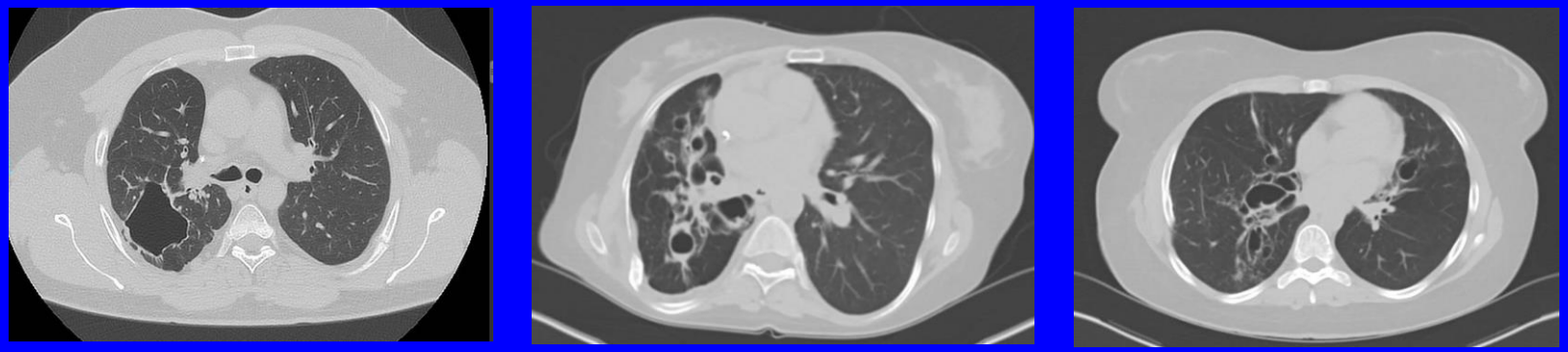
Pre-or no Vaccination: at least 13 COVID-19 Infections

- 5 hospitalized
  - All significant parenchymal lung disease (one full pneumonectomy)
  - Two with obesity, at least 4 with hypertension
  - One fatality (and only one to ICU)- 41 year old Hispanic male, obesity, bronchiectasis with MRSA and Pseudomonas, Hypertension, Prior MI with coronary artery aneurysm, busy hospital with many COVID cases.

Post- vaccination: > 26 COVID-19 infections

One hospitalization: secondary bacterial pneumonia.

No fatalities yet



Baseline CTs of patients who got COVID-19 post vaccination and did fine, no hospitalizations (but I worried); two got antivirals

Some Ongoing Projects

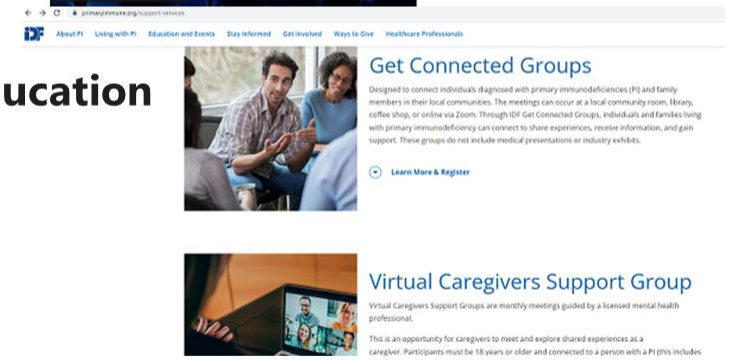
- COVID vaccine responses (Good! Important to get!)
- International collaboration (many sites around the world) to study quality of life for those with HIES and therapies or diseases processes that affect QOL
  - Transplant, dupilumab, etc
- Studies of the lung pathology for HIES
  - Germany, NIH/University of North Carolina
- Gene Editing
  - Trying to “fix” the mutation

THANKS!!

QUESTIONS?

Additional Resources

- **IDF Resource Center:** https://primaryimmune.org/resource-center
- **IDF Support Services:** https://primaryimmune.org/support-services
- **IDF's YouTube Channel (recordings of all IDF education sessions available):** https://www.youtube.com/user/IDFvideos



Have more Questions?

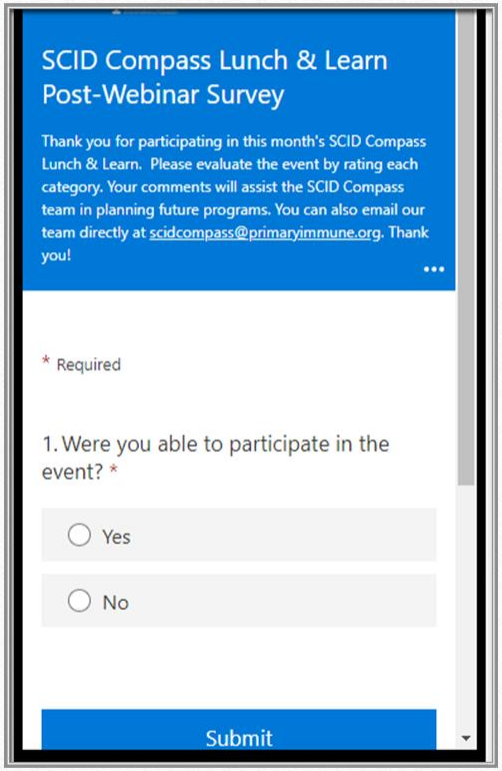
www.Primaryimmune.org/ask-idf

800-296-4433

Immune Deficiency Foundation

WE VALUE YOUR FEEDBACK…

Please take a moment to complete our Evaluation Survey after the Program!



Upcoming Events

IDF Lunch & Learn: NEMO

Wednesday, 11/9/22

Kelly Walkovich, MD

SCID Compass Lunch & Learn:

Organ Function and Long-term Follow-up outcomes

Wednesday, 11/16/22

Ami Shah, MD

For a list of all upcoming IDF Events, visit:

https://community.primaryimmune.org/s/events?language=en_US

THANK YOU!

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