Decoding PI: Antibody Deficiencies

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Disclosures

- Chiesi Global Rare Diseases
  - Clinical trial ADA-SCID
  - Advisory board
- Takeda Pharmaceuticals
  - Clinical trial subcutaneous IgG
- Global Genes: Rare-X
  - Immunodeficiency Work Group (Gratis)

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Objectives

- To review the well-defined antibody deficiencies
  - Including: Age of onset, immunologic characteristics, infections, other complications, treatment, prognosis
- To highlight the role of advanced testing for certain antibody deficiencies
- To identify targeted treatments available for some molecular diagnoses

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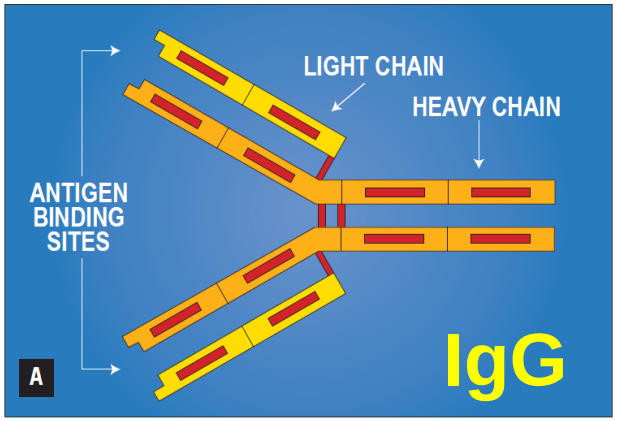
THE BASICS: ANTIBODIES

Immunoglobulin Structure

CHAPTER 1; FIGURE 3



IDF Patient and Family Handbook. 2013

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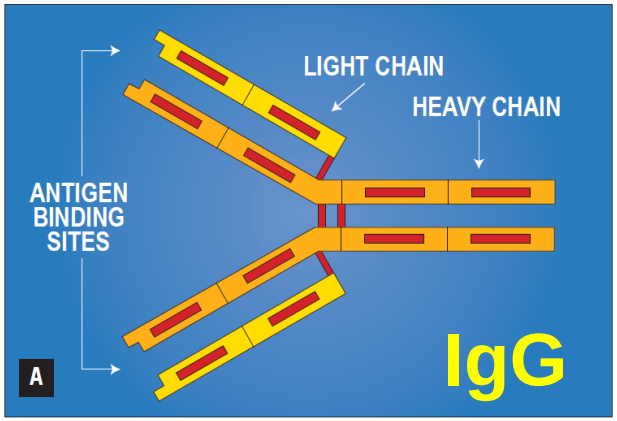
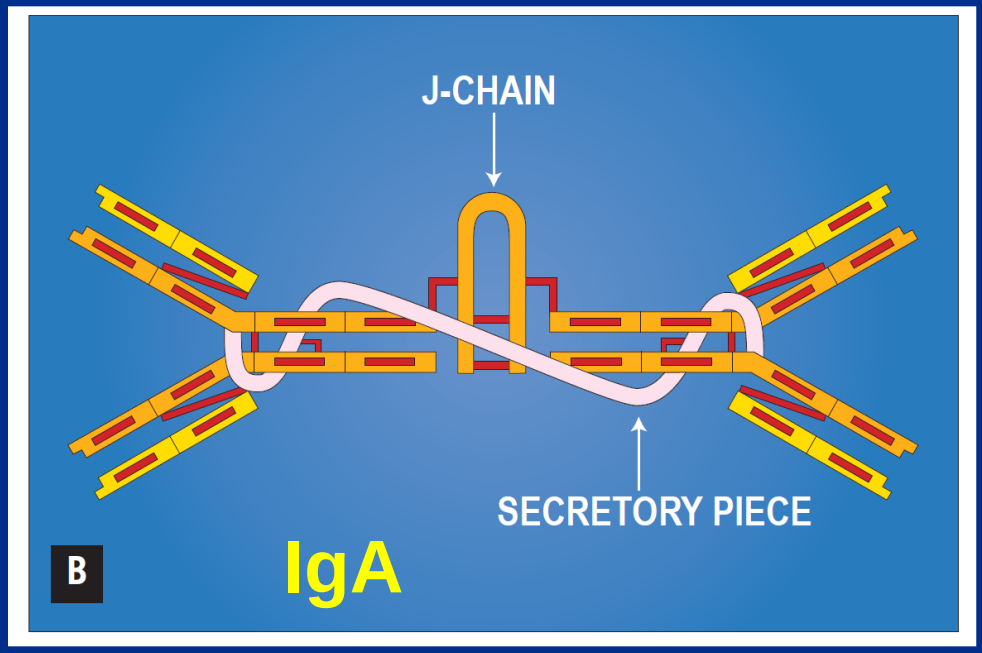
Immunoglobulin Structure

CHAPTER 1; FIGURE 3





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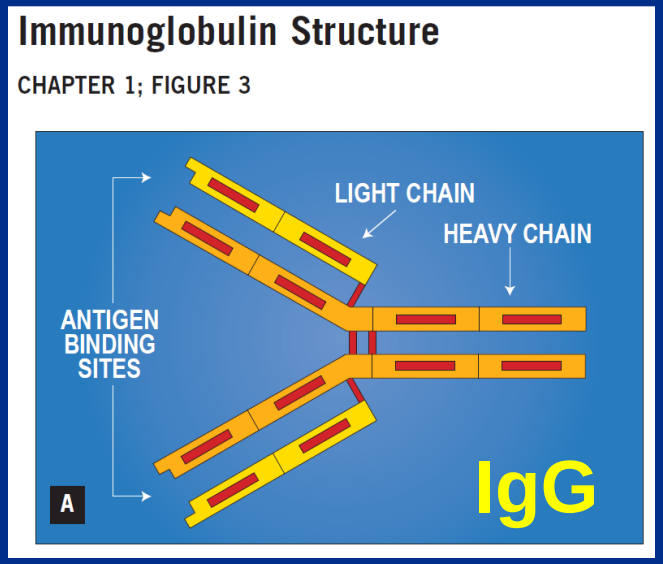

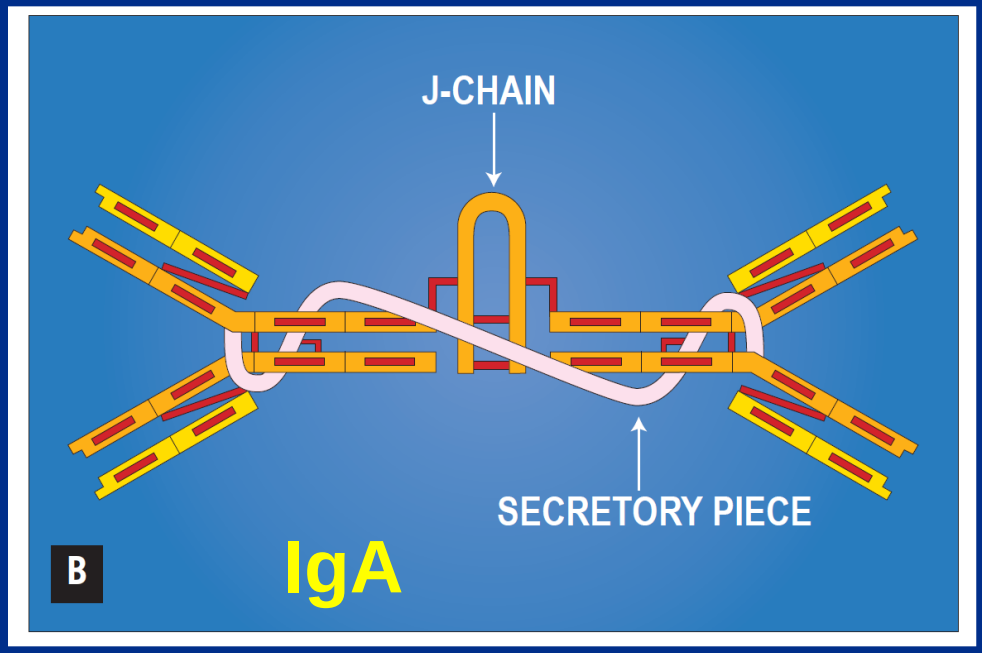

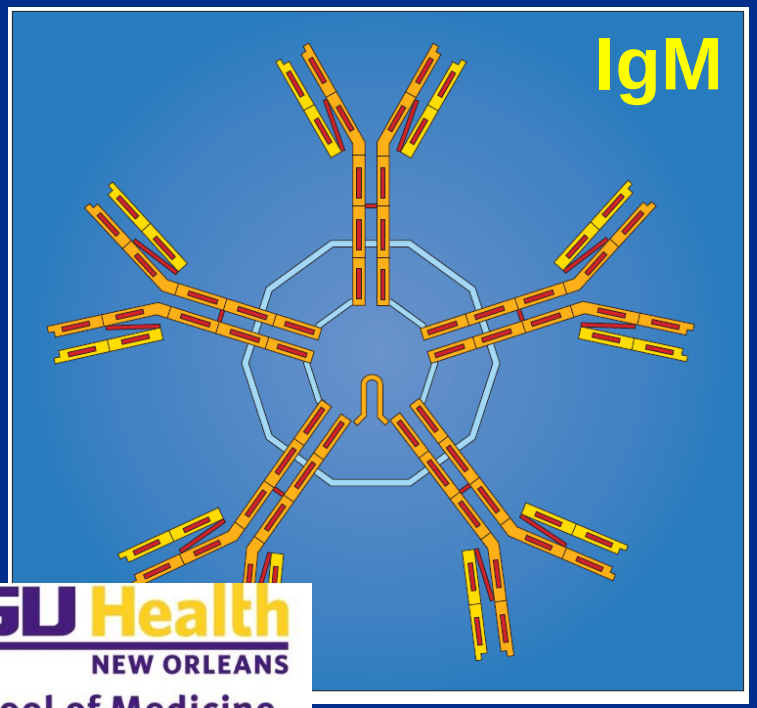

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Roles of Antibodies

- Bind to bacteria
  - Prevent bacteria from sticking to human cells
    - Prevents infection
  - Help immune cells to recognize and engulf the bacteria
  - Activate the Complement system
    - Directly destroy the bacteria (drill holes in surface)
    - Enhanced removal of bacteria from bloodstream
    - Enhanced phagocytosis
      - (immune cells eat the bacteria)

Role of Antibodies

- Bind to viruses
  - Neutralize viruses (prevent infection)
  - Form larger “clumps” which make it easier for cells of the immune system to engulf the viruses

Forms of Antibody Deficiencies

- Specific Antibody Deficiency (SAD)
- Selective IgA Deficiency
- IgG Subclass Deficiency
- Hypogammaglobulinemia
  - Transient Hypogam of Infancy
- Common Variable Immune Deficiency (CVID)
- X-Linked Agammaglobulinemia (XLA)

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SPECIFIC ANTIBODY DEFICIENCY (SAD)

SAD

- Age:
  - Children >2 years old
    - May have symptoms earlier
  - Adults
- Immunologic characteristics:
  - Low vaccine titers to Pneumovax-23
  - Normal titers to protein vaccines
  - Normal IgG, IgA, IgM
- Types of infections:
  - Ears, sinus, lungs

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SAD

- Treatment:
  - Treat infections early with prolonged course of antibiotics
  - Clinical severity:
    - Mild: Watch and wait
    - Moderate: Prophylactic antibiotics
    - Severe: IgRT (typically 1 to 2 years)
- Prognosis:
  - Excellent, most “outgrow”
  - Continue monitoring at least annually
  - Could be initial finding of a more severe immune defect (rarely)

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Many disorders are associated with impaired vaccine response

Box 1
Primary immunodeficiencies and secondary immunodeficient states that may be associated with impaired vaccine response

Primary	Acquired
Wiskott-Aldrich syndrome	Splenectomy
DiGeorge syndrome	Immunosuppression
Asplenia	Malnutrition
Hyper–immunoglobulin E (Job) syndrome	Protein-losing enteropathy
Common variable immune deficiency	Nephrotic syndrome
Dock8 deficiency	Chylothorax
NEMO deficiency	Human immunodeficiency virus infection
Class switch recombination defects	—
Selective immunoglobulin A deficiency	—
Immunoglobulin G subclass deficiency	—

Wall et.al. Immunol Allergy Clin N Am 35 (2015) 659-670

SELECTIVE IGA DEFICIENCY

Selective IgA Deficiency

- Age:
  - Childhood to Adulthood
  - Often silent (without symptoms). Normal life.
- Immunologic characteristics:
  - Absent IgA, with normal IgG and IgM
  - Normal vaccine titers (some exceptions)
  - IgG2 subclass deficiency in some
- Types of infections:
  - Respiratory and Intestinal infections

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Selective IgA Deficiency

- Other complications:
  - Autoimmunity
  - Celiac disease
- Treatment:
  - No treatment required for most
  - Antibiotics (longer course)
  - Antibiotic prophylaxis for some
- Prognosis:
  - Excellent, depending on autoimmunity
  - Those with worsening pattern of infection need to be re-evaluated

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IGG SUBCLASS DEFICIENCY

IgG Subclasses

- The total serum IgG level is composed of four subclasses:
  - IgG1: 60-70% of total serum IgG level
  - IgG2: 20-30%
  - IgG3: 5-8%
  - IgG4: 1-3%

IgG Subclasses

- IgG subclasses: Overlapping, yet different roles:
  - IgG1 and IgG3: viral antigens
  - IgG2: encapsulated bacteria
    - (Common resp bacteria: Streptococcus and H.flu)

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IgG Subclass Deficiency

- Individuals who appear to fight infections in normal fashion may have low IgG subclass.
- IgG Subclass Deficiency is therefore diagnosed when:
  - Patient demonstrates susceptibility to sinopulmonary infections
  - Persistently low IgG subclass (one or more)
  - Normal IgG, IgA, IgM

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IgG Subclass Deficiency

- Because IgG1 comprises at least 60% of the total serum IgG level:
  - Low IgG1 often results in low total serum IgG level: Hypogammaglobulinemia

TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY

(THI)

THI

- Age: >= 6 months old
  - Infants and toddlers
- Immunologic characteristics:
  - Low IgG
  - IgA and IgM might be low (but present)
  - Normal vaccine titers
- Types of infections:
  - Sinus and ear
  - Other types possible

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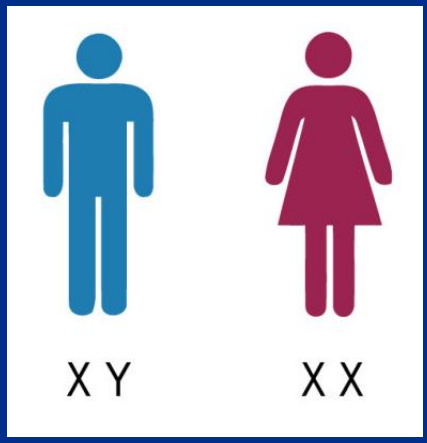
THI

- Other complications:
  - Allergy is common
- Treatment:
  - Treat infections early and aggressively
  - Monitor (watch and wait)
    - Some may need prophylactic antibiotics
    - Could warrant IgRT if clinically severe
- Prognosis:
  - Resolves over time (2 to 5 years old)
  - May continue to monitor annually into adulthood

X-LINKED AGAMMAGLOBULINEMIA

(XLA)

XLA



- X-Linked recessive inheritance
  - Mutation on the X chromosome
  - Passed to next generation
  - Females who have the gene mutation are “silent carrier”
  - Males who have the gene mutation have the disease

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XLA

- Age: >= 6 months of age
- Immunologic characteristics:
  - Absent B cells
  - Absent immunoglobulins (no antibodies)
- Types of infections:
  - Bacterial infections of ears, sinus, lungs
  - Skin and tissue infections
  - Viral meningitis (Enterovirus)

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XLA

- Other complications:
  - Neutropenia
  - Autoimmunity
- Treatment:
  - IgRT (essential)
  - Consider prophylactic antibiotics
  - Early and aggressive treatment of infections
- Prognosis:
  - Lifelong disorder
  - Do very well with treatment

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COMMON VARIABLE IMMUNE DEFICIENCY

(CVID)

CVID

- Age:
  - Adolescence to adulthood
- Immunologic characteristics:
  - Low IgG
  - Low IgA or IgM
  - Low vaccine titers
- Types of infections:
  - Bacterial infections of ears, sinus, lungs
  - Mycoplasma pneumonia “walking pneumonia”
  - Intestinal infections
  - Joint infections

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CVID

- Other complications:
  - Autoimmunity
    - Cytopenias
    - Organ involvement (lungs, bowel)
- Treatment:
  - IgRT
  - Aggressive treatment of infections
  - Treatment of autoimmunity
  - Monitor for organ involvement
  - Monitor for malignancy

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CVID

- Prognosis:
  - Good quality of life if diagnosed early and treated aggressively
  - Factors:
    - Organ damage at time of diagnosis
      - Bronchiectasis (Lung damage)
    - Autoimmunity or granulomatous inflammation
      - May require medications to control inflammation

Shift in the Tide:

- Decreased mortality from infections
- Increased longevity for CVID patients
- Increased noninfectious complications

1. Nonas, S. Pulmonary manifestations of PIDD. Immunol Allergy Clin N Am 35 (2015) 753-766.
2. Resnick, E. et al. Morbidity and mortality in CVID over 4 decades. Blood. 2012; 119(7).

CURRENT OPINION

The many faces of the clinical picture of common variable immune deficiency

Volume 12 • Number 6 • December 2012

Elena S. Resnick and Charlotte Cunningham-Rundles

- CVID: Clinical Manifestations
  - Infections 94%
  - Autoimmunity and cytopenia 29%
  - Chronic lung disease 29%
  - Inflammatory bowel disease 15%
  - Bronchiectasis 11%
  - Granulomatous disease 10%
  - Liver disease 9%
  - Lymphoma 8%
  - Other cancers 7%
  - Malabsorption 6%

CVID

- More aggressive monitoring / treatment
  - Bronchiectasis
  - Low Memory B Cells
  - Granulomatous disease
  - Other organ dysfunction
    - Lungs
    - Kidneys
    - Liver
    - Bowel

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Recap: Antibody Deficiencies

- Specific Antibody Deficiency (SAD)
  - Weak polysaccharide vaccine response ONLY
- Selective IgA Deficiency
  - Absent IgA ONLY
  - Not treated with IgRT
- IgG Subclass Deficiency
  - Low IgG subclass ONLY - controversial

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Recap: Antibody Deficiencies

- Transient Hypogam of Infancy
  - Low Immunoglobulins ONLY
    - (retrospective diagnosis- requires monitoring)
- CVID
  - Older child or adult
  - Low IgG (plus low IgA and/or IgM)
  - Weak vaccine response
  - Autoimmunity common and possibly severe
- X-Linked Agammaglobulinemia (XLA)
  - Infant
  - Absent immunoglobulins
  - Absent B cells

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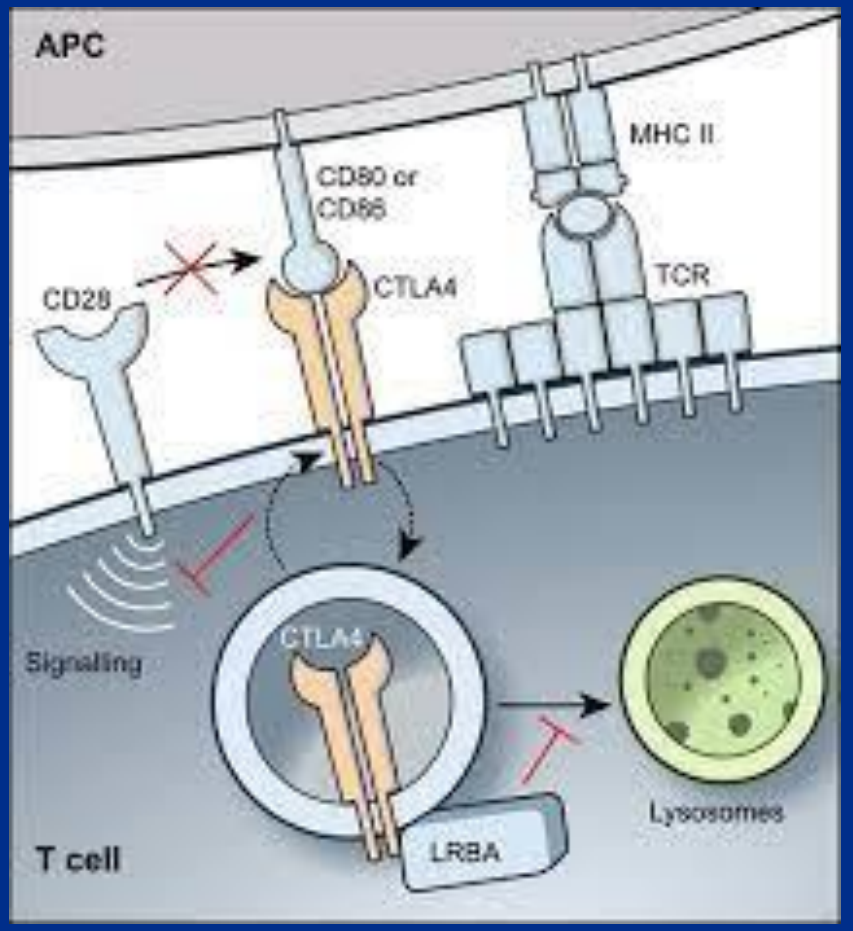
CVID LOOK-ALIKES DX → TREAT

The benefit of making a specific genetic diagnosis

CTLA4 / LRBA

- Common Variable Immune Deficiency phenotype
  - Low IgG, IgA, IgM
  - Weak vaccine response
- Severe autoimmunity
  - Refractory thrombocytopenia
  - Enlarged organs
  - Interstitial lung disease
- Genetic testing revealed:
  - CTLA4 mutation
- Treatment: Abatacept
  - (CTLA4 fusion protein)



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APDS: Activated PI3K Delta Syndrome

- PIK3CD gain-of-function
- Mutations in PIK3CD and PIK3R1 have overlapping features

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NIAID Health Information: PIK3CD Disorder. Sept 2016.

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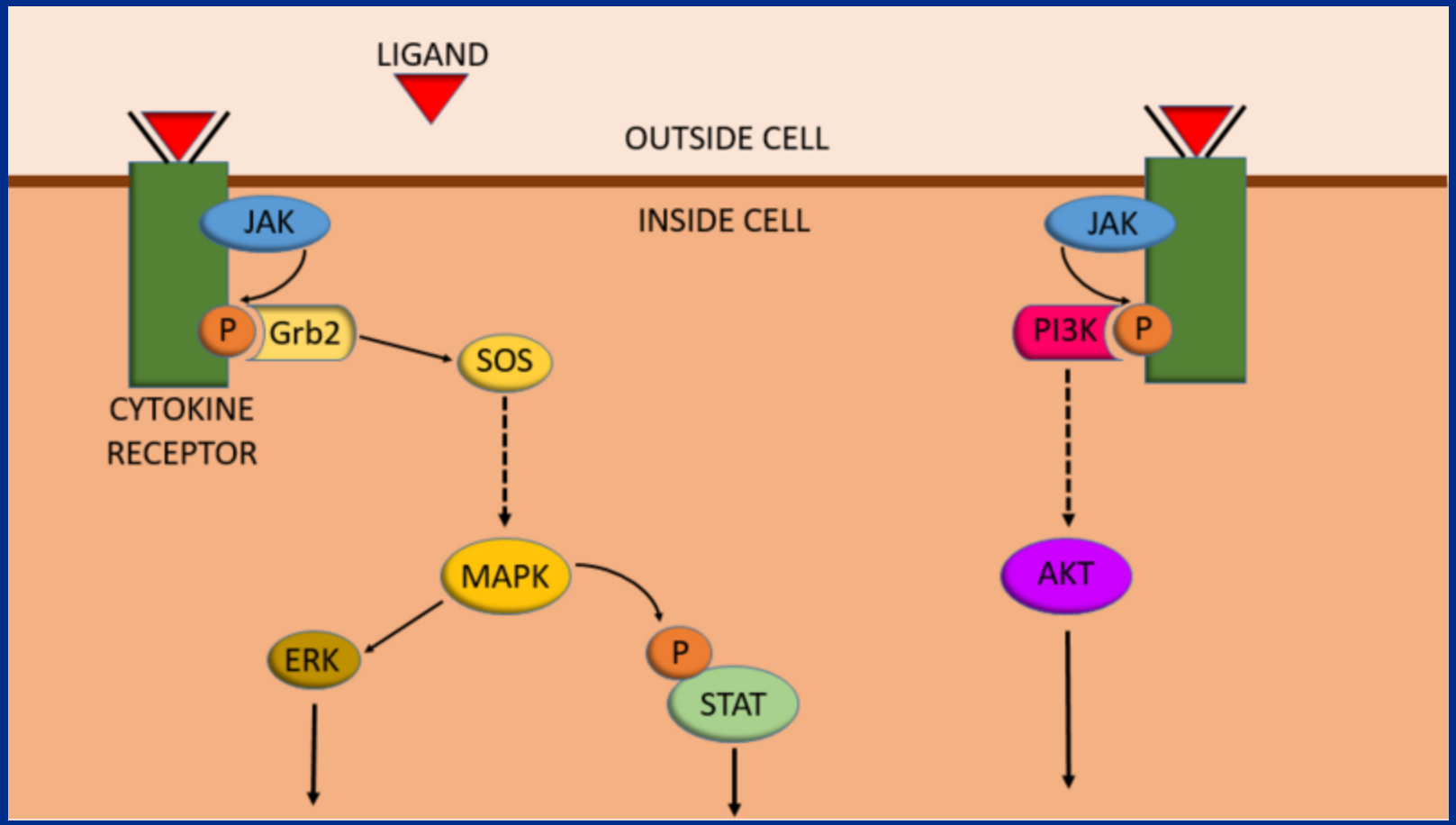
APDS: Activated PI3K Delta Syndrome



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APDS: Activated PI3K Delta Syndrome

- Autosomal dominant inheritance
- CVID immunologic phenotype
- Combined immunodeficiency

APDS: Activated PI3K Delta Syndrome

- Bacterial sinopulmonary infections
- Chronic viral infections
  - EBV
  - CMV
- Autoimmunity, Lymphoproliferation
- Increased risk for lymphoma
  - EBV-driven B-cell lymphoma

1.NIAID Health Information: PIK3CD Disorder. Sept 2016.
2.Lucas, C. L., Kuehn, H. S., Zhao, F., Niemela, J. E., Deenick, E. K., Palendira, U., ... & Uzel, G. (2014). Dominant-activating germline mutations in the gene encoding the PI (3) K catalytic subunit p110δ result in T cell senescence and human immunodeficiency. Nature immunology, 15(1), 88-97.

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APDS: Activated PI3K Delta Syndrome

- Overactivity of PI3K pathway
- Hyperactivation of mammalian target of rapamycin (mTOR)
- Treatment
  - Rapamycin (sirolimus)
    - Inhibits mTOR
  - Leniolisib – PI3K-delta inhibitor (>= 12 y/o)

Lucas, C. L., Kuehn, H. S., Zhao, F., Niemela, J. E., Deenick, E. K., Palendira, U., ... & Uzel, G. (2014). Dominant-activating germline mutations in the gene encoding the PI (3) K catalytic subunit p110δ result in T cell senescence and human immunodeficiency. Nature immunology, 15(1), 88-97.

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STAT3 Gain of Function

- Autosomal dominant
- Hypogam with low switched memory B cells
- Combined immunodeficiency
- Autoimmunity
  - Cytopenias, enteropathy, ILD, DM
- Short stature

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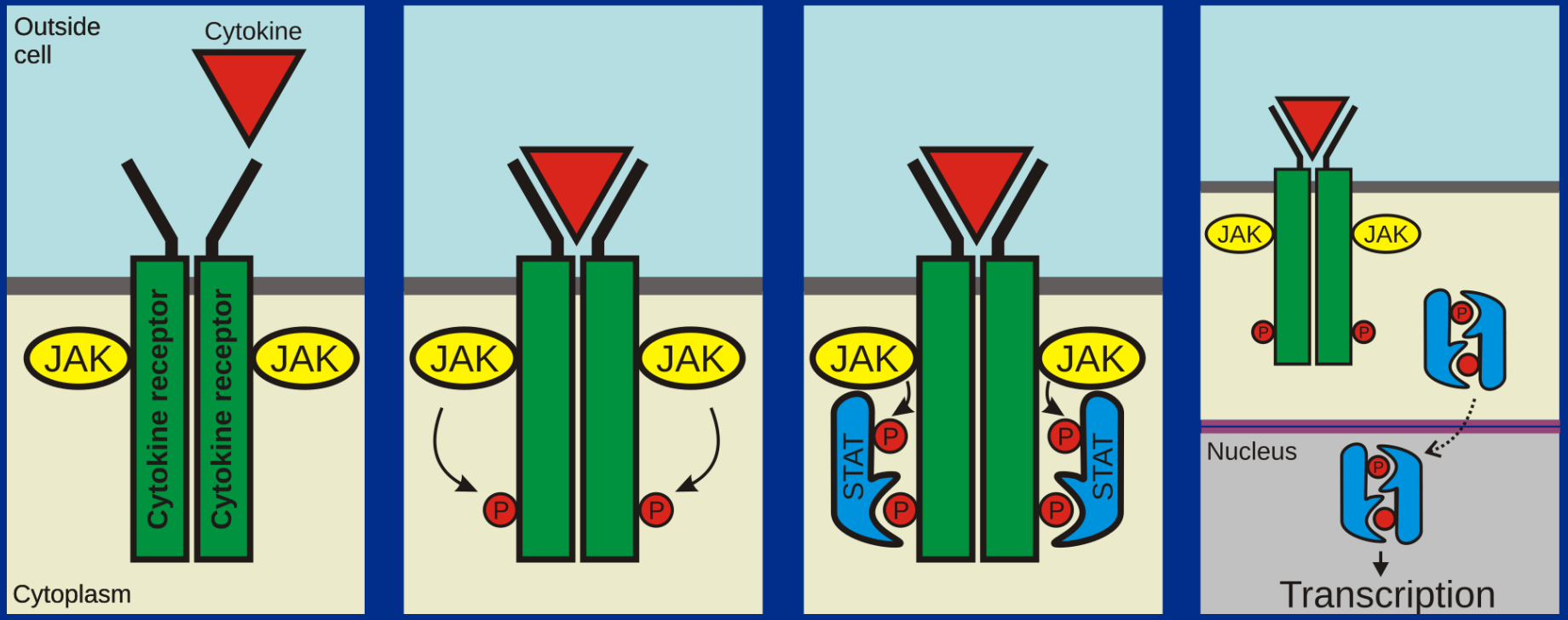
STAT3 Gain of Function



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STAT3 Gain of Function

- Treatment options:
  - Treatment with Tocilizumab (anti-IL6)
    - Dampens the IL6/JAK/STAT3 pathway
    - May be effective for autoimmunity
  - JAK Inhibitor
    - Dampens JAK/STAT signaling (larger reach)

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STAT3 Gain of Function

- Treatment options:
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    - Dampens the IL6/JAK/STAT3 pathway
    - May be effective for autoimmunity
  - JAK Inhibitor
    - Dampens JAK/STAT signaling (larger reach)

(Other STAT-GOFs have been identified- similar presentation)

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ADVANCED TESTING

Genetic Testing

- Not required for diagnosis and management
  - Especially those with infection-only phenotype
- In patients with immune dysregulation, autoimmunity, malignancy, or other complications, single-gene defects may be amenable to specific therapies and genetic diagnosis should be considered when possible.

1. Bonilla et. al. ICON:CVID. JACI, 2016

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Functional Testing (limited)

- Functional testing and/or protein expression can yield valuable insight.
- Valuable in resolving Variants of Uncertain Significance
- Availability now includes several CVID-like conditions:
  - APDS (Pharming)
  - LRBA (Mayo, Med College Wisconsin)
  - STAT-GOF studies (Med College Wisconsin)

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Summary

- Antibody deficiencies are widely variable
- Some require aggressive treatment
- Association with autoimmunity
- All should be monitored over time
- Consider genetic testing, especially if more than infection-only phenotype
- Majority of patients have a good life!

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Helpful Resources

- IDF Patient & Family Handbook for Primary Immunodeficiency Diseases, Sixth Edition | Immune Deficiency Foundation
  - primaryimmune.org/resources/print-material
- https://www.immunodeficiencysearch.com/
- https://www.medscape.com

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