Is it CVID?
Not Necessarily

HAIG TCHEUREKDJIAN, MD
Current Paradigm of Pathogenesis

- Genetic defect(s)
- Molecular defect(s)
- Cellular defect(s)
- Clinical disease
Current Paradigm of Pathogenesis

Genetic defect(s) → Molecular defect(s) → Cellular defect(s) → Clinical disease
<table>
<thead>
<tr>
<th>Clinical Disease</th>
<th>AMERATUNGA, ET AL 2013</th>
<th>ICON 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAGID 1999</td>
<td>Recurrent, severe, or unusual infections</td>
<td>Infection</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Poor response to antibiotics</td>
<td>Autoimmunity</td>
</tr>
<tr>
<td></td>
<td>Breakthrough infections despite prophylactic antibiotics</td>
<td>Lymphoproliferation</td>
</tr>
<tr>
<td></td>
<td>Infections in spite of appropriate immunization</td>
<td>None of the above</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis or chronic sinus disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammatory disorder or autoimmunity</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Disease**

- **PAGID 1999**
  - Immunodeficiency

- **AMERATUNGA, ET AL 2013**
  - Recurrent, severe, or unusual infections
  - Poor response to antibiotics
  - Breakthrough infections despite prophylactic antibiotics
  - Infections in spite of appropriate immunization
  - Bronchiectasis or chronic sinus disease
  - Inflammatory disorder or autoimmunity

- **ICON 2015**
  - Infection
  - Autoimmunity
  - Lymphoproliferation
  - None of the above
# Laboratory Phenotype

<table>
<thead>
<tr>
<th>PAGID 1999</th>
<th>AMERATUNGA, ET AL 2013</th>
<th>ICON 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked decrease in IgG and IgA (or IgM)</td>
<td>IgG &lt; 500 mg/dL</td>
<td>IgG &lt; 450 mg/dL (although near normal still consistent)</td>
</tr>
<tr>
<td>Absent isohemagglutinins and/or poor vaccine responses</td>
<td>Low IgA (&lt;80 mg/dL) and/or IgM (&lt;40 mg/dL)</td>
<td>Low IgA or IgM</td>
</tr>
<tr>
<td></td>
<td>B cells present but low # CD27+ and/or increased CD21low B cells</td>
<td>Poor vaccine responses</td>
</tr>
<tr>
<td></td>
<td>IgG3 deficiency (&lt;20 mg/dL)</td>
<td>Transient responses to vaccines</td>
</tr>
<tr>
<td></td>
<td>Poor vaccine response</td>
<td>Absent isohemagglutinins</td>
</tr>
<tr>
<td></td>
<td>Transient responses to vaccines</td>
<td>Serological support for autoimmunity</td>
</tr>
<tr>
<td></td>
<td>Absent isohemagglutinins</td>
<td>Sequence variations in predisposing genes</td>
</tr>
</tbody>
</table>
Current Paradigm of Pathogenesis

- Genetic defect(s)
- Molecular defect(s)
- Cellular defect(s)
- Clinical disease
sine qua non of CVID
Maybe a B cell defect?
Not necessarily an Ig production defect
## Function by Immunoglobulin Isotype

<table>
<thead>
<tr>
<th>Functional Activity</th>
<th>IgM</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
<th>IgA</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutralization</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Opsonization</td>
<td>+++</td>
<td>Genotype dependent</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitization for killing by NK cells</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitization of mast cells</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Complement activation</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Maybe a T cell defect?
Maybe a dendritic cell defect?
Likely multicellular defect
Historical model

Humoral PIDD

CVID
Current/Evolving model

Humoral PIDD

- CVID
- LRBA
- LOCID
- APDS
Current Paradigm of Pathogenesis

- Genetic defect(s)
- Molecular defect(s)
- Cellular defect(s)
- Clinical disease
Genetic defects

Inducible T cell co-stimulator (ICOS)

• ICOS expression
  • T cells
  • Dendritic cells

• ICOS ligand expression
  • B cells
  • Dendritic cells

• ICOS - ICOS ligand interactions
  • Germinal center formation
  • Terminal B cell differentiation
  • Effector T cell responses
  • Immune tolerance
ICOS Deficiency Clinical Features

• Autosomal recessive loss of function mutations
• Presents at any age

• Infections
  • Sinopulmonary
  • Gastrointestinal
  • Opportunistic
    • CMV viremia
    • Pneumocystis jirovecii pneumonia

• Immune Dysregulation
  • Autoimmune disease
  • Lymphoid hyperplasia
  • Granulomatous disease
  • Hepatosplenomegaly
  • Inflammatory bowel disease
ICOS Deficiency Laboratory Findings

• Low IgG (variable IgA and IgM)
• Impaired responses to protein and polysaccharide vaccines
• Absent to near absent memory B cells
• Absent plasma cells in marrow
ICOS Deficiency Therapy

• B-cell, T-cell, and Dendritic cell defects must be weighed

• Immunoglobulin replacement

• Prophylaxis against opportunistic infections
  • Trimethoprim/sulfamethoxazole
  • Acyclovir

• Hematopoietic stem cell transplantation
  • Infections
  • Inflammatory bowel disease
Who to genotype?

• Opportunistic infections
• Difficult to control inflammatory disease, especially enteropathy
• Absence or near absence of memory B cells
• Absence of marrow plasma cells
• Family history
Benefits of genotyping

• Opportunistic infection prophylaxis
• Consider HSCT in severe cases including enteropathy
• Family planning
TACI

- Transmembrane activator and calcium modulator and cyclophilin ligand interactor
- Expressed on B cells

**Ligands**
- B-cell activating factor (BAFF) or B Lymphocyte Stimulator (BLyS)
  - Membrane bound and soluble
- A Proliferation Inducing Ligand (APRIL)
  - Soluble

**Produced by**
- Dendritic cells
- Monocytes
- Neutrophils
- Bone marrow stromal cells
TACI Function

• Class switch recombination
• Differentiation of plasma cells
• Survival of plasma cells
• T-independent responses to polysaccharide antigens
• Central B-cell tolerance and peripheral B-cell expansion
TACI Mutation Clinical Features

- Biallelic mutations are disease causing
- Monoallelic mutations are disease predisposing
- Loss of function mutations

Clinical phenotype
- Common variable immunodeficiency
  - Sinopulmonary infections, granulomatous disease, lymphoid hyperplasia
  - Autoimmune disease primarily in heterozygous patients
- Selective IgA deficiency
- IgG subclass deficiency
TACI Mutation Laboratory Findings (in CVID)

- Low IgG (variable IgA and IgM)
- Impaired responses to polysaccharide vaccines
- Variable memory B cell numbers
TACI Mutation Therapy in CVID

- Traditional CVID therapy
  - Immunoglobulin replacement
  - Antimicrobial prophylaxis when appropriate
  - Management of inflammatory and autoimmune diseases
  - Malignancy surveillance
Phosphoinositide 3-kinase (PI3K)

- PIK3CD gene encodes the catalytic p110δ subunit of phosphoinositide 3-kinase (PI3K)
- Intracellular molecule in leukocytes including B-cells and T-cells
- Activated by binding of ligands to various cell surface receptors
  - Antigen receptors
  - Cytokine receptors
  - Surface integrins
- Modulates signaling through multiple downstream pathways including mechanistic target of rapamycin (mTOR) modulating
  - Gene expression
  - Regulation of protein and organelle function
  - Cellular metabolism
Immunodeficiency secondary to PIK3CD mutation

• Activated PI3Kδ Syndrome (APDS) OR p110δ Activating mutation causing Senescent T cells, Lymphadenopathy, and Immunodeficiency (PASLI Disease)

• Autosomal dominant

• Gain of function mutations
## APDS Infectious Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent respiratory tract infections</td>
<td>51/53</td>
<td>(98)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>39/46</td>
<td>(85)*</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>32/53</td>
<td>(60)</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>24/53</td>
<td>(45)</td>
</tr>
<tr>
<td>Recurrent otitis media</td>
<td>26/53</td>
<td>(49)</td>
</tr>
<tr>
<td>(with permanent hearing loss)</td>
<td>4/53</td>
<td>(8)</td>
</tr>
<tr>
<td>Severe or persistent herpesvirus infection</td>
<td>26/53</td>
<td>(49)</td>
</tr>
<tr>
<td>EBV</td>
<td>14/53</td>
<td>(26)</td>
</tr>
<tr>
<td>CMV</td>
<td>8/53</td>
<td>(15)</td>
</tr>
<tr>
<td>HSV and VZV</td>
<td>11/53</td>
<td>(21)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>15/53</td>
<td>(28)</td>
</tr>
<tr>
<td>(with tonsillectomy)</td>
<td>7/53</td>
<td>(13)</td>
</tr>
<tr>
<td>Ocular infections</td>
<td>10/53</td>
<td>(19)</td>
</tr>
</tbody>
</table>

*J Allergy Clin Immunol 2017;139:597-606*
## APDS Non-infectious Features

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy§</td>
<td>34/53 (64)</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>31/53 (58)</td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>24/53 (45)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>22/53 (42)</td>
<td></td>
</tr>
<tr>
<td>Nodular mucosal lymphoid hyperplasia</td>
<td>17/53 (32)</td>
<td></td>
</tr>
<tr>
<td>Enteropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td>10/53 (19)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7/53 (13)</td>
<td></td>
</tr>
</tbody>
</table>

*J Allergy Clin Immunol 2017;139:597-606*
### APDS Immunoglobulin levels

<table>
<thead>
<tr>
<th></th>
<th>Reduced, n/total (%)</th>
<th>Normal, n/total (%)</th>
<th>Increased, n/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>21/49 (43)</td>
<td>26/49 (53)</td>
<td>2/49 (4)</td>
</tr>
<tr>
<td>IgA</td>
<td>25/50 (50)</td>
<td>24/50 (48)</td>
<td>1/50 (0.5)</td>
</tr>
<tr>
<td>IgM</td>
<td>0/50 (0)</td>
<td>12/50 (24)</td>
<td>38/50 (76)</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>25/28 (89)</td>
<td>3/28 (11)</td>
<td></td>
</tr>
</tbody>
</table>

*Vaccine response*
APDS T cell phenotype

- Decreased CD4/CD8 ratio
- Increased number of terminally differentiated memory T cells (poor proliferative capacity)
- Increased number of senescent CD8+ memory T cells (poor functional capacity)
## APDS B cell phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced B-cell counts (CD19&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>32/48 (67)</td>
</tr>
<tr>
<td>Increased transitional B-cell counts (CD19&lt;sup&gt;+&lt;/sup&gt;IgM&lt;sup&gt;+&lt;/sup&gt;CD38&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>24/32 (75)</td>
</tr>
<tr>
<td>Reduced nonswitched memory B cells (CD19&lt;sup&gt;+&lt;/sup&gt;IgD&lt;sup&gt;+&lt;/sup&gt;CD27&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>15/30 (50)</td>
</tr>
<tr>
<td>Reduced class-switched memory B-cell counts (CD19&lt;sup&gt;+&lt;/sup&gt;IgD&lt;sup&gt;-&lt;/sup&gt;CD27&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>17/30 (57)</td>
</tr>
</tbody>
</table>
APDS Therapy

• Immunoglobulin replacement
• Antibacterial, antiviral, and/or antifungal prophylaxis in selective patients
• Frequent screening for lymphoma
• Rituximab for non-neoplastic lymphoproliferation and other autoimmune disease
• Rapamycin (sirolimus) for non-malignant lymphoproliferation and hepatosplenomegaly
• Consider selective PI3Kδ inhibitors
• Consider HSCT
Cellular effects of sirolimus therapy

Who to genotype?

• Hyper IgM
• Severe non-malignant lymphadenopathy
• Herpes family viremia
• Increased number of terminally differentiated (CCR7-) memory (RA-) T cells
• Increased number of senescent (CD57+) CD8+ T cells
• Family history
Benefits of genotyping

• Consider antiviral prophylaxis
• Consider sirolimus for non-malignant lymphoproliferation
• Implement aggressive lymphoma screening
• Consider HSCT in severe cases
• Family planning
Current Paradigm of Pathogenesis

Genetic defect(s)  Molecular defect(s)  Cellular defect(s)  Clinical disease
III. Predominantly antibody deficiencies

Recurrent bacterial infections eg: Otitis, pneumonia, sinusitis, diarrhea, sepsis

Serum Immunoglobulin Assays: IgG, IgA, IgM

- IgG, IgA and/or IgM ↓↓
  - Exclude 2° causes: drugs [Hx], myeloma [bone marrow], Lymphoma, Ig loss (not hypo-IgM) in urine, GI or skin

- B Lymphocyte (CD19+) enumeration (CMF)
  - B absent
  - B > 1%

- X-Linked Agammaglobulinemia ( Bruton
  - AR Agammaglobulinemia
  - μ heavy chain Def (IGHM)
  - IgG (CD79a)
  - IgM (CD79b)
  - BLNK (BIRC4)
  - IκB (IKAROS)
  - PI3Kγ-def (PI3Kγ)
  - AD E47 transcription factor def (TFC2)

- Congenital sideroblastic anemia, deafness, developmental delay: TRNT1 def (TRNT1)

- Trichorrhexis nodosa TTC37 def (TTC37)

- Dysmorphic facial features, Hypotonia, neurologic disorder; severe hypogammaglobulinemia CDG-Ilb (MOGS)

- Common Variable Immunodeficiency Disorders (CVID)
  - Very rare AR disorders: TACI/BAFF-R, CD19, CD21, CD23, TWEAK, TNFR2

- Thymoma with immunodeficiency
  - Bacterial opportunistic infections, autoimmunity

- Myelodysplasia with hypogammaglobulinemia
  - (Monosomy 7, trisomy 8 or DKC, GATA2)

- INO80 def (INO80)
  - MHSS def (MHSS) (cancer)

- Growth retardation, EBV, CMV viremia, PKR1 loss-of-function (PKR1)

- Healthy infant, no increased bacterial infections. Normalisation at 36-60 months
  - Transient hypogammaglobulinemia of infancy

- AR hyper-IgM disorders, with lymphoid hyperplasia
  - AID def (AICDA)
  - UNG def (UNG)
  - Others

- Low IgG Subclasses
  - IgA with IgG subclasses def

- Low Specific antibody responses
  - IgA with Specific Ab deficiency

- Congenital B cell lymphocytosis
  - AD, SPM, Adp.
  - Bacterial and viral infections, EBV chronic infection, Autoimmune cytopenia
  - CARD11 gain of function mutations (CARD11)

- IgG subclasses Low + impaired response to PPS and hib
  - Bronchiectasis, autoimmunity, chronic EBV, CMV infection

- Activated PI3Kδ (PIK3CD, p110)
  - IgG subclasses +/- IgA, absent IgE, asymptomatic: Ig heavy chain mutations or deletion (mutation or chromosomal deletion 14q32)

- All have lambda chain, asymptomatic
  - K chain def (IGKC)
III. Predominantly antibody deficiencies

Recurrent bacterial infections eg: Otitis, pneumonia, sinusitis, diarrhea, sepsis

Serum Immunoglobulin Assays: IgG, IgA, IgM

Congenital B cell lymphocytosis

AD, SPM, Adp.

Bacterial and viral infections, EBV chronic infection, Autoimmune cytopenia

CARD11 gain of function mutations (CARD11)
III. Predominantly antibody deficiencies

Recurrent bacterial infections eg: Otitis, pneumonia, sinusitis, diarrhea, sepsis

Serum Immunoglobulin Assays: IgG, IgA, IgM

IgG (achinery), IgA (achinery)
and IgM (N / 1) :

HIGM

Healthy infant, no increased bacterial infections. Normalisation at 36-60 months
Transient hypogamma-globulinemia of infancy

AR hyper-IgM disorders, with lymphoid hyperplasia
AID def (AIICDA)
UNG def (UNG)
Others

INO80 def (INO80)
MHSS def (MHSS) (cancer)

Growth retardation, EBV, CMV infection
PIK3R1 loss-of-function (PIK3R1)
III. Predominantly antibody deficiencies

Recurrent bacterial infections eg: Otitis, pneumonia, sinusitis, diarrhea, sepsis

Serum Immunoglobulin Assays: IgG, IgA, IgM

IgA

1. IgG subclasses 1, 2, 3 levels (measure at least two)
2. Specific antibody responses (anti-PPS antibodies and Tot/dip/Ph-b)

Selective IgA def

Low IgG
- IgG subclasses def

IgA with

Low Specific antibody responses
- IgA with Specific Ab deficiency
III. Predominantly antibody deficiencies

Recurrent bacterial infections eg: Otitis, pneumonia, sinusitis, diarrhea, sepsis

Serum Immunoglobulin Assays: IgG, IgA, IgM

**IgG, IgA and/or IgM ↓↓**

- Exclude 2° causes: drugs (HIV), myeloma (bone marrow), Lymphoma, Ig loss (not hypo-IgM) in urine, GI or skin

**B Lymphocyte (CD19+) enumeration (CMF)**

- **B absent**
- **B >1%**

**X-Linked Agammaglobulinemia (BAK)**

- AR Agammaglobulinemias
- μ heavy chain Def (IGHM)
- Igα (CD79a)
- Igδ (CD79b)
- BLNK (BLNK)
- IL (IgBL1)
- PI3K Def (PIK3R1)

**AD E47 transcription factor def (TCF2)**

**Common Variable Immunodeficiency (CVID)**

- Very rare AR disorders: TACI/BAFF-R, CD19, CD21, CD79a, TWEAK, NFKB2

**Thymoma with immunodeficiency**

- Bacterial opportunistic infections, autoimmune

**Myelodysplasia with hypogammaglobulinemia** (Moteosomy 7, trisomy 8 or DKC, GATA2)

**Congenital sideroblastic anemia, deafness, developmental delay:** TRNT1 Def (TRNT1)

**Trichorhachis nodosa** TTC37 Def (TTC37)

**Dysmorphic facial features, Hypotonia, neurologic disorder:** severe hypogammaglobulinemia CDG-l/b (MOGS)

**Normal IgA, IgG, IgM**

1. IgG subclasses 1,2,3 levels (measure at least two)?
2. Specific antibody responses (anti-PPS antibodies and TetDphils)?

**IgG subclasses Low**

- +/- poor Specific Ab response:
  - Isolated IgG subclass

**IgG2 Low + Impaired response to PPS and hib**

- Bronchiectasis, autoimmunity, chronic EBV, CMV infection
  - Activated PI3K-δ (PK3CD, p110)

**IgG subclasses +/- IgA,**

- absent IgE, asymptomatic: Ig heavy chain mutations or deletion (mutation or chromosomal deletion 14q32)

- All have lambda chain, asymptomatic
  - K chain def (IGKC)
sine qua non of CVID
Genetic defects