IMMUNE DEFICIENCY FOUNDATION

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.

IDF Immune Deficiency Foundation
Thank you to our Sponsor!

Pharming
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
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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.
To view all APDS Resources and Materials, visit:
https://primaryimmune.org/apds

Could it be APDS?
APDS (Activated PI3K Delta Syndrome) is often misdiagnosed, commonly with CVID or other PIDs.

Activated PI3K Delta Syndrome (APDS) is a rare primary immunodeficiency that was first discovered in 2013. It is caused by genetic variants in either one of two identified genes known as PIK3CD or PIK3R1, which are vital to the development and function of immune cells in the body.

Distinguishing between APDS is often difficult because of the wide variety of symptoms that patients suffer. It’s vital that you take note of your symptoms, their frequency, and share this information with your doctor.

Making a correct Pi diagnosis is crucial and can change the course of treatment and outcome for patients.

https://allaboutapds.com/about-apds/
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](https://community.primaryimmune.org/s/events?language=en_US)
REGISTRATION IS OPEN: www.primaryimmune.org/conference
WELCOME!

Eveline Wu, MD, MSCR
Assistant Professor of Pediatrics
Allergy & Immunology, Pediatric Rheumatology
University of North Carolina, Chapel Hill
IDF Lunch & Learn: All About APDS!

Eveline Wu, MD, MSCR
Associate Professor of Pediatrics
Allergy & Immunology, Pediatric Rheumatology
University of North Carolina, Chapel Hill
Disclosure

• Dr. Wu has received consulting fees from Pharming Healthcare, Inc.

• Dr. Wu has received grants as an investigator from AstraZeneca, Bristol-Myers Squibb, Enzyvant, and Janssen.

• Pharming Healthcare, Inc. supported the creation of this content.
Primary Immunodeficiencies Are An Expanding Group of Rare Genetic Disorders With Variable Manifestations

Primary Immunodeficiencies:  
- 400+ genetic disorders known in 2020\(^1\)  
- Full or partial lack of immune system function\(^2\)

Appear at any age\(^2\)  
- Severe cases commonly diagnosed in infancy or early childhood

Variable clinical presentations\(^1\)  
- Routine or severe infections  
- Autoimmune or autoinflammatory complications

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Patients present with infections (immunodeficiency) and immune-mediated pathology, such as:
- Autoimmunity
- Autoinflammation
- Lymphoproliferation
Activated PI3Kδ Syndrome (APDS) is a PIRD.

APDS = Activated PI3K Delta Syndrome \(^{1,2}\)
(previously known as PASLI)

**Discovered** in 2013\(^ {1,2}\)

**Rare:** Estimated 1-2 people per million\(^ {3}\)

Doctors are still learning about and becoming aware of the disease.

Caused by variants in one of two genes: \(PIK3CD\) and \(PIK3R1\)^{1,4}

These variants cause the immune system to not work properly\(^ {1,4}\)

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What Causes APDS?
The Immune System Is Made of T Cells and B Cells That Work Together To Protect the Body

**T cell**

Destroys specific germs or helps regulate the immune system, depending on the type of T cell

**B cell**

Makes antibodies to target specific germs for destruction

Antibodies: Special shaped proteins that attach to specific germs

Too much or too little T and B cell activity causes problems—it needs to be just right

B Cells and T Cells Must Follow Specific Steps To Mature or They Will Not Become Functional

Strangely, B and T cells do not start out functional. They must go through a series of specific steps\textsuperscript{1,2}


1. B cell development

- Newborn cell
- Immature cells multiply
- Immature cells develop

2. Mature cell development

- Mature, functional cell
- Mature cells multiply in response to germs
- Cell death
Pathways INSIDE of Each B and T Cell Instruct the Cell Precisely How to Mature

The only way for B cells and T cells to become functional is if they mature using specific pathways.

Some pathways are like this machine: a series of steps or cascades of events inside the cell that produce an effect.

Inside a B or T cell

The PI3Kδ Pathway Controls How B and T cells Mature and Function

PI3Kδ activity kick-starts cascades that instruct B and T cells to multiply, mature, or even die.

PI3Kδ, phosphoinositide 3-kinase delta.
Unbalanced PI3Kδ Pathway Activity Alters B and T Cells

In APDS, PI3Kδ is overactive.

PI3Kδ activity is unbalanced, leading to altered B and T cell development and function.

APDS, activated phosphoinositide 3-kinase delta syndrome; PI3Kδ, phosphoinositide 3-kinase delta.

Variants In PI3Kδ Genes Can Cause APDS

Genetic variants in either PI3Kδ subunit that result in enzyme hyperactivity cause APDS

APDS, activated phosphoinositide 3-kinase δ syndrome; PIK3CD, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; PIK3R1, phosphoinositide 3-kinase regulatory subunit 1; PI3Kδ, phosphoinositide 3-kinase δ.

Altered B And T Cells Lead To Many APDS Symptoms

APDS
Immune dysfunction
Autoimmune complications

PI3K activity unbalanced\(^ {1-3}\)

Symptoms\(^ {2,3}\)
Infections
Enteropathy
Lymphadenopathy, splenomegaly
Bronchiectasis
Lymphoma
Autoimmunity
Frequent infections


APDS, activated phosphoinositide 3-kinase δ syndrome; PI3Kδ, phosphoinositide 3-kinase δ.
APDS May Be Present in Multiple Members of a Family

- APDS can be passed down from a person’s mother or father.
- It can also spontaneously appear in a person with no family history.

Even within the same family, one person’s APDS symptoms may look different than another’s symptoms.

50% chance of APDS being passed down to a patient’s children.
What Are The Symptoms of APDS?
APDS Has A Wide Range Of Clinical Manifestations

- Chronic lymphadenopathy
- Nodular lymphoid hyperplasia
- Lymphoma
- Premature mortality
- Persistent, severe, or recurrent herpesvirus infections, particularly EBV and CMV
- Autoimmune cytopenias and autoinflammatory diseases
- Splenomegaly
- Hepatomegaly
- Recurrent sinopulmonary infections
- Pneumonia
- Bronchiectasis
- Enteropathy
- Developmental delay
- Failure to thrive

APDS, activated phosphoinositide 3-kinase δ syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

Recurrent Sinopulmonary Infections Are The Initial Hallmark Of APDS

Include\textsuperscript{1-4}

Upper respiratory tract infections

Otitis media Sinusitis

Pneumonia Bronchitis

Allergy/asthma are also common\textsuperscript{6}

APDS, activated phosphoinositide 3-kinase δ syndrome; yo, years old.

Patients With APDS Are Particularly Vulnerable To Herpesviruses

Acute and chronic viral infections reported in 36-49% of patients\textsuperscript{1,2}

- CMV\textsuperscript{1-3} 15-17%
- EBV\textsuperscript{1-5} 24-30%

Genetic testing for APDS should be considered in patients with unexplained EBV or CMV viremia\textsuperscript{6}

APDS, activated phosphoinositide 3-kinase \(\delta\) syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; yo, years old.

Lymphoproliferation Can Be A Manifestation Of Immune Dysregulation

71-89% of patients have been shown to be affected by lymphadenopathy, splenomegaly, hepatomegaly and/or nodular lymphoid hyperplasia\textsuperscript{1-5}

Manifests early
Median onset reported at 3 years of age (range, 1-6 years)\textsuperscript{4}

Timeline of the Most Common Pathologies Seen in APDS

<table>
<thead>
<tr>
<th>Ages are median ages of onset, in years</th>
<th>&lt;1 yo</th>
<th>3 yo</th>
<th>5 yo</th>
<th>10.5 yo</th>
<th>13 yo</th>
<th>18 yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant infections</td>
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<tr>
<td>Benign lymphoproliferation</td>
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<td>Autoimmunity</td>
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<td>Cytopenias, arthritis, or other immune dysregulation</td>
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*Open arrows indicate lymphadenopathy as imaged using positron emission tomography. Closed arrows indicate hepatosplenomegaly.
APDS, activated phosphoinositide 3-kinase δ syndrome; yo, years old.
Lymphoproliferation Can Result In Enteropathy

51% of patients reported experiencing gastrointestinal manifestations¹

• Includes bowel inflammation, chronic diarrhea, and malabsorption¹-³

• Can indicate nodular mucosal lymphoid hyperplasia in the GI tract²,³

Gastrointestinal endoscopy reveals lymphoid nodules in a 4-year-old patient with APDS⁴


Timeline of the Most Common Pathologies Seen in APDS

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APDS, activated phosphoinositide 3-kinase δ syndrome; GI, gastrointestinal; yo, years old.
Patients With APDS May Fail To Thrive

Failure to thrive reported in
45-62% of patients with APDS2 (variants in PIK3R1)1-3

Encompasses1,3-5
Short stature
Low weight
May be partially due to enteropathy3

Timeline of the Most Common Pathologies Seen in APDS

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Patients With APDS May Present With Autoimmunity In Addition To Immune Deficiency

Autoimmune cytopenias reported in around 30% of patients with APDS\textsuperscript{1-3}

Multiple blood lineages may be affected\textsuperscript{1-4}

- Autoimmune Hemolytic Anemia (AIHA)
- Immune thrombocytopenia (ITP)
- Neutropenia
- Trilineage cytopenia
- Evans syndrome

AIHA, autoimmune hemolytic anemia; APDS, activated phosphoinositide 3-kinase δ syndrome; ITP, immune thrombocytopenic purpura; yo, years old.

Neurological Deficits May Occur In Patients With APDS

Neurodevelopmental delay reported in

10-19% of patients with APDS1
(variants in PIK3CD)1-3

27-31% of patients with APDS2
(variants in PIK3R1)3,4

Includes1-5
• Global developmental delay
• Speech delay
• Learning disabilities
• Autism spectrum disorders
• Anxiety and depression disorders
• Behavioral disorders

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APDS, activated phosphoinositide 3-kinase δ syndrome; PIK3CD, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta gene; PIK3R1, phosphoinositide 3-kinase regulatory subunit 1 gene; yo, years old.

Benign Lymphoproliferation May Progress To Malignancy In Patients With APDS

Lymphomas are most common\textsuperscript{1,2}

Multiple lymphomas are not unusual\textsuperscript{3,4}

Leukemias and solid organ malignancies may also affect patients with APDS, though less frequently than lymphoma\textsuperscript{1,3}

\begin{itemize}
\item [\textsuperscript{*}] In a cohort of patients with variants in \textit{PIK3R1}.
\item APDS, activated phosphoinositide 3-kinase δ syndrome; \textit{PIK3R1}, phosphoinositide 3-kinase regulatory subunit 1 gene.
\item yo, years old.
\end{itemize}

\textsuperscript{5.} Carpier JM, Lucas CL. \textit{Front Immunol.} 2018;8:2005.
APDS Can Alter Immunoglobulin Levels In Complex Ways

Patients with APDS frequently have all or some of the below immunoglobulin characteristics\textsuperscript{1,2}

- Low to normal IgG levels
- Low to normal IgA levels
- High IgM levels
- Poor antibody responses to vaccine challenges

Hyperactive PI3Kδ Alters Immune Cell Phenotypes

Common Symptoms of APDS²,³

- **Severe, Recurrent, Persistent Infections:**
  - Sinopulmonary
  - Herpesvirus (especially EBV and CMV)

- **Lymphoproliferation:**
  - Lymphadenopathy
  - Splenomegaly/hepatomegaly
  - Nodular lymphoid hyperplasia

- **Enteropathy**

- **Autoimmunity:**
  - Cytopenias
  - Autoimmune disorders
  - Autoinflammatory disorders

- **Bronchiectasis**

- **Lymphoma**

CD4⁺

CD8⁺

Effector memory CD8⁺

Inverted CD4⁺/CD8⁺ ratio

Follicular T helper

Total CD8⁺ skewed to TEM/TEMRA (senescent)

NK cells

B cells (CD19⁺)

Transitional B cells

Memory B cells

Defects in class-switch recombination

CMV, cytomegalovirus; EBV, Epstein-Barr virus; NK, natural killer; PI3Kδ, phosphoinositide 3-kinase δ; TEM, T effector memory cell; TEMRA, T effector memory cells re-expressing CD45RA.

How Do You Treat APDS?
Current Management For APDS

Current APDS Management$^{1,2}$

Immune Deficiency

- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy

None of these therapies are FDA-approved for APDS treatment

APDS, activated phosphatidylinositol 3-kinase δ syndrome.

Antimicrobial prophylaxis is used to prevent infections, which are pervasive among patients with APDS\textsuperscript{1,2,6}.

APDS, activated phosphatidylinositol 3-kinase δ syndrome.

Immunoglobulin Replacement Therapy Can Be Used To Address Sinopulmonary Infections Or Autoimmune Cytopenias

IRT use reported in 63-89% of patients\(^1-4\)

Reported median age of IRT initiation - 5 years of age (range, 1-35 years)\(^3\)

Outcomes

- May reduce infections\(^2\)
- Well-tolerated\(^1\)

Limitations

- Does not prevent herpes virus infections\(^5,6\)
- May not be effective for all sinopulmonary infections\(^6,7\)
- Bronchiectasis can still progress\(^5,7\)
- Does not address immune dysregulation aspects of APDS such as lymphoproliferation, autoimmunity, and lymphoma\(^5,6,8\)

Immunoglobulins administered intravenously (IVIg) or subcutaneously (SCIg) may prevent infections by correcting secondary antibody deficiencies present in patients with APDS\(^2,3,5,7\)

Not FDA-approved for APDS treatment

APDS, activated phosphatidylinositol 3-kinase δ syndrome; IRT, immunoglobulin replacement therapy.

Current Management For APDS

Current APDS Management¹,²

**Immune Deficiency**
- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy

**Immune Dysregulation**
- Corticosteroids
- mTOR inhibitors
- Other immunosuppressants

None of these therapies are FDA-approved for APDS treatment

APDS, activated phosphatidylinositol 3-kinase δ syndrome; mTOR, mammalian target of rapamycin.

**Current Management Options Address Individual Symptoms Of APDS But Not The Root Cause: PI3Kδ Hyperactivation**

Normalization of the PI3Kδ pathway may mitigate both immunodeficiency and immune dysregulation.

APDS, activated phosphatidylinositol 3-kinase δ syndrome; FOXO, forkhead box O; IRT, immunoglobulin replacement therapy; mTOR, mammalian target of rapamycin; PDK1, phosphoinositide-dependent protein kinase 1; PI3Kδ, phosphoinositide 3-kinase δ; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PKB, protein kinase B.

Current Management For APDS

Current APDS Management\textsuperscript{1,2}

Immune Deficiency
- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy

Immune Dysregulation
- Corticosteroids
- mTOR inhibitors
- Other immunosuppressants

Hematopoietic stem cell transplant

None of these therapies are FDA-approved for APDS treatment

APDS, activated phosphatidylinositol 3-kinase \( \delta \) syndrome; mTOR, mammalian target of rapamycin.

Take Home Points

- APDS is a rare disorder characterized by **immune deficiency** and **immune dysregulation**.
- Common manifestations of APDS include recurrent respiratory infections, infections with herpes viruses, lymphoproliferation, autoimmunity, and lymphoma.
- Treatment currently consists of antimicrobial prophylaxis, immunoglobulin replacement therapy, and therapies for immune dysregulation and autoimmune features.
- APDS is due to variants in the *PIK3CD* and *PIK3R1* genes, and a genetic confirmation can direct treatment and care.
Resources Available To You!

Looking for more information on primary immunodeficiencies like APDS?

Want insight on genetic testing and genetic disease?

Want additional information on APDS?

You can find more APDS information and resources at AllaboutAPDS.com. Detailed videos from APDS experts are also available on the All about APDS YouTube page.
Pharming partnership with Invitae

- **NO CHARGE GENETIC TEST** – no cost to qualified patients in the USA and Canada
- **FAST** – results back to doctor within 2 weeks on average (10-21 days)
- **DESIGNED TO BE EASY FOR PROVIDERS** – online form
- **DESIGNED TO BE EASY FOR PATIENTS** – blood draw kits (preferred), buccal swab kits, saliva kits, or mobile phlebotomy
- **COMPREHENSIVE** – Choice of either 429-gene Primary Immunodeficiency Panel or 574-gene Inborn Errors of Immunity and Cytopenias Panel
- **SUPPORTED** – option for free genetic counseling provided by GeneMatters
- **FAMILY TESTING** – free genetic testing for blood relatives of patients with pathologic or likely pathologic variants

www.invitae.com/navigateAPDS
Questions?
THANK YOU!

Eveline Wu, MD, MSCR
Assistant Professor of Pediatrics
Allergy & Immunology, Pediatric Rheumatology
University of North Carolina, Chapel Hill

Pharming
Additional Resources

• Read about the brand-new diagnostic code for APDS: https://primaryimmune.org/news/new-diagnostic-code-ultrarare-primary-immunodeficiency-promises-multiple-benefits
• Learn about APDS: https://primaryimmune.org/apds
• IDF Resource Center: https://primaryimmune.org/resource-center
• IDF Support Services: https://primaryimmune.org/support-services
Have more Questions?

www.Primaryimmune.org/ask-idf
800-296-4433
WE VALUE YOUR FEEDBACK...

Please take a moment to complete our Evaluation Survey after the Program!
Upcoming Lunch & Learns

B Cell Reconstitution and IgG Infusion
Wednesday, 8/31/22
11:00 AM ET
Manish Butte, MD, PhD
Victoria Dimitriades, MD

ADA SCID Gene Therapy Update
Wednesday, 9/14/22
2:00 PM ET
Donald Kohn, MD

For a list of all upcoming IDF Events, visit:
https://community.primaryimmune.org/s/events?language=en_US
Pharming Healthcare, Inc.

Brian Hartline, MD

Senior Director, Medical Affairs
A global, commercial stage biopharmaceutical company developing innovative protein replacement therapies and precision medicines for the treatment of rare diseases and unmet medical needs.

Pharming’s main product candidate portfolio is focused on the rare diseases of hereditary angioedema (HAE), activated PI3Kδ syndrome (APDS) and Pompe disease.
What is activated PI3Kδ syndrome (APDS)?

**APDS***
Is a Primary Immune Regulatory Disorder (PIRD)

Caused by variants in the genes *(PIK3CD* or *PIK3R1)* encoding subunits of PI3Kδ enzyme complex and affects both B and T cells

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**Immune deficiency**
- Frequent infections

**Immune dysregulation**
- Autoimmune complications

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**Wide Range of Clinical Manifestations**

- Severe infections, permanent lung damage
- Severe swollen lymph nodes, spleen and liver
- Developmental delay, failure to thrive
- Severe, chronic herpes virus infections
- Enteropathy
- Lymphoma
- Autoimmunity including anemias & bleeding disorders

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*Also known as PASLI (p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immune deficiency).

APDS, activated phosphatidylinositol 3-kinase δ syndrome; PASLI, p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immune deficiency; PIRD, primary immune regulatory disorder.


For more information on APDS, visit: AllaboutAPDS.com
Definitive diagnosis through genetic testing may change treatment

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For more information: allaboutapds.com/diagnosing-apds/ or navigateapds.com