APDS

overview

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APDS

Activated PI3K Delta Syndrome

previously known as PASLI Disease

PASLI =p110 delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency

Introduction

APDS

✓First described in 2006

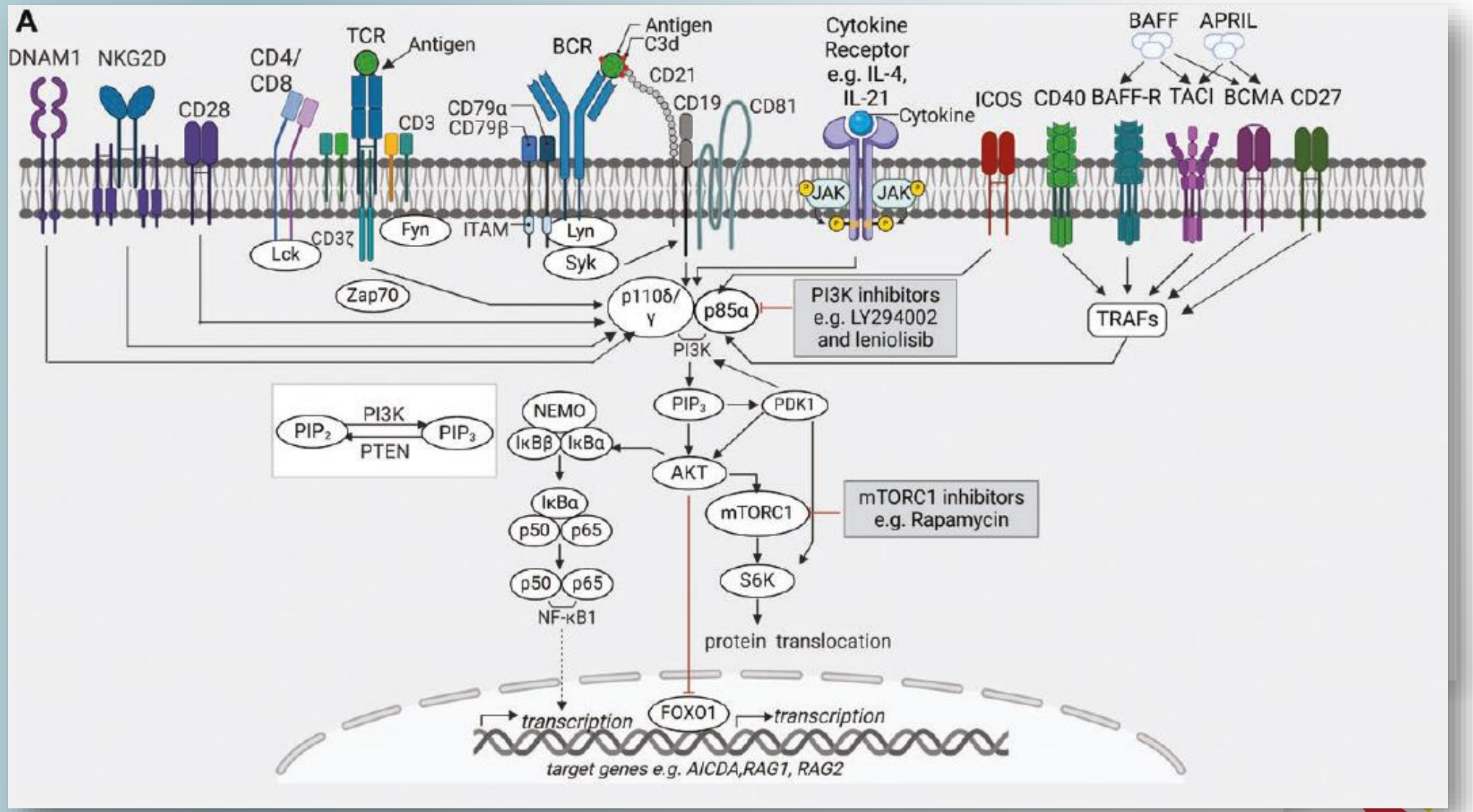
✓Caused by mutations that lead to

hyperactivation of the AKT-mTOR-Pi3kδ pathway

✓Pi3kδ plays a critical role in lymphocyte signaling and survival

Introduction

APDS



Background

Autosomal Dominant mutations

APDS

APDS1 : Gain-of-Function mutations in PIK3CD

encoding the p110δ catalytic subunit

APDS2 : Loss-of-Function mutations in PIK3R1

encoding the p85α regulatory subunit

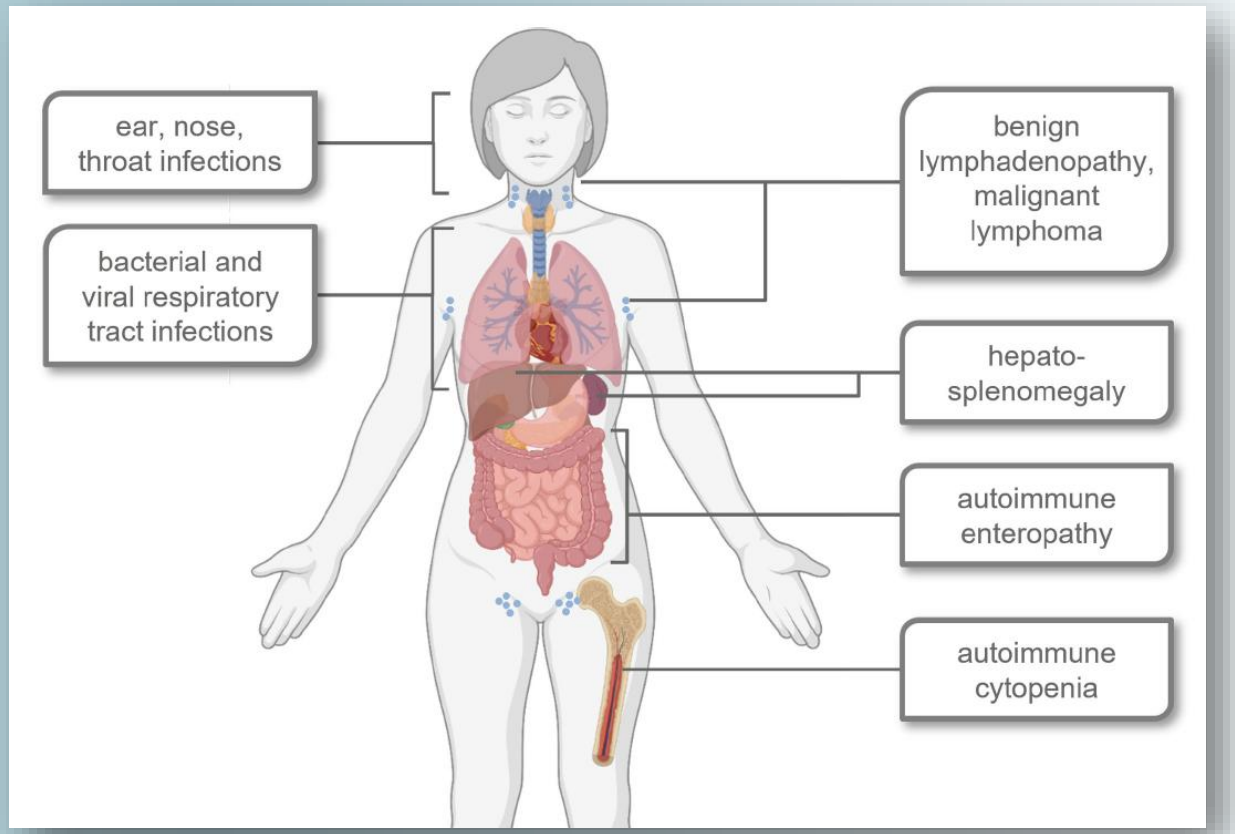
No clinically relevant genotype-phenotype correlations have been identified to date

Symtoms

APDS

Considerable clinical variability

from nearly asymptomatic with mild laboratory findings
to severe manifestations of the disease



Symptoms usually begin in childhood,
but diagnosis is often delayed until adolescence or adulthood

Symtoms

Recurrent infections

APDS

- ✓ Respiratory tract infections sinusitis, otitis media, bronchitis, and pneumonia
- ✓ Chronic viral infections
  particularly herpesviruses (EBV, CMV, HSV)
- ✓ Progressive lung damage such as bronchiectasis is a major cause of long-term morbidity

Lymphoproliferation

(non-malignant)

APDS

- ✓ Generalized lymphadenopathy
- ✓ Splenomegaly a/o hepatomegaly
- ✓ Lymphoid hyperplasia in various organs

Autoimmunity

APDS

- ✓ Autoimmune cytopenias
  ITP, AIHA, neutropenia
- ✓ Enteropathy and chronic diarrhea resembling inflammatory bowel disease
- ✓ Arthritis and other autoimmune disorders

Symtoms

APDS

10 Warning Signs of APDS

Primary Immunodeficiencies (PIs) like activated PI3k delta syndrome (APDS), are diseases where the immune system doesn't function properly. This means that people with APDS may experience a wide variety of signs and symptoms, making it challenging to recognize. The most common signs and symptoms are listed below. If you or someone you know is affected by two or more of the following Warning Signs, speak to a healthcare provider about the possibility of APDS.

1. **Two or more** of the following in one year:
   - Sinus Infections -or-
   - Pneumonias -or-
   - Ear Infections

2. **Persistent cough**, uncontrolled or difficult to control **asthma** or **scarring of lungs** for no clear reason (known as bronchiectasis)

3. Persistent **lymph node swelling**

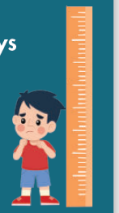
4. **Frequent and severe diarrhea** lasting more than four weeks

5. **Enlarged** liver and/or spleen

6. Diagnosed **autoimmune** or **autoinflammatory** conditions (especially if early age of onset or multiple autoimmune conditions)

7. Recurrent and difficult to treat **herpes viral infections** (especially if CMV/EBV are chronic)

8. **Developmental delays** including cognitive delays and/or growth delays (i.e. short stature)



9. **Lymphoma** or **family history of lymphoma** (a group of cancers affecting the lymph nodes)

10. **Family history** of another primary immunodeficiency disease or CVID

These warning signs were developed by the Jeffrey Modell Foundation (JMF) and Pharming and are being provided for informational purposes only. We believe this information to be reliable and accurate, but the information cannot be construed as medical advice, diagnosis, or treatment. **Consultation with PI experts or your healthcare provider is strongly suggested.**

Presented as a public service by:

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SCAN ME

Scan the QR code for more information about APDS or visit: Allaboutapds.com

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LABS

APDS

Antibodies

- ✓Low levels of IgG, often with elevated IgM
- ✓Impaired vaccine responses

B cells

- ✓Reduced class-switched memory B cells

T-cells

- ✓Impaired memory T cells
- ✓T cells show sign of senescence and exhaution
- ✓Reduced Tregs
- ✓Abnormal CD4/CD8 T cell ratio

Diagnosis

Diagnosis of APDS is based on a combination of:

Clinical features & **Immunological tests**

APDS

Definitive confirmation requires **genetic testing** for mutations in PIK3CD or PIK3R1

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Similarities and differences

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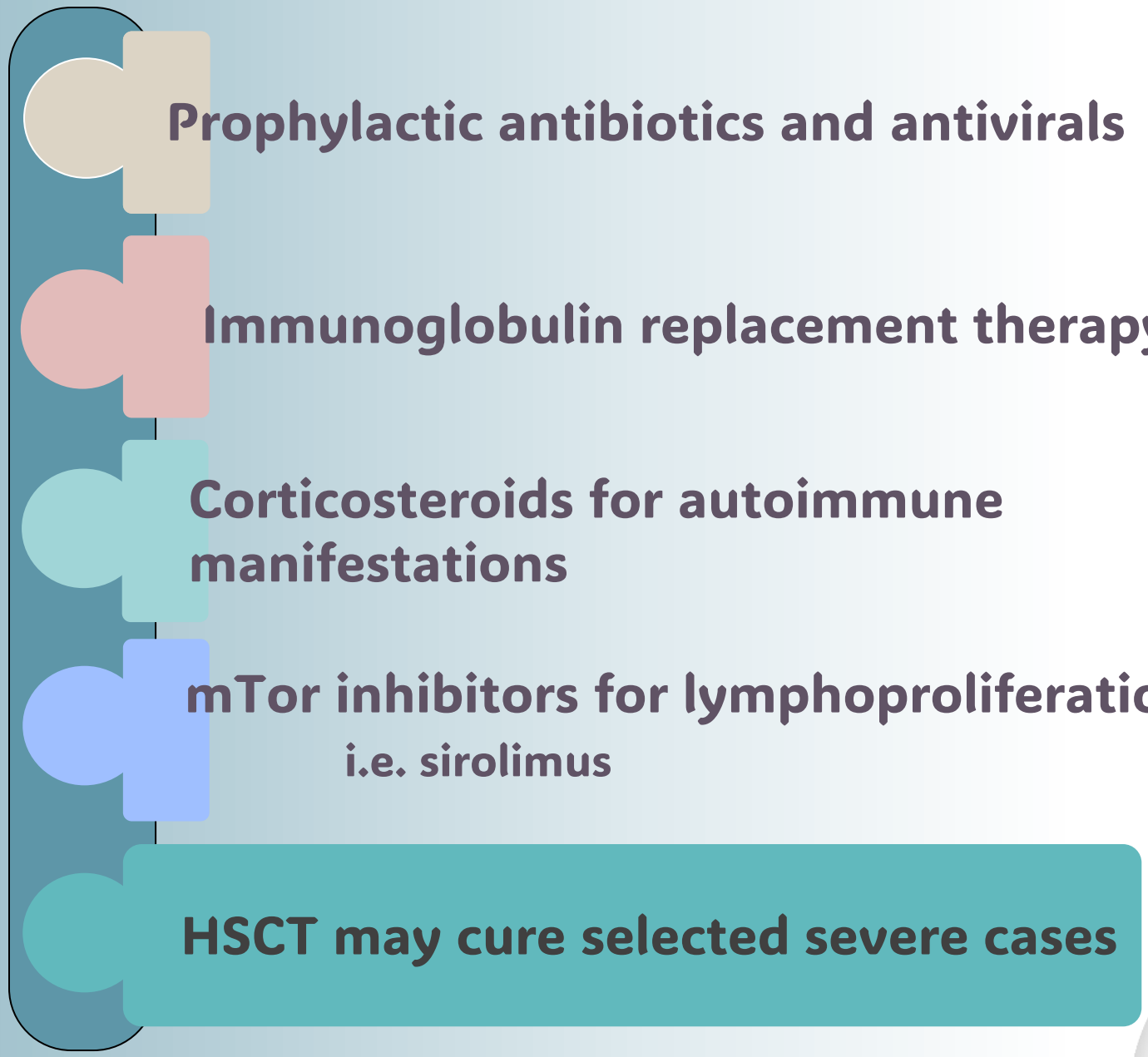
	APDS 1	APDS 2
Recurrent infections	++	++
Lymphoproliferation	++	++
Autoimmune cytopenias	++	++
Decreased IgA and IgG	++	++
Increased IgM	+	+
Herpes group virus infection.	+	+
Bronchiectasis	+	+
B-cell lymphopenia, Increased transitional B cells	+	++
Risk of lymphoma	+	++
Chronic diarrhea and enteropathy	+	++
Growth delay and short stature	-	+
Delayed tooth eruption	-	+
Neurodevelopmental delays.	+	++

Treatment

APDS



APDS

Targeted therapy

Specific PI3Kδ inhibitors

leniolisib (tabl, for ages ≥12 yrs)

Recommended Follow-up / Surveillance

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System/Concern	Evaluation	Frequency
Infections	Blood/sputum cultures	As needed for symptoms
	EBV/CMV/HSV PCR	Every 12 mos
Immune	• IgG, IgA, IgM • CD4+, CD8+, B cell subsets	
	Vaccine responses	At baseline
Lymphoproliferative disorders	CBC, B-cell counts, LDH	Every 6-12 months
	CT or MRI of chest	Every 3-5 years
	Abdominal US	Consider every 6-12 mos or more frequently in persons w/active lymphoproliferation or gastrointestinal &/or hepatic manifestations.
Autoimmune disorders	ANA testing, TSH, TPO	Annually
Respiratory issues	Regular pulmonary function tests incl spirometry	Every 12 mos (to monitor lung health & intervene early if issues are detected)
	Chest CT	Consider every 5 yrs.
Gastrointestinal manifestations	Colonoscopy	Symptomatically as needed to identify & manage gastrointestinal involvement
	Liver ultrasound studies	At baseline & every 6-12 mos
	Liver enzymes	Every 6-12 mos
Cognitive/ Developmental	Psychiatric assessment	As needed

Sacco K, Uzel G. Activated PI3K Delta Syndrome. 2025 Jan 30. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews®

APDS "Take homies"

1. Shares many features of other immunodeficiency disorders
   - APDS patients may be among your CVID / HyperIgM / CID patients
2. Signs and symptoms start in childhood
3. Recurrent infections, lymphoproliferation, autoimmune cytopenias
4. Genetic testing is the only way to definitively diagnose APDS
5. Antibiotic prophylaxis, immunoglobulin replacement and leniolisib