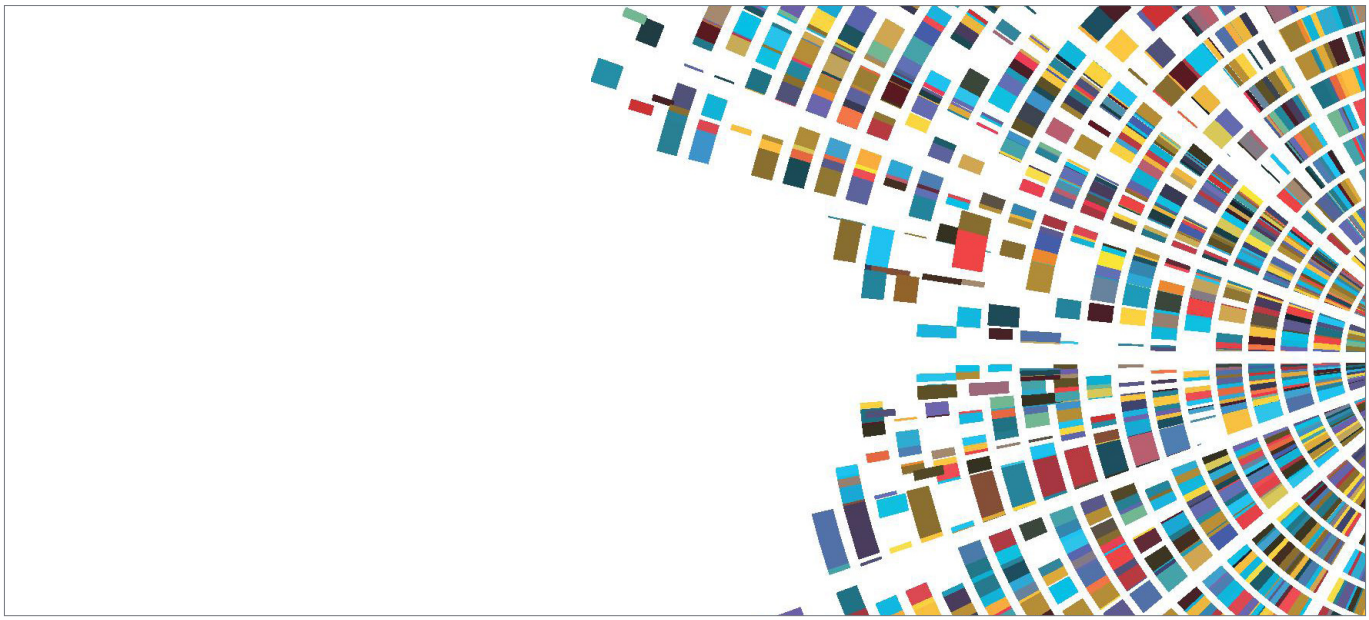
UNDERSTANDING ACTIVATED PI3K DELTA SYNDROME (APDS): A RARE, PROGRESSIVE PRIMARY IMMUNODEFICIENCY (PID)

Advances and challenges in diagnosis and management



Introduction

Activated PI3K delta syndrome (APDS) is a primary immunodeficiency (sometimes referred to an inborn error of immunity [IEI]), characterised by hyperactive PI3K delta signalling.[1,2,3] Usually starting in childhood, clinical features of this life-limiting condition include severe, recurrent sinopulmonary infections, lymphoproliferation, enteropathy, autoimmunity, end organ damage, and lymphoma.[1,2,3] Although APDS is inherited in an autosomal dominant manner,[1] evidence suggests that cases can also occur sporadically.[4] Over 240 patients with APDS have been identified by genetic testing since its first description in 2013.[2,5,6] However, the condition is likely to be under-diagnosed and the true global prevalence of APDS is unknown.[2,3]

Genetic basis of APDS and the PI3K delta signalling pathway

PI3K delta is a protein expressed predominantly in leukocytes, which plays an important role in T-cell and B-cell differentiation, proliferation, survival and activation.[2,7] The PI3K delta protein is composed of a catalytic subunit (p110δ) and a regulatory subunit (p85α).[2,8] Binding of p85α to its membrane-bound receptor leads to p110δ-mediated phosphorylation of PIP2 to PIP3 and subsequent phosphorylation of AKT [**Figure 1**].[2,8] AKT has several critical functions in immune regulation, including activating the mTOR pathway and suppressing activity of the transcription factor FOXO1, which is key to lymphocyte development and maturation.[2] In people with APDS, the dynamic regulation of PI3K/AKT/mTOR pathway is disrupted by PI3K hyperactivity, leading to mTOR hyperactivation and reduced lymphocyte differentiation owing to continual FOXO suppression.[2,8]

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Figure 1. Schematic representation of PI3K delta activation and downstream effects in lymphocytes.[2]

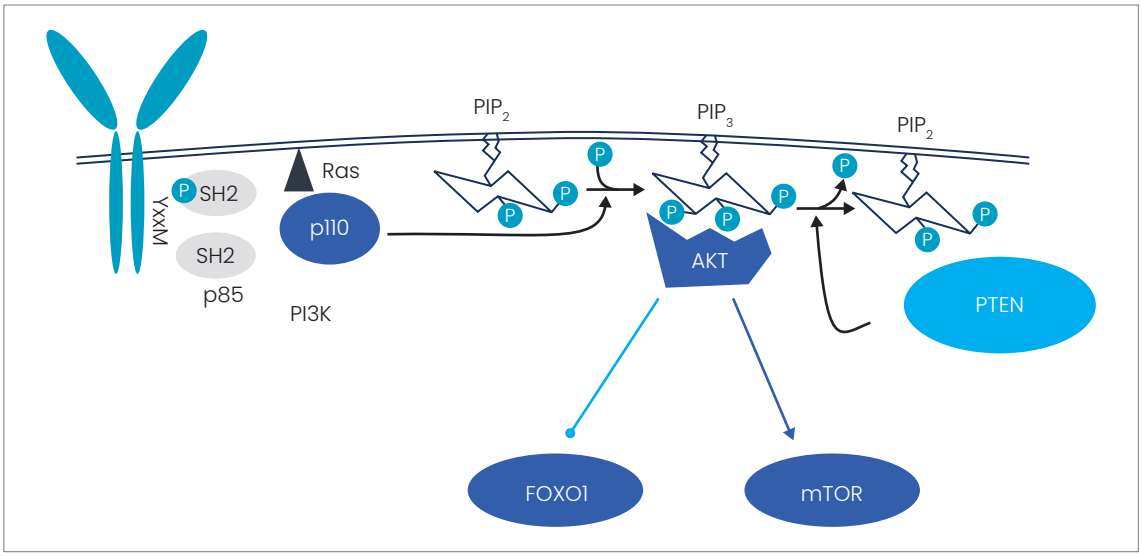
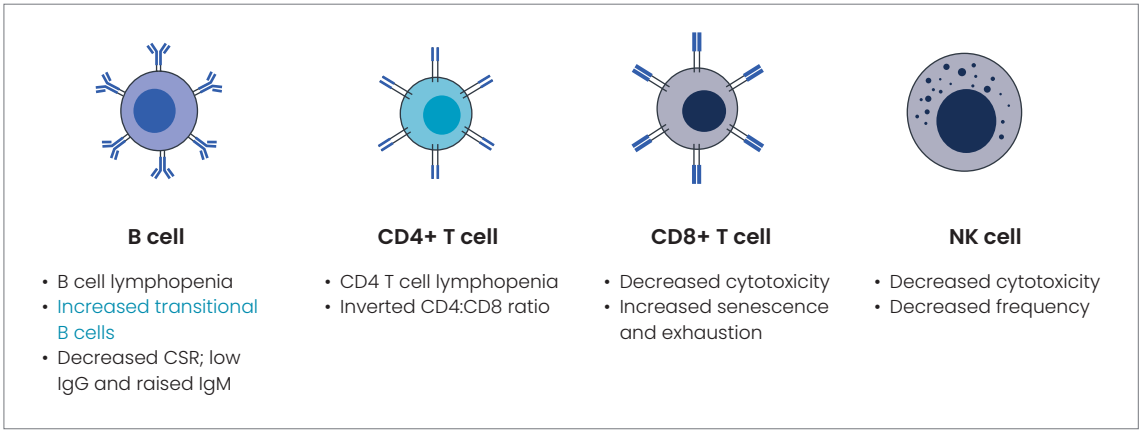


Figure 2. Immunophenotypic features of APDS.[2,6,10]



The first reports of APDS were in patients with gain-of-function variants of the gene *PIK3CD*, encoding the P110δ subunit of PI3K delta.[2,8] These variants have since been associated with a phenotype known as APDS1.[2] A second APDS phenotype (APDS2) has been associated with loss-of-function variants of the gene *PIK3R1*, encoding P85α, the regulatory subunit of PI3K delta.[2,4] More recently, gene variants have been identified that lead to reduced activity of a regulatory protein called PTEN, which is expressed ubiquitously, but can manifest within leukocytes leading to immune cell dysfunction.[2,5,9] PTEN gene variants have been associated with an APDS-like syndrome (APDS-L), as well as PTEN hamartoma tumour syndrome (PHTS) or Cowden's syndrome.[2]

Immunophenotypic features of APDS

As a result of hyperactive PI3K delta signalling, the majority of patients with APDS have abnormal lymphocyte subset counts in peripheral blood, with features of immune deficiency and immune dysregulation [**Figure 2**].[2] Key immunological findings include progressive B-cell lymphopenia, with reduction in naïve B-cell levels and elevated transitional B cells.[1,2] Patients with APDS typically have CD4+ T-cell lymphopenia, an inverted CD4+/CD8+ ratio, and increased senescence and exhaustion of CD8+ cells.[1,2] Decreased differentiation and cytotoxicity of natural killer (NK) cells is also evident in some APDS phenotypes.[2,6,10]

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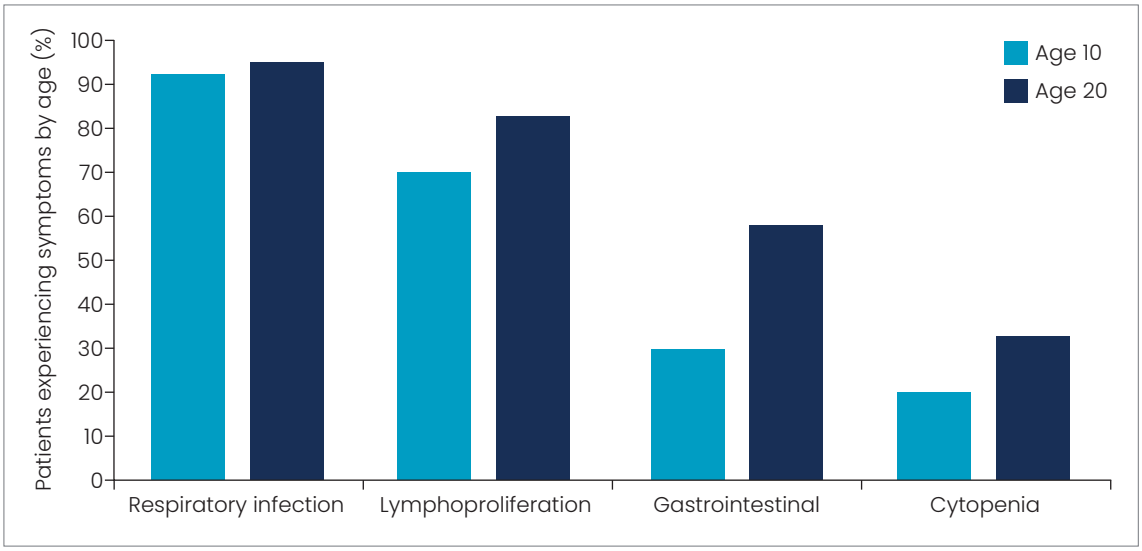
Figure 3. Evolution of disease manifestations over time from European Society for Immunodeficiencies (ESID)-APDS Registry. Information regarding age at onset available for: respiratory infections n=62/65; lymphoproliferation n=59/59; gastrointestinal manifestations n=33/35; cytopenia n=20/21.[1]



Serum immunoglobulin levels are highly variable in patients with APDS, ranging from mild IgG subclass deficiencies to severe combined immunodeficiency.[2] IgG and IgA levels are typically low or normal, with elevated IgM, due to a class-switch recombination defect leading to immature B cell populations.[2,7] Hyper-IgM syndrome was seen in 48% of patients in a systematic review of 243 APDS cases.[6]

Clinical characteristics of APDS

The clinical course of APDS is characterised by early onset of respiratory infections and non-neoplastic lymphoproliferation, followed by other manifestations of immune dysregulation, such as enteropathy and autoimmune cytopenia [**Figure 3**].[1] Recurrent infection of the ears, sinuses or lungs in infancy or childhood is the most common reason for first presentation to medical services.[5,6] Impaired lung function is common, and recurrent respiratory tract infections often progress rapidly to irreversible lung damage in the form of bronchiectasis.[3]

Recurrent ear, sinus or lung infections are commonly associated with bacterial pathogens such as *Haemophilus influenzae* and *Streptococcus pneumoniae*.[2,7] Cellulitis, and abscesses associated with *Staphylococcus* infection have also been reported.[7] Acute viral infections with varicella or herpes simplex, and chronic viral infections and reactivations are often documented, notably including Epstein-Barr Virus (EBV) or cytomegalovirus (CMV) infection.[1,7,11] Opportunistic infections are rare, but case reports have included cryptosporidium, toxoplasmosis, and local infection following vaccination with bacillus Calmette-Guérin (BCG), consistent with deficiencies within the T-cell compartment.[7] Fungal infections of the respiratory tract are thought to be rare in APDS.[2,7]

Lymphoproliferation in APDS ranges from benign lymphadenopathy, hepatomegaly and splenomegaly to focal nodular lymphoid hyperplasia.[1,2] A proportion of people with APDS go on to develop malignancies, with lymphomas affecting 13% of patients, in some cases associated with EBV infection.[7]

Gastrointestinal manifestations, such as chronic diarrhoea or inflammatory bowel disease, and other features of immune dysregulation typically occur later in the course of disease.[1] Autoimmune hepatitis, eczema, glomerulonephritis and autoimmune thyroiditis have been reported.[1] Thirty percent (30%) of patients with APDS develop immune cytopenia, such as haemolytic anaemia, thrombocytopenia and/or leukopenia.[1,7] Neurodevelopmental delay has been associated with some APDS phenotypes.[6]

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Table 1. Clinical features of patients with APDS, APDS-L, or CVID.[12]

	APDS-1 (%)	APDS-2 (%)	APDS-L (%)	CVID (%)
Autoimmunity	42	17	N.D	22-29
Enteropathy	25	24	N.D	9
Granuloma	0	N.D	N.D	8-9
IVIG therapy	77	89	19	80
Lymphoproliferation	75	89	44	N.D
Malignancy	13	28	22	3-8
Neurodevelopmental delay	19	31	50	N.D
Pneumonia	85	71	50	32-77
Splenomegaly	58	43	N.D	15-30

Adapted from Asano et al., 2018.

Diagnosing APDS

Manifestations of APDS are highly variable, even within families carrying the same gene variant.[3] Clinical and immunophenotypic features overlap with other primary immune deficiencies, which can complicate diagnosis.[7] In a systematic review of 243 patients with APDS, diagnosis was delayed on average 7 years (range 3.4 to 14 years).[6] Many patients with APDS have a historical primary diagnosis of specific antibody deficiency, subclass deficiency, common variable immune deficiency (CVID), combined immune deficiency (CID) or hyper-IgM syndrome.[3,6]

Compared to the more common diagnosis of CVID, available data suggest APDS is more often associated with features of severe immune dysregulation, such as autoimmunity, enteropathy, lymphoproliferation and malignancies (including lymphoma) [**Table 1**].[12,13]

Genetic testing to identify an activating PI3K delta gene variant is critical to provide a definitive diagnosis of APDS.[7] It has been proposed that genetic screening for activating PI3K delta gene variants should be considered for any patients presenting with reduced IgG and IgA levels and normal or increased IgM levels, and for those with early-onset bronchiectasis with any degree of immunoglobulin abnormality.[7]

Current treatment options for APDS

There is as yet no specific treatment to address the underlying cause of APDS, so current treatments tend to focus on symptom control and prevention of infection.[1,3] Most patients receive standard therapies for primary immune deficiency, including antibiotic prophylaxis and long-term immunoglobulin replacement therapy (IRT), starting early in life.[1,3] Immunosuppressive therapies, such as corticosteroids, calcineurin inhibitors, or rituximab, are used to manage autoimmune or inflammatory complications of APDS.[1,3] However, despite optimal IRT and symptom management, many patients with APDS still progress to end organ damage, such as bronchiectasis.[3]

The only potentially curative therapy available for APDS is haematopoietic stem cell transplant (HSCT).[1] A global systematic review suggests that 13% of patients with APDS receive HSCT,[6] with over 70% of those patients able to be weaned off IRT.[10] However, HSCT carries a considerable risk of complications including rejections or graft failure.[6] In a Japanese cohort of 9 patients with APDS receiving HSCT, 91% experienced adverse complications of HSCT and 36% experienced initial engraftment failure and 2 patients died.[14] In a US and European APDS cohort of 57 patients receiving HSCT, 2-year overall survival was 86% and 2-year graft-failure free survival was 68%.[15] Among the 8 patients who died during follow-up, 63% of deaths occurred in the first 100 days following HSCT.[15]

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An increasing understanding of the monogenic basis for APDS suggests a role for targeted treatment approaches.[1,3] The mTOR inhibitor rapamycin (sirolimus) has been studied for the treatment of APDS, owing to the downstream role of mTOR in hyperactive PI3K delta signalling.[1] Based on physician assessment of 26 patients with APDS, rapamycin was effective for the treatment of lymphoproliferative symptoms, but less effective for bowel inflammation or cytopenia.[1] Direct PI3K delta inhibition may be another valid therapeutic target and research is ongoing.[3]

Summary

- Activated PI3K Delta Syndrome (APDS) is a rare progressive PID (increasingly known as Inborn Error of Immunity [IEI]), characterised by hyperactive PI3K delta signalling that causes both immune deficiency and immune dysregulation.[1]
- Patients wait on average 7 years for a diagnosis, and without a definitive genetic test can remain incorrectly or incompletely diagnosed with PID, CVID or CID.[6]
- APDS may be associated with significantly increased morbidity, having a negative impact on quality of life, and can be the cause of death in some patients.[1,6]
- There are no licensed therapies for APDS and current treatment revolves around specific symptom management, and in some cases higher-risk HSCT.[3]

For more information about APDS and its management, visit www.allaboutapds.eu.

This report was developed as part of the touchFEATURE activity, **"Understanding activated PI3K delta syndrome (APDS): a rare progressive primary immunodeficiency (PID)"**. To view the full touchFEATURE activity, which also includes a video, please visit http://www.touchimmunologytmc.com/primary-immunodeficiencies/learning-zone/understanding-activated-PI3K-delta-syndrome-APDS/.

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References

1. Maccari ME, Abolhassani H, Aghamohammadi A, et al. Disease evolution and response to rapamycin in Activated Phosphoinositide 3-Kinase δ syndrome: the european society for immunodeficiencies-Activated Phosphoinositide 3-Kinase δ syndrome registry. *Front Immunol.* 2018;9:543.
2. Nunes-Santos C, Uzel G, Rosenzweig SD, et al. PI3K pathway defects leading to immunodeficiency and immune dysregulation. *J Allergy Clin Immunol.* 2019;143(5):1676-1687.
3. Coulter TI, Cant AJ. The Treatment of Activated PI3Kd Syndrome. *Front Immunol.* 2018;9:2043.
4. Elkaim E, Neven B, Bruneau J, et al. Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase d syndrome 2: A cohort study. *J Allergy Clin Immunol.* 2016;138(1):210-218.
5. Condliffe AM, Chandra A. Respiratory Manifestations of the Activated Phosphoinositide 3-Kinase Delta Syndrome. *Front Immunol.* 2018;9:338.
6. Jamee M, Moniri S, Zaki-Dizaji M, et al. Clinical, Immunological, and Genetic Features in Patients with Activated PI3Kδ Syndrome (APDS): a Systematic Review. *Clin Rev Allergy Immunol.* 2020;59(3):323-333.
7. Coulter TI, Chandra A, Bacon CM, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: A large patient cohort study. *J Allergy Clin Immunol.* 2017;139(2):597-606.e4.
8. Lucas CL, Kuehn HS, Zhao F, et al. Dominant-Activating, Germline Mutations in Phosphoinositide 3-Kinase p110δ Cause T Cell Senescence and Human Immunodeficiency. *Nat Immunol.* 2014;15:88-97.
9. Browning MJ, Chandra A, Carbonaro V, et al. Cowden's syndrome with immunodeficiency. *J Med Genet.* 2015;52(12):856-859.
10. Brodsky NN, Lucas CL. Infections in activated PI3K delta syndrome (APDS). *Curr Opin Immunol.* 2021;72:146-157.
11. Ewertowska M, Grzesk E, Urbanczyk A, et al. Activated phosphoinositide 3-kinase delta syndrome 1 and 2 (APDS 1 and APDS 2): similarities and differences based on clinical presentation in two boys. *Allergy Asthma Clin Immunol.* 2020;16:22.
12. Asano T, Okada S, Tsumura M, et al. Enhanced AKT Phosphorylation of Circulating B Cells in Patients With Activated PI3Kδ Syndrome. *Front Immunol* 2018;9:568.
13. Yakaboski E, Fuleihan RL, Sullivan KE, et al. Lymphoproliferative Disease in CVID: a Report of Types and Frequencies from a US Patient Registry. *J Clin Immunol* 2020;40(3):524-530.
14. Okano T, Imai K, Tsujita Y, et al. Hematopoietic stem cell transplantation for progressive combined immunodeficiency and lymphoproliferation in patients with activated phosphatidylinositol-3-OH kinase δ syndrome type 1. *J Allergy Clin Immunol.* 2019;143(1):266-275.
15. Dimitrova D, Nademi Z, Maccari ME, et al. International retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-delta syndrome. *J Allergy Clin Immunol.* 2022;149(1):410-421.e7.

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