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# Activated phosphoinositide 3-kinase $\delta$ syndrome: Update from the ESID Registry and comparison with other autoimmune-lymphoproliferative inborn errors of immunity

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1                   **Activated Phosphoinositide 3-Kinase  $\delta$  Syndrome:**  
2                   **Update from the ESID Registry and comparison with other**  
3                   **autoimmune-lymphoproliferative inborn errors of immunity**

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260 **Abstract**

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262 **Background:** Activated phosphoinositide-3-kinase (PI3K)  $\delta$  Syndrome (APDS) is an inborn  
263 error of immunity (IEI) with infection susceptibility and immune dysregulation, clinically  
264 overlapping with other conditions. Management depends on disease evolution, but predictors  
265 of severe disease are lacking.

266 **Objectives:** Report the extended spectrum of disease manifestations in APDS1 versus  
267 APDS2, compare these to CTLA-4 deficiency, NF $\kappa$ B1 deficiency, and STAT3 gain-of-function  
268 (GOF) disease; identify predictors of severity in APDS.

269 **Methods:** Data collection with the European Society for Immunodeficiencies (ESID)-APDS  
270 registry. Comparison with published cohorts of the other IEIs.

271 **Results:** The analysis of 170 APDS patients outlines high penetrance and early-onset of  
272 APDS compared to the other IEIs. The large clinical heterogeneity even in individuals with the  
273 same *PIK3CD* variant E1021K illustrates how poorly the genotype predicts the disease  
274 phenotype and course. The high clinical overlap between APDS and the other investigated  
275 IEIs suggests relevant pathophysiological convergence of the affected pathways.  
276 Preferentially affected organ systems indicate specific pathophysiology: bronchiectasis is  
277 typical of APDS1; interstitial lung disease and enteropathy are more common in STAT3 GOF  
278 and CTLA-4 deficiency. Endocrinopathies are most frequent in STAT3 GOF, but growth  
279 impairment is also common particularly in APDS2. Early clinical presentation is a risk factor  
280 for severe disease in APDS.

281 **Conclusion:** APDS illustrates how a single genetic variant can result in a diverse  
282 autoimmune-lymphoproliferative phenotype. Overlap with other IEI is substantial. Some  
283 specific features distinguish APDS1 from APDS2. Early-onset is a risk factor for severe  
284 disease course calling for specific treatment studies in younger patients.

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## 288 **Clinical Implications**

289 We report the largest APDS-cohort worldwide. APDS illustrates how a single genetic variant  
290 can cause a highly diverse autoimmune-lymphoproliferative phenotype overlapping with  
291 similar IEI. Early disease onset confers more severe disease.

292

## 293 **Capsule summary**

294 When comparing the phenotypic overlap of autoimmune-lymphoproliferative inborn errors of  
295 immunity (IEI) APDS demonstrates high penetrance, low genetic heterogeneity, early-onset  
296 as risk factor for severe disease and high phenotypic overlap with other IEIs.

297

## 298 **Key words**

299 APDS; PIK3CD; PIK3R1; PI3K; STAT3; CTLA-4; NF $\kappa$ B1; IEI; ESID; immunodeficiency.

300

## 301 **Abbreviations**

302 AD: autosomal dominant

303 AIHA: autoimmune haemolytic anemia

304 APDS: Activated phosphoinositide 3-kinase (PI3K)  $\delta$  Syndrome

305 BCG: Bacillus Calmette-Guérin

306 CMV: cytomegalovirus

307 CTLA-4: cytotoxic T lymphocyte antigen 4

308 EBV: Epstein-Barr-Virus

309 ESID: European Society for Immunodeficiencies

310 GLILD: granulomatous-lymphocytic interstitial lung disease

311 GOF: gain of function

312 HPV: human papillomavirus

313 HSCT: hematopoietic stem cell transplantation

314 IEI: inborn error of immunity

315 NF $\kappa$ B1: nuclear factor of kappa light polypeptide gene enhancer in B cells

316 PASLI: p110-delta-activating mutation causing senescent T cells, lymphadenopathy, and  
317 immunodeficiency

318 STAT3: signal transducer and activator of transcription 3

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## 343 **Introduction**

344 Activated phosphoinositide 3-kinase (PI3K)  $\delta$  Syndrome (APDS), also called PASLI (p110-  
345 delta-activating mutation causing senescent T cells, lymphadenopathy, and  
346 immunodeficiency), is an autosomal-dominant (AD) inborn error of immunity (IEI).  
347 Heterozygous gain-of-PI3K $\delta$ -activity variants in *PIK3CD* or *PIK3R1* cause APDS 1 and 2  
348 respectively (1–5), which show large phenotypic overlap. APDS is characterized by early-  
349 onset recurrent respiratory infections, chronic lymphoproliferation (benign and malignant) and  
350 other signs of immune dysregulation such as enteropathy and cytopenia (6–10). While  
351 previous cohort studies have illustrated a variety of clinical features of APDS, the identification  
352 and standardized documentation of additional patients allows extending the spectrum of  
353 disease manifestations that can be reliably associated with the two variants of the disease.

354 Interestingly, many clinical features of APDS are shared with other autoimmune-  
355 lymphoproliferative IEIs, including cytotoxic T lymphocyte antigen 4 (CTLA-4) deficiency (11–  
356 13), nuclear factor of kappa light polypeptide gene enhancer in B cells (NF $\kappa$ B1) deficiency  
357 (14,15) and signal transducer and activator of transcription (STAT3) gain-of-function (GOF)  
358 disease (16,17). All four IEI present an AD mode of inheritance, can cause increased infection  
359 susceptibility, early-onset benign lymphoproliferation, multisystem autoimmunity and an  
360 increased risk of lymphoma. Biomarkers facilitating diagnosis such as soluble FAS ligand and  
361 vitamin B12 for ALPS are lacking, rendering the differential diagnosis between these 4 IEI  
362 particularly challenging. However, a comparison of clinical manifestations between these  
363 conditions has not been performed. Delineation of entity-specific disease patterns can have  
364 diagnostic implications, while overlapping disease features may indicate pathophysiological  
365 convergence of affected signalling pathways, potentially offering opportunities for shared  
366 targeted interventions.

367 The clinical course of APDS is highly variable. While it can be life-threatening in childhood,  
368 stable disease into late adulthood has also been reported (6–8). This variability makes it  
369 difficult to advise patients about their individual prognosis and best treatment approach. The

370 most promising current therapeutic options include rapamycin, PI3K $\delta$  inhibitors, and  
371 hematopoietic stem cell transplantation (HSCT) (8,18–22). Yet, the standard of care and use  
372 of these therapies in the long-term management of APDS patients remains to be defined.  
373 These interventions and their potential side effects must be balanced against the risks of the  
374 natural disease course. However, information on the natural history of APDS is still limited,  
375 and no clear risk factors for severe disease evolution have been identified.

376 In this study, we used an updated dataset of the European Society for Immunodeficiencies  
377 (ESID)-APDS registry of 170 patients with APDS and published datasets on other  
378 autoimmune-lymphoproliferative IELs to address the following questions: (i) what are the  
379 clinical overlaps and characteristic differences between APDS, CTLA-4 deficiency, NF $\kappa$ B1  
380 deficiency, and STAT3 GOF disease? (ii) are there differences in the spectrum of disease  
381 manifestations between APDS1 and APDS2? and (iii) can we identify early predictors of  
382 severe disease evolution in APDS patients?

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## 397 **Methods**

### 398 The ESID-APDS Registry

399 The European Society for Immunodeficiencies (ESID) is a non-profit association whose aim  
400 is to improve knowledge in the field of IEIs. The APDS subregistry is the first level 3 dataset  
401 within the international internet-based ESID registry (<https://esid.org/Working-Parties/Registry-Working-Party/ESID-Registry/The-3-levels-datasets-and-driving-questions>).  
402  
403 Documentation into the ESID-Registry is organized in three Levels. Level 1 is open to capture  
404 all IEI patients and includes a minimal dataset on initial manifestations, age at diagnosis,  
405 immunoglobulin replacement and HSCT with yearly follow-up on survival and changes in  
406 therapy (23). Level 2 allows to set up research projects that include some laboratory values  
407 and more details on treatments for a selected group of diseases. Level 3 allows to implement  
408 large datasets designed to address specific and extended clinical questions on a single IEI  
409 defined by a study protocol, including a statistical evaluation plan. All level 2 and 3 projects  
410 include level 1 data. Requirements for patients' registration are: positive vote from the local  
411 ethics committees; agreement between treating centre and ESID; signed ESID patient  
412 consent. Patient registration in the APDS subregistry also requires approval of evidence  
413 supporting the functional relevance of the mutation by one of the principal investigators.  
414 Patient data can be entered by authorized users via a standard web browser through  
415 encrypted communication (24). The first patient was registered in September 2015. The  
416 number of new patients documented per year is shown in Figure E1 A, the percentage of  
417 patients registered by the different countries in Figure E1 B.

418

### 419 Patients

420 46 centres collected data on 170 APDS patients (data closure for analysis: November 10<sup>th</sup>,  
421 2022). 68 patients were already reported (8) (Table E1). The study was carried out in  
422 accordance with the recommendations of Section 15 of the Code of Conduct of the General  
423 Medical Council of Baden-Württemberg, Germany. The protocol was approved by the Ethics

424 committee of the University of Freiburg, Germany (IRB approval No. ESID registry: 493/14;  
425 IRB approval No. APDS registry: 458/15). All subjects or their parents/legal caregivers gave  
426 written informed consent in accordance with the Declaration of Helsinki.

427 To perform the comparison with other AD IEIs, the largest published cohort studies (13,15,17)  
428 were taken as reference and the frequency of reported clinical and immunological features  
429 were compared between all four IEI, since there are currently no level 3 ESID registry data on  
430 the other IEIs. A study proposal was written and was approved by the ESID registry steering  
431 committee, to collect level 1 data on the initial presentation of the analysed IEIs from the ESID  
432 Registry. Subsequently, complete data from patients whose documenting centres agreed to  
433 the protocol were included in the analysis.

434

#### 435 Statistical Analysis

436 Data were exported and organized using Microsoft Excel (Microsoft, Redmond WA). Data  
437 visualisation and statistical analysis were performed using R version 4.1.0. Proportions  
438 between all IEI were compared using Pearson's chi-squared test. Analyses with a p value <  
439 0.05 (\*) were considered to be statistically significant. Only significant comparisons between  
440 all IEIs were shown in the figures. We performed a logistic regression to analyse the probability  
441 of severity in dependency of variables shown in Figure E4. For missing value imputation, we  
442 used the R package mice with predictive mean matching for numeric data and logistic  
443 regression imputation for binary data. To avoid overfitting, we performed bidirectional stepwise  
444 model selection by AIC. Weighted Cox Regression: Data are doubly truncated since the age  
445 at severity onset falls in the time interval between age at disease onset and age at study entry.  
446 We used inverse probability weighted Cox regression for doubly truncated data (25) to analyse  
447 the cumulative probability of severity in dependency of the binary variable age at onset  
448 under/over 1 year.

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450



451 **Results**452 ***APDS has low genetic heterogeneity, early onset and strong penetrance***

453 Among the 170 APDS patients, 115 had heterozygous disease-causing variants in *PIK3CD*  
454 and 55 in *PIK3R1* (Table E1). Eight different disease-causing variants were found spanning  
455 p110 $\delta$  with E1021K accounting for 90% (Figure 1A and 1B). All APDS2 patients carried  
456 deleterious splice site disease-causing variants resulting in “skipping” of exon 11 of p85 $\alpha$   
457 (Table E1). In contrast, 45 different *CTLA4* disease-causing variants were found among 133  
458 patients (13), 56 disease-causing variants were identified in 157 NF $\kappa$ B1 deficient patients (15)  
459 and 72 different variants were reported in 191 STAT3 GOF patients (17). Thus, genetic  
460 heterogeneity of APDS appears to be lower compared to the other three IELs. Median age at  
461 first clinical manifestation was 1 year in APDS patients, with no gender difference and no  
462 difference between APDS1 and 2. Age at onset was lower than that reported for CTLA-4  
463 (median 11y) (13) and NF $\kappa$ B1 (median 12y) (15) deficiency, while patients with STAT3 GOF  
464 disease also presented early in life (median 2.3y) (17) (Figure 2A). The initial clinical  
465 manifestations experienced by APDS patients were most frequently infections (54%) and  
466 infections combined with immune dysregulation (29%), less frequently immune dysregulation  
467 without infections (8%) (Figure 2B). This was similar to NF $\kappa$ B1 deficiency (Figure 2B), while  
468 patients with STAT3 GOF and CTLA-4 deficiency more frequently first presented with immune  
469 dysregulation without infection (37% and 44%, respectively). Only 4 APDS patients were  
470 reported to be without clinical symptoms at registration (age at registration 1, 1, 3 and 44y),  
471 but two of them received immunoglobulin replacement for hypogammaglobulinemia. In the  
472 CTLA-4 and NF $\kappa$ B1 cohorts, 19.5% and 23% were reported to be clinically healthy,  
473 respectively. While unaffected STAT3 GOF carriers were not included in the Leiding cohort  
474 (17), a recent review (26) included 18% asymptomatic STAT3 GOF individuals. Hence,  
475 compared to these 3 other IELs with overlapping phenotypes disease penetrance appears to  
476 be higher in APDS.

477

**478 APDS has an earlier and more severe infection profile**

479 Respiratory infections were frequent in all 4 IELs with the highest occurrence in APDS (92%)  
480 (Figure 3A). Other common infections in APDS included invasive bacterial infections (53%)  
481 and infectious lymphadenitis (30%). Only one case of CMV-associated lymphadenitis was  
482 reported in the CTLA-4 cohort, and no cases were mentioned among the NF $\kappa$ B1 or STAT3  
483 GOF patients. *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus*  
484 *aureus* were the most frequently reported respiratory pathogens in all diseases, while  
485 infections with *Pseudomonas aeruginosa* were reported more frequently in APDS (n=15/169)  
486 and STAT3 GOF (n=8/191). *Escherichia coli* and *Salmonella* were the most frequently isolated  
487 pathogens in bacterial intestinal infections. Chronic EBV (22%, age range 1-37y, median 5y)  
488 and chronic CMV (14%, age range 1-35y, median 8.5y) were present in APDS patients (Figure  
489 3A). Similarly, in CTLA-4 deficient patients EBV and CMV led to clinically relevant infections  
490 in 18% and 10% respectively, while the reported incidence was below 5% in NF $\kappa$ B1 deficiency  
491 and STAT3 GOF. Acute viral infections were reported in 47% APDS patients. No cases of  
492 *Pneumocystis jirovecii* infection were reported in the APDS cohort and mycobacterial  
493 infections were rare (4 patients with Bacillus Calmette-Guérin (BCG) disease and 1 with  
494 pneumonia due to *Mycobacterium xenopi*). Parasitic infections were rare in all conditions; 2  
495 cases of infection with *Cryptosporidium parvum*, 2 with *Giardia lamblia* and 2 with *Toxoplasma*  
496 were reported in the APDS cohort. Opportunistic infections were all prior to HSCT.

497

**498 Bronchiectasis is more prominent than interstitial lung disease in APDS**

499 143 APDS patients had chest imaging (CT-scan or MRI) performed: pathological findings were  
500 detected in 73%. Bronchiectasis was most frequent in APDS (50%, age range 1-43y; median  
501 7y), but was also reported in the other IELs (Figure 3B). Small airway disease was noted in  
502 29% of APDS patients (age range 1-50y; median 8y). Interstitial lung disease (ILD) was only  
503 reported in 2% of APDS and in 7% of NF $\kappa$ B1 deficient patients. In contrast, CTLA-4 deficient  
504 patients were often (36%) reported to have granulomatous-lymphocytic interstitial lung

505 disease (GLILD) (Figure 3B). Similarly, ILD occurred in 43% of STAT3 GOF patients. Lung  
506 disease was severe enough to justify lung transplantation in 2 CTLA-4 patients and 2 STAT3  
507 GOF patients. Interestingly, 30 APDS patients (18%) had asthma as concomitant diagnosis,  
508 compared to 6% in the CTLA-4 cohort and no reported cases in the other two cohorts. Lung  
509 function, assessed in 91 APDS patients, was abnormal in 47%.

510

### 511 ***APDS is characterized by chronic benign lymphoproliferation and early malignancy***

512 Chronic benign lymphoproliferation, including both splenomegaly and persistent  
513 lymphadenopathy (defined as lymph nodes larger than 1 cm, affecting more than 1 site for  
514 longer than 1 month), was most frequent in APDS (86%), followed by CTLA-4 deficiency (73%)  
515 and STAT3 GOF disease (73%) with a lower incidence of 52% in NF $\kappa$ B1 deficiency (Figure  
516 3C). Conversely, cytopenia was significantly less frequent in APDS (19%, most frequent: AIHA  
517 in 12 patients) than in CTLA-4 deficiency (62%), NF $\kappa$ B1 deficiency (43.9%), and STAT3 GOF  
518 disease (68%) (Figure 3C). Lymphoma was documented in 14% of APDS, 11% of NF $\kappa$ B1, 9%  
519 of CTLA-4 patients, but only 4% of STAT3 GOF patients (Figure 3D). Lymphomas in APDS  
520 included 7 Hodgkin lymphomas, 10 non-Hodgkin lymphomas, 1 intestinal large B cell  
521 lymphoma with plasmablastic differentiation, 1 follicular lymphoma, 1 large B-cell lymphoma,  
522 1 mature T/NK lymphoma, 1 lymphoma without further histological information; 17/22  
523 lymphoma cases were preceded by chronic benign lymphoproliferation. Of note, 10/20  
524 lymphoma cases in APDS were EBV-associated. Moreover, of the 22 APDS patients with  
525 lymphoma, 4 suffered also from other malignancies (2 ovary neoplasms; 1 papillary renal cell  
526 carcinoma; 1 malignant neoplasm of the submandibular gland). Furthermore, one APDS  
527 patient had a B cell chronic lymphocytic leukaemia, one suffered from hepatocellular  
528 carcinoma, one had a breast ductal carcinoma *in situ*, one patient had a papillary thyroid  
529 carcinoma and one a rhabdomyosarcoma. The median age at diagnosis of any malignancy  
530 was much lower in APDS (19y) than in NF $\kappa$ B1 (46y) patients.

531

532 ***Autoimmune and inflammatory diseases are relevant in APDS, but less frequent than***  
533 ***in the other diseases***

534 Enteropathy, ranging from protracted diarrhoea to inflammatory bowel disease, was reported  
535 in 35% of APDS patients, less frequently than in the other IELs (Figure 3E). Rare cases of  
536 eosinophilic oesophagitis and sclerosing cholangitis were also reported (27). Autoimmune  
537 hepatitis was particularly frequent in STAT3 GOF (Figure 3E). Non-infectious skin disease  
538 was reported in 25% of APDS patients and mainly included eczema and granulomas (Figure  
539 3E). This was less prominent than in CTLA-4 deficiency (56%, mainly eczema) and STAT3  
540 GOF disease (48% skin lesions including eczema, psoriasis and alopecia) but more frequent  
541 than in the NF $\kappa$ B1 cohort (15%), where patients suffered more frequently from skin infections.  
542 Endocrinopathies, including autoimmune thyroiditis and type 1 diabetes mellitus were reported  
543 in all four IELs (Figure 3F) but were most frequent in STAT3 GOF disease. Renal disease  
544 affected 6-12% of APDS, CTLA-4 and STAT3 GOF patients, while it was not reported in  
545 NF $\kappa$ B1 deficiency. Moreover, 5 APDS patients were diagnosed with vasculitis and 2 different  
546 patients had systemic lupus erythematosus. One patient was diagnosed with chronic kidney  
547 disease, two received a kidney transplantation. Arthritis incidence was similar in all IELs  
548 studied (Figure 3E). Less than 5% of APDS, STAT3 GOF and NF $\kappa$ B1 patients had  
549 inflammatory brain disease, while this was significantly more frequent in CTLA-4 patients  
550 (12%). In APDS non-inflammatory neurological manifestations including neurodevelopmental  
551 delay were observed in 16% of patients. Growth impairment was frequent in APDS (32%) and  
552 STAT3 GOF disease (57%), less frequent in CTLA-4 deficiency (14%), and not reported in  
553 NF $\kappa$ B1 deficiency (Figure 3F).

554

555 ***Increased immunoglobulin M and reduced naïve T cells are characteristic***  
556 ***immunological abnormalities of APDS***

557 Hypogammaglobulinemia was common in all four IELs, but most frequent in NF $\kappa$ B1 deficiency.  
558 APDS is often characterized by elevated serum IgM (35%), while low IgM, a common feature

559 in the other 3 diseases, was rare in APDS (Figure 4A). While T-cell lymphopenia is common  
560 in all four IEIs, a low frequency of naïve CD4 T cells was most frequently reported in APDS.  
561 Reduced switched memory B cells and increased transitional B cells were reported but not  
562 particularly characteristic for APDS patients (Figure 4B).

563

#### 564 ***Distinct features of APDS1 versus APDS2 indicate pathophysiological differences***

565 Among initial presenting manifestations, syndromic features, mainly growth impairment and  
566 facial dysmorphism, were more frequent in APDS2 (Figure 5A; details are provided in Table  
567 E2). Infectious complications were equally distributed (Figure E2), but opportunistic infections  
568 were more frequent in APDS1. Significantly, bronchiectasis was more frequent in APDS1  
569 (60%) than in APDS2 (26%) (Figure 5B). The prevalence of asthma was similar (18% vs.  
570 16%). Splenomegaly and cytopenia were more frequent in APDS1 but lymphoma was more  
571 frequent in APDS2 (Figure 5C). Growth impairment was more frequent in APDS2, skin disease  
572 in APDS1 (Figure 5D). Among immunological abnormalities, low T-cell counts were more  
573 frequent in APDS1, while IgA reduction was more frequent in APDS2 (Figure 5E).

574

#### 575 ***Age at first clinical presentation predicts disease severity in APDS***

576 The majority of APDS patients received immunoglobulin replacement treatment (73%), many  
577 patients received immunomodulating therapies (Figure E3 A and B), ranging from rapamycin  
578 (37%) to PI3K $\delta$  inhibitors (5%). 29/168 (17%) APDS patients underwent allogeneic HSCT  
579 between the age of 5 and 51 years (median 13.5y). 14/170 (8%) APDS patients died at a  
580 median age of 18,5 years (5-44y). 5 deaths were lymphoma-related, 5 were HSCT-related, 1  
581 related to both. Two patients died from severe respiratory infection, one from intracranial  
582 bleeding secondary to thrombocytopenia. To evaluate prognostic factors for a severe disease  
583 course in APDS, we defined severe disease as follows: (i) severe invasive infection *and*  
584 immune dysregulation (excluding chronic benign lymphoproliferation and cytopenia) *or* chronic  
585 lung disease, (ii) severe immune dysregulation, (iii) malignancy. If a patient had already  
586 developed a severe invasive infection or severe immune dysregulation or chronic lung disease

587 before age 13 years, the disease course was also considered severe. Criteria for severe  
588 disease were fulfilled by 93/169 patients (range 2-50y; median age at transition to severe  
589 disease 9.5y) (Figure 6A, Table E3). All deceased patients had severe disease with a median  
590 time between fulfilling these criteria and death of 6 years (range 1-21y). The risk for severe  
591 disease increased with patient age (Figure 6B) and with years since the first clinical disease  
592 manifestation (Figure 6C). The risk doubled in the age range 10-15 years compared to age  
593 range 0-10 years. Age at onset below 1 year significantly correlated with the probability of  
594 developing severe disease (Figure 6D). Other significant risk factors could not be identified  
595 through a multivariate logistic regression analysis (Figure E4).

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## 612 **Discussion**

613 We report the evaluation of the so far largest APDS cohort of 170 patients with functionally  
614 validated, germline heterozygous variants in *PIK3CD* or *PIK3R1* documented through a  
615 standardised registry.

616 While highlighting the low genetic heterogeneity among APDS patients, we show that APDS1  
617 patients, the majority of which carry the *PIK3CD* E1021K mutation, display high phenotypic  
618 diversity. This illustrates that identical variants in a disease causing-gene can lead to diverse  
619 clinical consequences. This emphasizes the significance of additional genetic, epigenetic and  
620 environmental factors in determining disease manifestations in autoimmune-  
621 lymphoproliferative diseases. This clinical variability is associated with a very high penetrance,  
622 as there was only one patient above the age of 5 years reported to be asymptomatic in the  
623 registry. However, systematic segregation studies would be needed in APDS as well as in the  
624 other IEI cohorts to better evaluate the true penetrance of these diseases and indirectly  
625 estimate the extent of underdiagnosed cases.

626 We structured the updated analysis of the APDS cohort in the context of a comparison with  
627 three other AD autoimmune-lymphoproliferative IEIs for which substantial cohorts have been  
628 published: CTLA-4 deficiency, NF $\kappa$ B1 deficiency, and STAT3 GOF disease. In general, there  
629 was a high clinical overlap between the investigated IEI, indicating relevant pathophysiological  
630 convergence of the different affected pathways. This convergence is supported by  
631 experimental observations: for example, a link between mTOR activation and disease  
632 pathophysiology is evident not only in APDS (4), but also in STAT3 GOF (28) and CTLA-4  
633 deficiency (29). This justifies the frequent use of the mTOR inhibitor rapamycin in these three  
634 diseases, although variable treatment success indicates involvement of additional pathways.  
635 A potential link of mTOR activation to NF $\kappa$ B1 deficiency is less clear, mirrored by the reported  
636 use of rapamycin in only 2% of the patients in the largest published cohort (15).

637 Variability and overlap between the IEIs render it difficult to predict the diagnosis prior to  
638 genetic evaluation. However, some differences emerge from the comparative analysis. APDS

639 has the earliest onset, mainly with recurrent respiratory infections and this is in contrast to the  
640 frequent initial presentation with immune dysregulation typical of CTLA-4 deficiency and  
641 STAT3 GOF disease. Of note, the initial presentation with recurrent infections only rarely leads  
642 to the diagnosis of APDS, as recently highlighted by Ahmed et al. (30) who could diagnose  
643 only 1 APDS patient among 79 children admitted to the hospital for severe or recurrent  
644 respiratory infections. Infections are a crucial aspect in all 4 IELs throughout the disease  
645 course, with highest frequencies observed in APDS and NF $\kappa$ B1 deficiency. These two  
646 conditions present mechanistically different but equally profound B-cell dysfunction (14,31–  
647 33). Regarding infections, it is important to note that regional exposure to different pathogens  
648 can influence the reported frequency of the infections. For example, a recent paper on a  
649 Chinese APDS cohort (34) reported a much higher incidence of primary mycobacterial  
650 infections than in this APDS series of patients. Chronic viral infections are confirmed to be  
651 relevant, especially in APDS and CTLA-4 insufficiency. On the other hand, our extended  
652 APDS registry cohort analysis reveals that opportunistic infections are rather rare in this  
653 disease.

654 Lung disease is a prominent feature in APDS and its early identification is crucial in the  
655 management of IEL patients. Of note, bronchiectasis and small airway disease were  
656 characteristic, while ILD was reported infrequently in APDS. It is important to note that small  
657 airway disease is likely underestimated in APDS, since specific expiratory imaging is needed  
658 for early detection (35). Importantly, asthma was recently pointed out as a relevant  
659 manifestation in an American APDS cohort (36) and had been already reported in some  
660 patients of small case series (37). The ESID-APDS registry does not specifically ask for  
661 asthma, but it was repeatedly documented as “further diagnosis”, thereby providing additional  
662 evidence to consider it an APDS-related manifestation.

663 Of the IELs evaluated, APDS had the highest incidence of benign and malignant  
664 lymphoproliferation. This implies a diagnostic challenge of differentiating between benign and  
665 malignant lymphoproliferation (38). Imaging and FDG-PET do not provide a definitive



666 diagnosis, similar to other lymphoproliferative IELs (39). For this reason, a thorough evaluation  
667 of the clinical course by experienced clinicians and an adequate histological analysis by  
668 pathologists trained in analysing lymphoid tissue of patients with IELs is paramount to rule out  
669 lymphoma in these patients. The high incidence of non-lymphoid malignancies reported in our  
670 APDS cohort is noteworthy: while the increased risk of malignancy in IEL patients has long  
671 been known (40), increased awareness of APDS as cancer predisposition syndrome (41) calls  
672 for improved clinical care and research at the critical interface between immunology and  
673 oncology (42).

674 The analysis of the large APDS registry cohort also identifies arthritis, renal disease,  
675 neuroinflammatory disease or type 1 diabetes as rare but possible APDS-related  
676 complications. Overall, the differences between APDS and clinically overlapping IEL  
677 highlighted by our work are not sufficient to define a specific APDS-pattern or clinical  
678 diagnostic criteria for the disease. It is possible that including a higher resolution  
679 immunological analysis (such as high-dimensional multi-omics single cell data) may help  
680 identifying diagnostic biomarkers but at the moment, identification of a genetic variant in  
681 combination with its functional validation remains the only valid criteria.

682 Our analysis also highlights some new differences between the two forms of APDS  
683 corroborates others already noted through confirmation in a larger cohort and does not confirm  
684 others previously observed (6–8,36,43,44): thus, we report a significantly higher incidence of  
685 cytopenia and skin disease in APDS1 patients and a significantly higher incidence of reduced  
686 IgA in APDS2; we confirmed a higher incidence of bronchiectasis and reduced CD3 T cells in  
687 APDS1 and a higher incidence of lymphoma, growth retardation and syndromic features  
688 (detailed in this study) in APDS2. Regarding syndromic features, APDS2 can be differentiated  
689 from the SHORT (Short stature, hyperextensibility of joints and/or inguinal hernia, ocular  
690 depression, Rieger anomaly, and teething delay) syndrome, caused by mutations in the same  
691 gene (*PIK3R1*) but affecting another region (C-terminal Src homology 2 domain) resulting in  
692 a different effect (impairment of interaction with phosphorylated receptor tyrosine kinases)

693 (45). However, patients with overlapping clinical features have been reported (46–48). These  
694 clinical observations are relevant for the patient management and for research studies that  
695 further investigate pathophysiological differences between the catalytic and regulatory kinase  
696 components encoded by the mutated genes. Indeed, a recent work could identify relevant  
697 differences in B-cell abnormalities between APDS1 and APDS2 and highlight an increased  
698 perinatal mortality in APDS2 mice, but not in the APDS1 counterpart (49). Finally, a recently  
699 reported higher incidence of enteropathy in APDS1 patients and of elevated IgM in APDS2  
700 patients (44) could not be confirmed.

701 It should be noted, that this registry analysis bears some relevant limitations: (i) The compared  
702 IELs were not assessed using the same dataset, which may affect the reported frequency of  
703 some symptoms or diagnoses. (ii) Some manifestations are *per se* difficult to categorize, e.g.  
704 enteropathy can be difficult to distinguish from infectious enteritis. Internationally accepted  
705 standards of diagnosis and monitoring of these patients could help defining comparable data-  
706 sets and efforts are already taken in that direction (50). (iii) The registry- and the retrospective  
707 cohort study-structure are inevitably linked to the problem of missing data which leads to  
708 incomplete information and the eventual need of statistical corrections. In this study missing  
709 values were particularly relevant for laboratory parameters. Data completeness was only  
710 sufficient for some basic parameters, revealing that increased immunoglobulin M and reduced  
711 naïve T cells are characteristic, but not specific for APDS. It would be of interest to correlate  
712 more in-depth immunological parameters to identify possible disease-specific immune  
713 signatures and their role as prognostic factors.

714 One further aim of the current study was to identify predictors for severe disease in APDS,  
715 which could be useful for treatment and management choices. The number of variables  
716 evaluated as severe disease predictors was limited by the fact that many parameters were  
717 used in the definition of severe disease. Moreover, a registry-dependent bias in the  
718 identification and registration of younger patients with clinical symptoms of the disease must  
719 be taken into consideration, since the disease is not diagnosed through a screening but based

720 on clinical suspicion. The analysis revealed early disease onset as a prognostic factor, with  
721 the clinical implication that early-onset cases should be followed closely and evaluated early  
722 for treatments such as HSCT. It will be interesting to see in the future how targeted therapy  
723 with PI3K $\delta$  inhibitors will impact on the long-term evolution of disease manifestations in APDS.  
724 Recent results of a phase 3 trial show promising efficacy, especially regarding the  
725 lymphoproliferative disease, with a very good safety profile (22). The poorer prognosis for  
726 patients with early disease onset identified in this study highlights the importance of clinical  
727 trials involving younger patients (such as the recently started NCT05438407).

728

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774 **References**

775

- 776 1. Jou ST, Chien YH, Yang YH, Wang TC, Shyur SD, Chou CC, et al. Identification of  
777 variations in the human phosphoinositide 3-kinase p110 $\delta$  gene in children with  
778 primary B-cell immunodeficiency of unknown aetiology. *Int J Immunogenet.*  
779 2006;33(5):361–9.
- 780 2. Angulo I, Vadas O, Garçon F, Banham-Hall E, Plagnol V, Leahy TR, et al.  
781 Phosphoinositide 3-kinase  $\delta$  gene mutation predisposes to respiratory infection and  
782 airway damage. *Science (80- ) [Internet].* 2013;342(6160):866–71. Available from:  
783 [http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L528](http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52818443)  
784 18443
- 785 3. Lucas CL, Zhang Y, Venida A, Wang Y, Hughes J, McElwee J, et al. Heterozygous  
786 splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation  
787 due to dominant activation of PI3K. *J Exp Med.* 2014;211(13):2537–47.
- 788 4. Lucas CL, Kuehn HS, Zhao F, Niemela JE, Deenick EK, Palendira U, et al. Dominant-  
789 Activating, Germline Mutations in Phosphoinositide 3-Kinase p110 $\delta$  Cause T Cell  
790 Senescence and Human Immunodeficiency. *Nat Immunol.* 2014;15(1):88–97.
- 791 5. Deau MC, Heurtier L, Frange P, Suarez F, Bole-Feysot C, Nitschke P, et al. A human  
792 immunodeficiency caused by mutations in the PIK3R1 gene. *J Clin Invest.*  
793 2014;124(9):3923–8.
- 794 6. Coulter TI, Chandra A, Bacon CM, Babar J, Curtis J, Screatton N, et al. Clinical  
795 spectrum and features of activated phosphoinositide 3-kinase  $\delta$  syndrome: A large  
796 patient cohort study. *J Allergy Clin Immunol.* 2017;139(2):597-606.e4.
- 797 7. Elkaim E, Neven B, Bruneau J, Mitsui-Sekinaka K, Stanislas A, Heurtier L, et al.  
798 Clinical and immunologic phenotype associated with activated phosphoinositide 3-  
799 kinase  $\delta$  syndrome 2: A cohort study. *J Allergy Clin Immunol.* 2016;138(1):210-  
800 218.e9.
- 801 8. Maccari ME, Abolhassani H, Aghamohammadi A, Aiuti A, Aleinikova O, Bangs C, et

- 802 al. Disease evolution and response to rapamycin in activated phosphoinositide 3-  
803 kinase  $\delta$  syndrome: The European society for immunodeficiencies-activated  
804 phosphoinositide 3-kinase  $\delta$  syndrome registry. *Front Immunol.* 2018;9(MAR):1–8.
- 805 9. Redenbaugh V, Coulter T. Disorders Related to PI3K $\delta$  Hyperactivation:  
806 Characterizing the Clinical and Immunological Features of Activated PI3-Kinase Delta  
807 Syndromes. *Front Pediatr.* 2021;9(August):1–7.
- 808 10. Bloomfield M, Klocperk A, Zachova R, Milota T, Kanderova V, Sediva A. Natural  
809 Course of Activated Phosphoinositide 3-Kinase Delta Syndrome in Childhood and  
810 Adolescence. *Front Pediatr.* 2021;9(July):1–12.
- 811 11. Kuehn HS, Ouyang W, Lo B, Deenick EK, Niemela JE, Avery DT, et al. Immune  
812 dysregulation in human subjects with heterozygous germline mutations in CTLA4.  
813 *Science* (80- ) [Internet]. 2014 Sep 26;345(6204):1623–7. Available from:  
814 <https://www.science.org/doi/10.1126/science.1255904>
- 815 12. Schubert D, Bode C, Kenefeck R, Hou TZ, Wing JB, Kennedy A, et al. Autosomal  
816 dominant immune dysregulation syndrome in humans with CTLA4 mutations. *Nat*  
817 *Med.* 2014;20(12):1410–6.
- 818 13. Schwab C, Gabrysch A, Olbrich P, Patiño V, Warnatz K, Wolff D, et al. Phenotype,  
819 penetrance, and treatment of 133 CTLA-4-insufficient individuals. *J Allergy Clin*  
820 *Immunol* [Internet]. 2018;142(6):1932–46. Available from:  
821 <http://www.ncbi.nlm.nih.gov/pubmed/29729943>  
822 [http://linkinghub.elsevier.com/retri  
eve/pii/S0091674918306304](http://linkinghub.elsevier.com/retrieve/pii/S0091674918306304)
- 823 14. Fliegau M, L. Bryant V, Frede N, Slade C, Woon ST, Lehnert K, et al.  
824 Haploinsufficiency of the NF- $\kappa$ B1 Subunit p50 in Common Variable Immunodeficiency.  
825 *Am J Hum Genet.* 2015;97(3):389–403.
- 826 15. Lorenzini T, Fliegau M, Klammer N, Frede N, Proietti M, Bulashevskaya A, et al.  
827 Characterization of the clinical and immunologic phenotype and management of 157  
828 individuals with 56 distinct heterozygous NFKB1 mutations. *J Allergy Clin Immunol.*  
829 2020;146(4):901–11.

- 830 16. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Allen HL, De Franco E, et al.  
831 Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune  
832 disease. *Nat Genet* [Internet]. 2014 Aug 20;46(8):812–4. Available from:  
833 <http://www.nature.com/articles/ng.3040>
- 834 17. Leiding JW, Vogel TP, Santarlas VGJ, Mhaskar R, Smith MR, Carisey A, et al.  
835 Monogenic early-onset lymphoproliferation and autoimmunity: Natural history of  
836 STAT3 gain-of-function syndrome. *J Allergy Clin Immunol* [Internet]. 2022 Oct;1–15.  
837 Available from: <https://doi.org/10.1016/j.jaci.2022.09.002>
- 838 18. Rao VK et al. Effective “activated PI3K $\delta$  syndrome”-targeted therapy with the PI3K $\delta$   
839 inhibitor leniolisib. *Blood*. 2017;130(21):2307–16.
- 840 19. Diaz N, Juarez M, Cancrini C, Heeg M, Soler-Palacín P, Payne A, et al. Seletalisib for  
841 Activated PI3K $\delta$  Syndromes: Open-Label Phase 1b and Extension Studies. *J*  
842 *Immunol*. 2020;205(11):2979–87.
- 843 20. Dimitrova D, Nademi Z, Maccari ME, Ehl S, Uzel G, Tomoda T, et al. International  
844 retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-  
845 delta syndrome. *J Allergy Clin Immunol* [Internet]. 2021;(April). Available from:  
846 <https://doi.org/10.1016/j.jaci.2021.04.036>
- 847 21. Okano T, Imai K, Tsujita Y, Mitsuiki N, Yoshida K, Kamae C, et al. Hematopoietic  
848 stem cell transplantation for progressive combined immunodeficiency and  
849 lymphoproliferation in patients with activated phosphatidylinositol-3-OH kinase  $\delta$   
850 syndrome type 1. *J Allergy Clin Immunol* [Internet]. 2019;143(1):266–75. Available  
851 from: <https://doi.org/10.1016/j.jaci.2018.04.032>
- 852 22. Rao VK, Webster S, Šedivá A, Plebani A, Schuetz C, Shcherbina A, et al.  
853 Randomized, placebo-controlled phase 3 trial of PI3K $\delta$  inhibitor leniolisib for activated  
854 PI3K $\delta$  syndrome. *Blood*. 2023;141(9).
- 855 23. Thalhammer J, Kindle G, Nieters A, Rusch S, Seppänen MRJ, Fischer A, et al. Initial  
856 presenting manifestations in 16,486 patients with inborn errors of immunity include  
857 infections and noninfectious manifestations. *J Allergy Clin Immunol*. 2021;

- 858 24. Scheible R, Rusch S, Guzman D, Mahlaoui N, Ehl S, Kindle G. The NEW ESID online  
859 database network. *Bioinformatics*. 2019;35(24):5367–9.
- 860 25. Mandel M, de Uña-Álvarez J, Simon DK, Betensky RA. Inverse probability weighted  
861 Cox regression for doubly truncated data. *Biometrics*. 2018;74(2):481–7.
- 862 26. Faletti L, Ehl S, Heeg M. Germline STAT3 gain-of-function mutations in primary  
863 immunodeficiency: Impact on the cellular and clinical phenotype. *Biomed J [Internet]*.  
864 2021;(March):1–11. Available from: <https://doi.org/10.1016/j.bj.2021.03.003>
- 865 27. Hartman HN, Niemela J, Hintermeyer MK, Garofalo M, Stoddard J, Verbsky JW, et al.  
866 Gain of Function Mutations of PIK3CD as a Cause of Primary Sclerosing Cholangitis.  
867 *J Clin Immunol*. 2015;35(1):11–4.
- 868 28. Chi H. Regulation and function of mTOR signalling in T cell fate decisions. *Nat Rev*  
869 *Immunol*. 2012;12(5):325–38.
- 870 29. Jung S, Gámez-Díaz L, Proietti M, Grimbacher B. “Immune TOR-opathies,” a novel  
871 disease entity in clinical immunology. *Front Immunol*. 2018;9(MAY):1–14.
- 872 30. Ahmed AA, El Shahaway AA, Hussien SA. Activated PI3K-delta syndrome in an  
873 Egyptian pediatric cohort with primary immune deficiency. *Allergol Immunopathol*  
874 *(Madr)*. 2020;48(6):686–93.
- 875 31. Kaileh M, Sen R. NF- $\kappa$ B function in B lymphocytes. *Immunol Rev*. 2012;246(1):254–  
876 71.
- 877 32. Avery DT, Kane A, Nguyen T, Lau A, Nguyen A, Lenthall H, et al. Germline-activating  
878 mutations in PIK3CD compromise B cell development and function. *J Exp Med*  
879 *[Internet]*. 2018 Aug 6;215(8):2073–95. Available from:  
880 <https://doi.org/10.1084/jem.20180010>
- 881 33. Wentink M, Dalm V, Lankester AC, van Schouwenburg PA, Schölvinck L, Kalina T, et  
882 al. Genetic defects in PI3K $\delta$  affect B-cell differentiation and maturation leading to  
883 hypogammaglobulinemia and recurrent infections. *Clin Immunol [Internet]*.  
884 2017;176:77–86. Available from: <http://dx.doi.org/10.1016/j.clim.2017.01.004>
- 885 34. Qiu L, Wang Y, Tang W, Yang Q, Zeng T, Chen J, et al. Activated Phosphoinositide



- 886 3-Kinase  $\delta$  Syndrome: a Large Pediatric Cohort from a Single Center in China. *J Clin*  
887 *Immunol* [Internet]. 2022;42(4):837–50. Available from:  
888 <https://doi.org/10.1007/s10875-022-01218-4>
- 889 35. Condliffe AM, Chandra A. Respiratory manifestations of the activated  
890 phosphoinositide 3-kinase delta syndrome. *Front Immunol*. 2018;9(MAR):4–11.
- 891 36. Oh J, Garabedian E, Fuleihan R, Cunningham-Rundles C. Clinical Manifestations and  
892 Outcomes of Activated Phosphoinositide 3-Kinase  $\delta$  Syndrome from the USIDNET  
893 Cohort. *J Allergy Clin Immunol Pract* [Internet]. 2021 Aug; Available from:  
894 <https://linkinghub.elsevier.com/retrieve/pii/S2213219821008850>
- 895 37. Tessarin G, Rossi S, Baronio M, Gazzurelli L, Colpani M, Benvenuto A, et al.  
896 Activated phosphoinositide 3-kinase delta syndrome 1: Clinical and immunological  
897 data from an italian cohort of patients. *J Clin Med*. 2020;9(10):1–16.
- 898 38. Pham MN, Cunningham-Rundles C. Evaluation of Lymphoproliferative Disease and  
899 Increased Risk of Lymphoma in Activated Phosphoinositide 3 Kinase Delta  
900 Syndrome: A Case Report With Discussion. *Front Pediatr*. 2018;6(December):1–7.
- 901 39. Carrasquillo JA, Chen CC, Price S, Whatley M, Avila NA, Pittaluga S, et al. 18F-FDG  
902 PET Imaging Features of Patients with Autoimmune Lymphoproliferative Syndrome.  
903 *Clin Nucl Med*. 2019;44(12):949–55.
- 904 40. Lederman HM. Cancer in children with primary or secondary immunodeficiencies. Vol.  
905 127, *The Journal of Pediatrics*. 1995. p. 335.
- 906 41. Kindler O, Quehenberger F, Benesch M, Seidel MG. The Iceberg Map of germline  
907 mutations in childhood cancer: Focus on primary immunodeficiencies. *Curr Opin*  
908 *Pediatr*. 2018;30(6):855–63.
- 909 42. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and  
910 mortality in common variable immune deficiency over 4 decades. *Blood*.  
911 2012;119(7):1650–7.
- 912 43. Olbrich P, Lorenz M, Cura Daball P, Lucena JM, Rensing-Ehl A, Sanchez B, et al.  
913 Activated PI3K $\delta$  syndrome type 2: Two patients, a novel mutation, and review of the

- 914 literature. *Pediatr Allergy Immunol*. 2016;27(6):640–4.
- 915 44. Jamee M, Moniri S, Zaki-Dizaji M, Olbrich P, Yazdani R, Jadidi-Niaragh F, et al.  
916 Clinical, Immunological, and Genetic Features in Patients with Activated PI3K $\delta$   
917 Syndrome (APDS): a Systematic Review. *Clin Rev Allergy Immunol*. 2020;59(3):323–  
918 33.
- 919 45. Dornan GL, Burke JE. Molecular mechanisms of human disease mediated by  
920 oncogenic and primary immunodeficiency mutations in class IA phosphoinositide 3-  
921 kinases. *Front Immunol*. 2018;9(MAR):1–9.
- 922 46. Bravo García-Morato M, García-Miñaúr S, Molina Garicano J, Santos Simarro F, Del  
923 Pino Molina L, López-Granados E, et al. Mutations in PIK3R1 can lead to APDS2,  
924 SHORT syndrome or a combination of the two. *Clin Immunol*. 2017;179:77–80.
- 925 47. Petrovski S, Parrott RE, Roberts JL, Huang H, Yang J, Gorentla B, et al. Dominant  
926 Splice Site Mutations in PIK3R1 Cause Hyper IgM Syndrome, Lymphadenopathy and  
927 Short Stature. *J Clin Immunol*. 2016;36(5):462–71.
- 928 48. Ramirez L, Tamayo W, Ale H. APDS2 and SHORT Syndrome in a Teenager with  
929 PIK3R1 Pathogenic Variant. *J Clin Immunol*. 2020;40(7):1020–5.
- 930 49. Nguyen T, Lau A, Bier J, Cooke KC, Lenthall H, Ruiz-Diaz S, et al. Human PIK3R1  
931 mutations disrupt lymphocyte differentiation to cause activated PI3K $\delta$  syndrome 2. *J*  
932 *Exp Med* [Internet]. 2023 Jun 5;220(6). Available from:  
933 <https://doi.org/10.1084/jem.20221020>
- 934 50. Seidel MG, Tesch VK, Yang L, Hauck F, Horn AL, Smolle MA, et al. The Immune  
935 Deficiency and Dysregulation Activity (IDDA2.1 ‘Kaleidoscope’) Score and Other  
936 Clinical Measures in Inborn Errors of Immunity. *J Clin Immunol* [Internet].  
937 2022;42(3):484–98. Available from: <https://doi.org/10.1007/s10875-021-01177-2>  
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942 **Figure Legends**

943 **Figure 1. Overview of the *PIK3CD* disease-causing variants in the registry. A,**

944 Localization of the variants in the *PIK3CD* gene. **B,** Frequency of the different variants. ABD  
945 = adaptor-binding domain. RBD = Ras binding domain.

946

947 **Figure 2. Initial clinical presentation. A,** Age at disease onset of APDS patients (median

948 represented by the blue line, APDS patients represented by triangles). The median age at  
949 onset of NF $\kappa$ B1 deficiency (red), CTLA-4 deficiency (green) and STAT3 GOF (yellow)

950 patients is superimposed as a dotted line. **B,** Initial clinical presentation of APDS patients (n =  
951 170) compared to patients with NF $\kappa$ B1 deficiency (n = 83), CTLA-4 deficiency (n = 113) and  
952 STAT3 GOF (n = 41). Malignancy refers to both lymphoid and non-lymphoid malignancy. Data  
953 on all four IEIs were extracted from the ESID registry.

954

955 **Figure 3. Main clinical manifestations. A,** Main infectious complications of APDS patients

956 (n = 170) compared to patients with NF $\kappa$ B1 deficiency (n = 121), CTLA-4 deficiency (n = 90)  
957 and STAT3 GOF (n = 191). **B,** Lung disease. **C,** Haematological complications. **D,** Malignancy.

958 **E,** Other inflammatory manifestations. **F,** Endocrinological manifestations. \* indicates p value  
959 < 0.05 in a t-test performed between every IEI. Data on NF $\kappa$ B1 insufficiency, CTLA-4  
960 insufficiency and STAT3 GOF were extracted from published cohort papers.

961

962 **Figure 4. Immunological abnormalities. A,** Immunoglobulin abnormalities of APDS patients

963 (IgG n = 145, IgA n = 137, IgM n = 137, IgE n = 56) compared to patients with NF $\kappa$ B1

964 insufficiency (n = n.a.), CTLA-4 insufficiency (n = 77) and STAT3 GOF (IgG n = 169, IgA n =  
965 161, IgM n = 161, IgE n = 52). **B,** Cellular abnormalities of APDS patients (CD3 n = 152, CD4

966 n = 151, naïve CD4 n = 106, transitional B n = 46, switched memory B n = 83, NK cells n =

967 116) compared to patients with NF $\kappa$ B1 insufficiency (n = n.a.), CTLA-4 insufficiency (CD3 n =

968 44, CD4 n = 62, naïve CD4 n = 57, switched memory B n = 30, NK cells n = 61) and STAT3

969 GOF (CD3 n = 171, CD4 n = 169, naïve CD4 n = 31, switched memory B n = 31, NK cells n =  
970 151). \* indicates p value < 0,05 in a t-test performed between every IEI. N.a. = not available.  
971 Data on NFκB1 insufficiency, CTLA-4 insufficiency and STAT3 GOF were extracted from  
972 published cohort papers.

973

974 **Figure 5. APDS1 vs APDS2. A**, Initial presentation. Malignancy refers to both lymphoid and  
975 non-lymphoid malignancy. **B**, Lung disease. **C**, Haematological complications. **D**, Other  
976 inflammatory and endocrinological manifestations. **E**, Immunological abnormalities.

977

978 **Figure 6. APDS disease evolution. A**, Lexis diagram displaying all patients as lines from  
979 birth to time of last follow-up with the time of onset (blue dot), severity (red dot) and death  
980 (black dot). The line changes from gray to black at the time of entry into the registry  
981 (prospective observation). **B**, Cumulative probability of fulfilling criteria for a severe disease  
982 course with 95% confidence band; time scale is age in years. **C**, Cumulative probability of  
983 severe disease with 95% confidence band; time scale is years since onset. **D**, Weighted Cox  
984 regression to analyse the cumulative probability of severe disease depending on the variable  
985 age at onset </> 1 year.

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