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Mutations in *PIK3R1* can lead to APDS2, SHORT syndrome or a combination of the two

M. Bravo García-Morato [a,b,*], S. García-Miñaúr [c,d], J. Molina Garicano [e], F. Santos Simarro [c,d], L. Del Pino Molina [a,b], E. López-Granados [a,b], A. Ferreira Cerdán [a,b], R. Rodríguez Pena [a,b]

[a] Department of Clinical Immunology, IdiPAZ, La Paz University Hospital, Madrid, Spain
[b] Lymphocyte Pathophysiology Group, La Paz Institute of Biomedical Research, IdiPAZ, Madrid, Spain
[c] Clinical Genetics Section, Institute of Medical and Molecular Genetics (INGEMM), IdiPAZ, La Paz University Hospital, Madrid, Spain
[d] Unit 753, Biomedical Research Networking Center on Rare Diseases, (CIBERER), Health Institute Carlos III, Madrid, Spain
[e] Department of Pediatrics, Pediatrics Oncology Unit, Navarra Hospital Center, Pamplona, Spain

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ABSTRACT

Mutations in *PIK3R1* gene have been associated to two different conditions: a primary immunodeficiency, called APDS2, of recent description and SHORT syndrome. 47 patients with APDS2 have been reported to date, only one of them sharing both *PIK3R1*-related phenotypes. Here we describe two more patients affected by APDS2 and SHORT syndrome, which highlights that this association may not be so infrequent. We recommend that patients with mutations in *PIK3R1* gene should be assessed by both clinical immunologists and clinical geneticists.

Phosphatidylinositol 3 kinases (PI3Ks) are a family of enzymes that participate in several major signal transduction pathways in different types of cells. Class I PI3K enzymes are expressed in leukocytes and synthesise phosphatidylinositol 3,4,5-trisphosphate (PIP3), which acts as a second messenger. PI3Ks are heterodimers, formed by a catalytic and a regulatory subunit. There are many different types of class I PIK3 enzymes in humans, through the various combinations of catalytic and regulatory subunits and due to their differing cellular expression patterns [1] (Supplemental Fig. 1).

Heterozygous loss of function mutations in *PIK3R1* (MIM 171833), located on chromosome 5q13.1, which encodes the regulatory subunits p85α, p55α and p50α as alternative splicing products, are associated with two different conditions: APDS2 (Activating PI3K-delta Syndrome 2, MIM 615513) and SHORT syndrome (MIM 269880).

APDS2 is a primary immunodeficiency disorder described for the first time in 2014 in four patients from three unrelated kindreds [2]. To date, 47 APDS2 cases have been reported [2–8]. APDS2 is characterised by recurrent upper tract respiratory infections and lymphoproliferation, reported in 100% and 77% of patients, respectively. Infectious episodes also include viral infections (25%), such as cytomegalovirus (CMV) and Epstein Barr Virus (EBV), and parasitic and fungal infections (<10%).

Lymphoproliferation usually presents as lymphadenopathies at different locations. Splenomegaly is also common. Lymphoma or leukaemia has also been reported in 21% of APDS2 patients, suggesting a substantial risk for developing haematological malignancies.

On immunological evaluation, the majority of patients show a hyper-IgM phenotype, but some may show hypogammaglobulinemia or IgA deficiency. The cellular phenotype is characterised mainly by low CD4 and CD8 naïve T cell counts and B lymphopenia (80–90% of cases); CD8 effector/senescent T cell expansion and high transitional B cells have also been reported in about half of them. Some individuals also have low memory B cell counts.

In addition to these findings, half of the reported patients showed growth restriction and/or intellectual disability (21%). Three patients had microcephaly, two glucose metabolism alterations, and one SHORT syndrome.

Seven different heterozygous splicing mutations in *PIK3R1* have been reported in APDS2, all of which result in the skipping of exon 11: c.1425 + 1G>(T,C,A), c.1425 + 2G>(T,A), c.1425 + 2delTG and c.1300-1G>C (NM_181523). This exon encodes the inter-SH2 domain of the p85 regulatory subunit, implicated in the p110δ catalytic subunit binding [1].

SHORT syndrome is a rare disorder characterised by short stature, hyperextensibility of joints and/or hernias, ocular depression, Rieger anomaly and delays of tooth eruption, which provide the condition's acronym. In addition, there is a recognisable facial gestalt, insulin

* Corresponding author at: Hospital Universitario La Paz, IdiPaz, Paseo de la Castellana, 261, 28046 Madrid, Spain.
E-mail address: maria.bravo@salud.madrid.org (M. Bravo García-Morato).

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resistance, nephrocalcinosis and hearing deficits. Speech development is often delayed but cognition is usually normal.

SHORT syndrome was initially described in 1975 in two siblings whose parents showed no obvious features, suggesting an autosomal-recessive mode of inheritance [9,10]. However, most of the cases reported later were sporadic, and the evidence of male-to-male transmission in some instances argued in favour of autosomal-dominant inheritance. Recently, several research groups identified heterozygous loss of function mutations in *PIK3R1* as the cause of SHORT syndrome; mainly missense changes located in the last exons of *PIK3R1* [11–13].

To date, only one patient with both APDS2 and SHORT syndrome has been reported [6]. He was found to have a splicing mutation in *PIK3R1*, c.1425 + 1G>A (NM_181523), previously described in patients with APDS2. However, SHORT syndrome associated features in the patient were not described. Here we report two further patients with mutations at the same splice donor site and in whom both PIK3R1-related phenotypes: APDS2 and SHORT syndrome are present.

Patient 1 is a 10-year-old Spanish boy, born at term to healthy unrelated parents. He presented with poor weight gain from birth and required nasogastric tube feeding from the fifth month of life until he was ten months old. His feeding problems improved but his weight remained on the 3rd centile. At the age of five months he was diagnosed with mitral stenosis and at two years with pulmonary hypertension, which eventually required surgery at the age of three years. His overall psychomotor development was within the normal range with mild motor and speech delay. His current school performance is good.

Regarding his previous history of infectious episodes, at the age of one month he had bronchiolitis due to VRS infection. From the age of 10 months he suffered recurrent episodes of acute otitis media, requiring insertion of ventilation tubes. At the age of nine he was diagnosed with mild conductive hearing loss and was prescribed hearing aids. He has had recurrent upper respiratory tract infections, three pneumonias and several episodes of periorbital conjunctivitis and cellulites, requiring hospital admission on one occasion, when he was four years old. He has had positive viral loads to EBV twice, when he was seven and nine years old. CMV loads were always negative. At the age of six he presented with lymphadenopathies but without hepatosplenomegaly. He has been treated with corticosteroids and has undergone adenoidectomy two times. Currently, he is on treatment with ivGG (intravenous gammaglobulin), trimethoprim/sulfamethoxazole and azithromycin. His immunological phenotype at diagnosis is summarised in Table 1.

In view of his immunological phenotype and associated features, we asked our Clinical Genetics colleagues to assess this patient. On examination, he showed normal body proportions with no asymmetries. He was very thin, with reduced subcutaneous fat and aged appearance. His height was 129 cm (10th centile), weight 23 kg (3rd centile), and head circumference 51.5 cm (25th centile). He had thin translucent skin with no pigmentary changes and joint laxity. He showed distinctive facial features: a rather triangular face with broad forehead and micrognathia, a short philtrum and thin upper lip, and dental crowding (Fig. 1). He had a mild thoracic deformity with the sternotomy scar and a straight back. He had normal male genitalia. His hands, feet, fingers and toes were normal. Our colleagues considered that he showed features consistent with SHORT syndrome, although they were unaware that a significant immunological deficit could be part of the condition. This prompted us to perform Sanger sequencing of *PIK3R1* which resulted in the identification of a heterozygous mutation c.1425 + 1G>A (NM_181523), confirming both the diagnosis of APDS2 and SHORT syndrome in this patient.

Patient 2 is a Spanish male born at term to healthy unrelated parents. He presented with poor growth and weight gain from early infancy. According to the reports by the paediatrics specialists, he always had facial dysmorphisms with an aged appearance. At the age of eight months his height was on the 10th centile and his weight on the 3rd. He remained on the same centiles for the next seven years. He received recombinant growth hormone treatment at the age of 14 with good response. He was diagnosed with congenital heart disease (a dysplastic mitral valve and aortic valve insufficiency). He showed delayed teeth eruption, which required removal of the primary teeth when he was 13 years old. He developed autoimmune hypothyroidism at the age of 15, and atrophic gastritis at the age of 20. He had normal cognition and his school performance was good.

Regarding his previous history of infectious episodes, he had recurrent upper respiratory tract infections and gastroenteritis from the first month of life. He subsequently suffered from *S. aureus* skin infections, including omphalitis and granuloma inguinale at the age of one month, and blistering skin lesions in the hands several times during childhood and early adulthood. From the age of four years, he had recurrent episodes of acute otitis media, requiring insertion of ventilation tubes. He was diagnosed with mixed hearing loss at the age of 17 and was prescribed hearing aids. He suffered repeated episodes of periorbital conjunctivitis and dacryocystitis, requiring surgery at the age of 18. He also had viral, parasitic and fungal infections in infancy: herpetic and fungal cutaneous lesions and Giardia and Cryptosporidium infections. He started treatment with ivGG at the age of two years and with trimethoprim/sulfamethoxazole from the age of 14.

Table 1
Clinical and immunological findings of patients 1 and 2.

Humoral immunophenotype	P1 (10 years old)	P2 (23 months old)
IgG levels, mg/dl	1140 [608–1572]*	36 [424–1051]*
IgA levels, mg/dl	<7 [45–236]*	5 [14–123]*
IgM levels, mg/dl	137 [52–242]*	199 [48–168]*
Vaccination response to tetanus/diphtheria	Positive	Negative/ND
Vaccination response to neumococo	Negative	ND
Cellular immunophenotype	**P1 (10 years old)**	**P2 (23 months old)**
Total lymphocytes counts/μl	1900 [1200–4700]**	ND
%CD3 +	84 [55–97]**	78 [36–100]**
%CD4 +	16 [28.4–44.4]***	48 [33–55]***
%CD4 + CD45RA +	15.8 [53.4–74.7]]***	ND
%CD4 + CD45RO +	64 [21.4–40.3]***	ND
%CD8 +	67 [16.4–36.2]***	31 [14–26]***
%CD8 + CD45RA +	21 [49.2–82.7]***	ND
%CD8 + CD45RO +	51.6 [11.5–30.7]***	ND
%CD4 + CD45RA + CD31 +	13.7 [40.1–54.8]***	ND
%CD19 +	3 [4–33]**	6 [8–45]**
%B transitional cells	45 [4–28]**	ND
%Non-switched memory B cells	7.2 [0.5–8]**	ND
%Switched memory B cells	4.6 [3–18]**	ND
%CD16 + CD56 +	10 [2–31]**	14 [1–96]**
Proliferation assays (PHA, ConA, PWM, OKT3)	Moderately reduced	Moderately reduced

ND: Not done. IgG levels are not under ivGG treatment in any of the patients.
* Jolliff CR et al. Clin Chem. 1982 Jan;28(1):126–8.
** Schatorjé EJ et al. Scand J Immunol. 2011 Nov;74(5):502–10.
*** van Gent R et al. Clin Immunol. 2009 Oct;133(1):95–107.

Fig. 1. Patient 1 at age 11 years. Note the distinctive facial features: a rather triangular face with broad forehead and micrognathia, a short philtrum and thin upper lip, and dental crowding.

At the age of four, he presented with lymphadenopathies and hepatomegaly, and developed nodular gastritis at the age of six. He received treatment with corticosteroids and underwent adenoidectomy twice. At the age of 20, he developed non-Hodgkin lymphoma that responded to treatment. Six months later, he developed classic Hodgkin lymphoma that also responded to treatment. However, the non-Hodgkin lymphoma recurred and he died at the age of 26. EBV and CMV loads were negative every time they were evaluated, including in gastrointestinal biopsies during the diagnosis of the lymphoma. His immunological phenotype is summarised in Table 1.

Although no photographs were available in his clinical notes, our Clinical Genetics colleagues reviewed his social network and recognised features consistent with SHORT syndrome. NGS sequencing on a DNA sample stored in our department identified the heterozygous *PIK3R1* mutation c.1425 + 1G>T (NM_181523).

To test whether or not this type of mutations lead to a gain of function of the PI3K pathway in peripheral blood, the intracellular content of phospo-Akt (p-Akt) and phospo-S6 (p-S6), activated forms of Akt and S6, respectively, was measured in peripheral blood of patient 1 by using the *PhosFlow System* (BD Biosciences) (Supplemental material).

Results showed an increase of p-S6 in peripheral B cells of the patient in comparison with a healthy donor under basal conditions (Fig. 2A) and after stimulation with anti-IgM during five, 10 and 15 min (Fig. 2B). However, p-Akt and p-S6 both in stimulated and unstimulated T lymphocytes of the patient and the healthy donor were similar (data not showed).

This means that the PI3K signaling pathway is up-regulated in B lymphocytes of the patient, specifically at the point of the phosphorylation of the protein S6, which mediates the captation of glucose [14], while it remains normal in T lymphocytes.

Thus, we describe two additional patients with both APDS2 and SHORT syndrome, due to different splicing mutations at the same donor site in *PIK3R1*. These mutations have previously been associated to APDS2 [7] and one of them, to APDS2 and SHORT syndrome in the same patient [6]. They both result in the skipping of exon 11 [6]. Exon 11 encodes part of the inter-SH2 domain of the regulatory subunits p85α, p55α and p50α, which are alternative splicing products of the gene.

In leukocytes, the main class I PI3K that mediates intracellular signalling is the heterodimer formed by the regulatory subunit p85α and the catalytic subunit p110δ. The first one binds to the second one by the inter-SH2 domain. Therefore, mutations that lead to the loss of this domain of the protein impair its binding ability and the formation of heterodimers. The consequence in lymphocytes is that the p110δ catalytic subunit is deregulated and over-activated, resulting in an increase of the PI3K signalling-dependent processes. This situation resembles that observed in APDS1 patients, where gain of function mutations in *PIK3CD*, encoding the p110δ subunit, lead to a similar clinical and immunological phenotype [14,15].

As opposed to APDS2, what has been demonstrated in the case of SHORT syndrome is that the PI3K signalling pathway has increased basal activity but remains downregulated after activation with specific ligands, as insulin in the case of adipocytes, so its dependent processes are decreased [11–13]. It seems that mutations that cause SHORT syndrome diminish the affinity between p85α and tyrosine-phosphorylated peptides, which are implicated in many signalling mechanisms.

Here we hypothesize that, in patients with mutations that lead to exon 11 skipping, both situations can happen at the same time: PI3K signalling pathway might be upregulated in peripheral blood, as it has been showed for patient 1, while it might be downregulated in other tissues, generating the phenotype characteristic of SHORT syndrome.

Interestingly, mutations in *PIK3CD* have never been associated with SHORT syndrome. It is probably that, as p110δ is predominantly expressed in leukocytes [16], alterations in its coding gene mainly affect this type of cells. By contrast, p85α expression is ubiquitous, which means that mutations in its coding gene affect many tissues, including leukocytes and others, such as those altered in SHORT syndrome.

In addition, patients with SHORT syndrome due to mutations in the last exons of *PIK3R1* do not develop APDS2. It could be hypothesised that those exons are not implicated in p110δ subunit binding and, therefore, leukocytes are spared.

The reason why some APDS2 patients develop SHORT syndrome but others do not, remains to be elucidated. To date, only three patients - including ours - sharing both APDS2 and SHORT syndrome phenotypes have been reported. However, some of the APDS2 patients described showed other features such as growth restriction, learning disability, microcephaly and glucose metabolism alterations. We wonder whether SHORT syndrome may not be recognised in some of them.

We recommend that APDS2 patients should be assessed by a Clinical geneticist or dysmorphologist. Conversely, SHORT patients should be assessed and followed up by a Clinical immunologist, particularly if they have a history of recurrent respiratory infections and/or lymphoproliferation. The potential risk of developing haematological malignancies should also be considered. Thus, a multidisciplinary approach is required to diagnose, monitor and treat these patients.

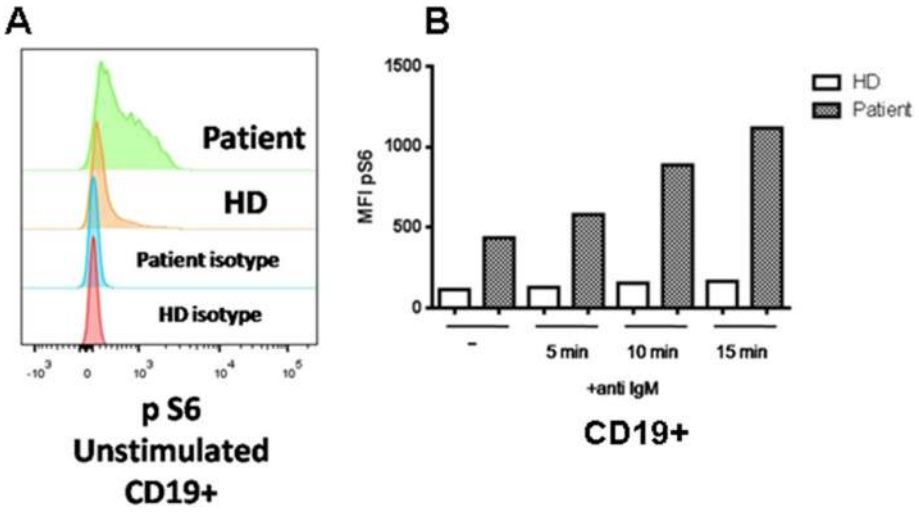

Fig. 2. A. Basal phosphorylation (unstimulated) of S6 and each isotype control in the patient and a healthy donor. B. Mean Fluorescence Intensity of p-S6 in unstimulated (−) and stimulated with anti-IgM (15 μg/ml for 5, 10 and 15 min) CD19+ cells of the patient and a healthy donor.

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Conflict of interest

The authors have no conflict of interests to disclose.

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References

[1] C.L. Lucas, A. Chandra, S. Nejentsev, A.M. Condliffe, K. Okkenhaug, PI3Kδ and primary immunodeficiencies, Nat. Rev. Immunol. 16 (11) (Nov 2016) 702–714.
[2] M.C. Deau, L. Heurtier, P. Frange, F. Suarez, C. Bole-Feysot, P. Nitschke, M. Cavazzana, C. Picard, A. Durandy, A. Fischer, S. Kracker, A human immunodeficiency caused by mutations in the PIK3R1 gene, J. Clin. Invest. 125 (4) (Apr 2015) 1764–1765.
[3] Carrie L. Lucas, Yu Zhang, Anthony Venida, Ying Wang, Jason Hughes, Joshua McElwee, Morgan Butrick, Helen Matthews, Susan Price, Matthew Biancalana, Xiaochuan Wang, Michael Richards, Tamara Pozos, Isil Barlan, Ahmet Ozen, V. Koneti Rao, Helen C. Su, Michael J. Lenardo, Heterozygous splice mutation in *PIK3R1* causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K, J. Exp. Med. 211 (13) (Dec 15 2014) 2537–2547.
[4] V. Lougaris, F. Faletra, G. Lanzi, D. Vozzi, A. Marcuzzi, E. Valencic, E. Piscianz, A. Bianco, M. Girardelli, M. Baronio, C. Loganes, A. Fasth, F. Salvini, A. Trizzino, D. Moratto, F. Facchetti, S. Giliani, A. Plebani, A. Tommasini, Altered germinal center reaction and abnormal B cell peripheral maturation in PI3KR1-mutated patients presenting with HIGM-like phenotype, Clin. Immunol. 159 (1) (Jul 2015) 33–36.
[5] Michaela Kuhlen, Andrea Hönscheid, Loizos Loizou, Schafiq Nabhani, Ute Fischer, Polina Stepensky, Jörg Schaper, Wolfram Klapper, Meinolf Siepermann, Friedhelm Schuster, Roland Meisel, Arndt Borkhardt, De novo PIK3R1 gain-of-function with recurrent sinopulmonary infections, long-lasting chronic CMV-lymphadenitis and microcephaly, Clin. Immunol. 162 (Jan 2016) 27–30.
[6] Slavé Petrovski, Roberta E. Parrott, Joseph L. Roberts, Hongxiang Huang, Jialong Yang, Balachandra Gorentla, Talal Mousallem, Endi Wang, Martin Armstrong, Duncan McHale, Nancie J. MacIver, David B. Goldstein, Xiao-Ping Zhong, Rebecca H. Buckley, Dominant splice site mutations in PIK3R1 cause hyper IgM syndrome, lymphadenopathy and short stature, J. Clin. Immunol. 36 (5) (Jul 2016) 462–471.
[7] Elodie Elkaim, Benedicte Neven, Julie Bruneau, Kanako Mitsui-Sekinaka, Aurelie Stanislas, Lucie Heurtier, Carrie L. Lucas, Helen Matthews, Marie-Celine Deau, Svetlana Sharapova, James Curtis, Janine Reichenbach, Catherine Glastre, David A. Parry, Gururaj Arumugakani, Elizabeth McDermott, Sara Sebnem Kilic, Motoi Yamashita, Despina Moshous, Hicham Lamrini, Burkhard Otremba, Andrew Gennery, Tanya Coulter, Isabella Quinti, Jean-Louis Stephan, Vassilios Lougaris, Nicholas Brodszki, Vincent Barlogis, Takaki Asano, Lionel Galicier, David Boutboul, Shigeaki Nonoyama, Andrew Cant, Kohsuke Imai, Capucine Picard, Sergey Nejentsev, Thierry Jo Molina, Michael Lenardo, Sinisa Savic, Marina Cavazzana, Alain Fischer, Anne Durandy, Sven Kracker, Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase d syndrome 2: a cohort study, J. Allergy Clin. Immunol. 138 (1) (Jul 2016) 210–218.
[8] Peter Olbrich, Myriam Lorenz, Paola Cura Daball, Jose Manuel Lucena, Anne Rensing-Ehl, Berta Sanchez, Marita Fuhrer, Marisol Camacho-Lovillo, Marta Melon, Klaus Schwarz, Olaf Neth, Carsten Speckmann, Activated PI3Kd syndrome type 2: two patients, a novel mutation, and review of the literature, Pediatr. Allergy Immunol. 27 (6) (Sep 2016) 640–644.
[9] R.J. Gorlin, J. Cervenka, K. Moller, M. Horrobin, C.J. Witkop, Rieger anomaly and growth retardation (the S-H-O-R-T syndrome), in: D. Bergsma (Ed.), Malformation Syndromes, Excerpta Medica for the National Foundation – March of Dimes, New York 1975, pp. 46–48.
[10] J.A. Sensenbrenner, I.E. Hussels, L.S. Levin, CC – a low birth-weight syndrome? Rieger syndrome, in: D. Bergsma (Ed.), Malformation Syndromes, Excerpta Medica for the National Foundation – March of Dimes, New York 1975, pp. 423–426.
[11] C. Thauvin-Robinet, M. Auclair, L. Duplomb, M. Caron-Debarle, M. Avila, J. St-Onge, M. Le Merrer, B. Le Luyer, D. Héron, M. Mathieu-Dramard, P. Bitoun, J.M. Petit, S. Odent, J. Amiel, D. Picot, V. Carmignac, J. Thevenon, P. Callier, M. Laville, Y. Reznik, C. Fagour, M.L. Nunes, J. Capeau, O. Lascols, F. Huet, L. Faivre, C. Vigouroux, J.B. Rivière, PIK3R1 mutations cause syndromic insulin resistance with lipoatrophy, Am. J. Hum. Genet. 93 (1) (2013 Jul 11) 141–149.
[12] D.A. Dyment, A.C. Smith, D. Alcantara, J.A. Schwartzentruber, L. Basel-Vanagaite, C.J. Curry, I.K. Temple, W. Reardon, S. Mansour, M.R. Haq, R. Gilbert, O.J. Lehmann, M.R. Vanstone, C.L. Beaulieu, FORGE Canada Consortium, J. Majewski, D.E. Bulman, M. O'Driscoll, K.M. Boycott, A.M. Innes, Mutations in PIK3R1 cause SHORT syndrome, Am. J. Hum. Genet. 93 (1) (Jul 11 2013) 158–166.
[13] K.K. Chudasama, J. Winnay, S. Johansson, T. Claudi, R. König, I. Haldorsen, B. Johansson, J.R. Woo, D. Aarskog, J.V. Sagen, C.R. Kahn, A. Molven, P.R. Njølstad, SHORT syndrome with partial lipodystrophy due to impaired phosphatidylinositol 3 kinase signaling, Am. J. Hum. Genet. 93 (1) (Jul 11 2013) 150–157.
[14] Carrie L. Lucas, Hye Sun Kuehn, Fang Zhao, Julie E. Niemela, Elissa K. Deenick, Umaimainthan Palendira, Danielle T. Avery, Leen Moens, Jennifer L. Cannons, Matthew Biancalana, Jennifer Stoddard, Weiming Ouyang, David M. Frucht, V. Koneti Rao, T. Prescott Atkinson, Anahita Agharahimi, Ashleigh A. Hussey, Les R. Folio, Kenneth N. Olivier, Thomas A. Fleisher, Stefania Pittaluga, Steven M. Holland, Jeffrey I. Cohen, Joao B. Oliveira, Stuart G. Tangye, Pamela L. Schwartzberg, Michael J. Lenardo, Gulbu Uzel, Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency, Nat. Immunol. 15 (1) (Jan 2014) 88–97.
[15] Ivan Angulo, Oscar Vadas, Fabien Garçon, Edward Banham-Hall, Vincent Plagnol, Timothy R. Leahy, Helen Baxendale, Tanya Coulter, James Curtis, Changxin Wu, Katherine Blake-Palmer, Olga Perisic, Deborah Smyth, Mailis Maes, Christine Fiddler, Jatinder Juss, Deirdre Cilliers, Gašper Markelj, Anita Chandra, George Farmer, Anna Kielkowska, Jonathan Clark, Sven Kracker, Marianne Debré, Capucine Picard, Isabelle Pellier, Nada Jabado, James A. Morris, Gabriela Barcenas-Morales, Alain Fischer, Len Stephens, Phillip Hawkins, Jeffrey C. Barrett, Mario Abinun, Menna Clatworthy, Anne Durandy, Rainer Doffinger, Edwin Chilvers, Andrew J. Cant, Dinakantha Kumararatne, Klaus Okkenhaug, Roger L. Williams, Alison Condliffe, Sergey Nejentsev, Phosphoinositide 3-kinase δ gene mutation predisposes to respiratory infection and airway damage, Science 342 (6160) (Nov 15 2013) 866–871.
[16] Tanya I. Coulter, Anita Chandra, Chris M. Bacon, Judith Babar, James Curtis, Nick Screaton, John R. Goodlad, George Farmer, Cathal Laurence Steele, Timothy Ronan Leahy, Rainer Doffinger, Helen Baxendale, Jolanta Bernatoniene, David M. Edgar, Hilary J. Longhurst, Stephan Ehl, Carsten Speckmann, Bodo Grimbacher, Anna Sediva, Tomas Milota, Saul N. Faust, Anthony P. Williams Grant Hayman, Zeynep Yesim Kucuk, Rosie Hague, Paul French, Richard Brooker, Peter Forsyth, Richard Herriot, Caterina Cancrini, Paolo Palma, Paola Ariganello, Niall Conlon, Conleth Feighery, Patrick J. Gavin, Alison Jones, Kohsuke Imai, Mohammad A.A. Ibrahim, Gasper Markelj, Mario Abinun, Frederic Rieux-Laucat, Sylvain Latour, Isabelle Pellier, Alain Fischer, Fabien Touzot, Jean-Laurent Casanova, Anne Durandy, Siobhan O. Burns, Sinisa Savic, D.S. Kumararatne, Despina Moshous, Sven Kracker, Bart Vanhaesebroeck, Klaus Okkenhaug, Capucine Picard, Sergey Nejentsev, Alison M. Condliffe, Andrew James Cant, Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: a large patient cohort study, J. Allergy Clin. Immunol. (Jul 16 2016) (pii: S0091-6749(16)30623-6).