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Letter to the Editor

A novel monoallelic gain of function mutation in p110δ causing atypical activated phosphoinositide 3-kinase δ syndrome (APDS-1)

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ABSTRACT

This study reports on a novel activating p110δ mutation causing adult-onset hypogammaglobulinemia with lymphopenia without the classical presentation of atypical Activated phosphoinositide 3-kinase δ syndrome (ADPS-1), underlining thus the heterogeneous clinical and immunological presentation of p110δ mutated individuals and offers additional data on the role of p110δ in early and late B cell development in humans.

To the Editor,

Class I Phosphatidylinositol-3 kinases (PI3Ks) are expressed in leukocytes and play a major role in diverse cell functions including cell growth, proliferation, differentiation and survival [1]. They are formed by heterodimers comprising a catalytic and a regulatory subunit. There are five variants of the p85 regulatory subunit, designated p85α, p55α, p50α, p85β, and p55γ, while the p110 catalytic subunit includes three variants designated p110α, β, or δ catalytic subunits [1]. In recent years, monoallelic gain of function mutations in p110d or p85a were identified as responsible for a novel form of immunodeficiency named Activated phosphoinositide 3-kinase δ syndrome (APDS1 and 2 respectively) [2,3]. Regarding APDS1 in particular, the clinical presentation is mainly characterized by lymphopenia, normal to elevated IgM serum levels, recurrent respiratory infections, lymphoproliferation and increased risk of lymphomas [2–6]. The immunological phenotype includes perturbed T and B cell maturation and increased activation of the AKT/S6/mTOR pathway [2,3]. To date, the majority of affected patients present a recurrence of monoallelic mutations in p110δ, with a limited number of novel ones reported since the identification of this disorder [2,3,5–7]. We report on a female patient affected with adult onset hypogammaglobulinemia with lymphopenia harbouring a novel gain of function mutation in p110δ. B cell development was impaired both in the bone marrow and in the periphery. Of note, the patient did not present lymphoproliferation nor did she develop bronchiectasis during long-time follow-up.

The index patient is of Italian descent born to Italian non-consanguineous parents. She came to our attention at the age of 27 years due to recurrent respiratory infections mainly of the upper tract. Her clinical history included upper respiratory tract infections during adolescence and an episode of hidradenitis suppurativa at the age of 21 years. Family history was negative for primary immunodeficiencies. Immunological work up showed lymphopenia with hypogammaglobulinemia of all classes and absent response to vaccinations (Supplementary Table 1). T cells were present at normal percentages, while B cells were slightly below the lower range of the norm (Supplementary Table 1). The patient was diagnosed with CVID at 27 years of age and was started on immunoglobulin replacement treatment. During 20 years of follow-up, the clinical course of the patient was particularly mild: she only presented one episode of gastroenteritis at the age of 36 years, and occasional upper respiratory tract infections were treated with oral antibiotics. She has always remained negative for CMV and EBV. Annual abdominal ultrasonography showed a normal spleen size and no lymphoadenopathies. Lung CT scanning did not reveal mediastinal lymphoadenopathies or development of bronchiectasis during sequential lung CT scans (Supplementary Fig. 1). Endoscopic evaluation at 39 years revealed mild gastritis and duodenitis without T cell infiltrate with complete lack of plasma cells (Supplementary Fig. 2). Regarding the immunological evolution during follow-up, lymphopenia was persistent over time (Fig. 1A). In addition, the patient showed a progressive reduction of peripheral B cells (Fig. 1A and Supplementary Table 1) with lack of terminal B cell differentiation (Supplementary Table 2). Bone marrow evaluation showed impaired B cell maturation with an accumulation of precursors at the pro-B to pre-B1 stage (Fig. 1B).

Next generation sequencing revealed the presence of the novel c.1973C > T; p.P658L mutation in p110δ. Sanger sequencing confirmed the presence of this mutation in the patient (Fig. 1C). This mutation has not been reported before, but the P658 position is highly conserved among species (Fig. 1D). Since activating mutations in p110δ have been reported to cause an increased activation of the Akt/pS6K/mTOR pathway, phospho-S6K levels were evaluated in T cell blasts from the index patient, from an APDS-1 patient harbouring the p.E1021K previously reported mutation [2,3] and from two healthy controls (Fig. 1E and F). The phosphorylation pattern of S6K of the index patient was increased when compared to the healthy controls and was similar to the one observed in the classical APDS-1 patient (Fig. 1E and F). Of note, T cell blasts from the two patients treated with CAL-

Abbreviations: p110δ, phosphatidylinositol 3-kinase catalytic delta; PI3K, Phosphatidylinositol-3 kinase; APDS-1, activated PI3K syndrome; CVID, Common Variable Immunodeficiency

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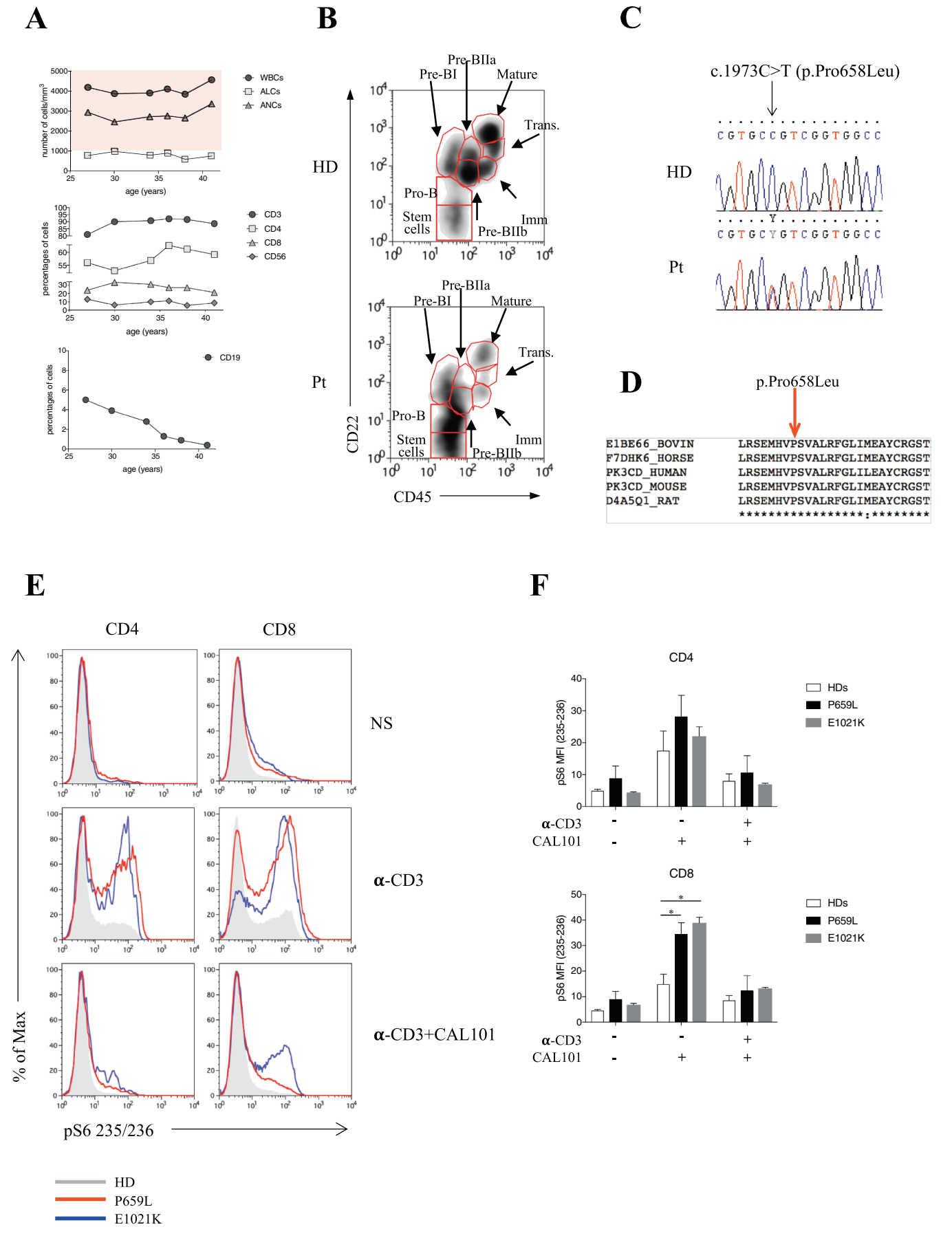

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Fig. 1. Immunological evaluation during long-term follow-up of the index patient harbouring the novel p110d activating mutation. A. Absolute counts of white blood cells (WBCs), neutrophils (ANCs) and lymphocytes (ALCs) during 20 year follow-up (upper panel); percentages of peripheral lymphocyte subsets during 20 year follow-up (mid and lower panel). B. Early B cell development in the bone marrow from the index patient (Pt) and a healthy control (HD). C. Electropherograms showing the novel c.1973C > T mutation in p110δ. D. The P658 is highly conserved among species. E. Evaluation of pS6 levels in T cell blasts from the index patient (P659L), an APDS-1 patient harbouring the E1021K mutation (E1021K) and a healthy control (HD) after anti-CD3 stimulation with or without CAL101 inhibition. F. Summarized data from three replicates of pS6 levels in T cell blasts from the index patient (P659L), an APDS-1 patient harbouring the E1021K mutation (E1021K) and a healthy control (HD) after anti-CD3 stimulation with or without CAL101 inhibition. Statistical analysis was performed using the unpaired *t*-test (* ≤ 0.05).

101, a selective p110δ potent inhibitor [8], down-regulated pS6K levels in a similar manner (Fig. 1E and F), confirming that the p.P658L mutation behaves as the other mutations reported in patients affected with APDS-1.

Two large cohort studies in patients with APDS-1 have recently better defined the clinical hallmarks of this disorder [5,6]. Recurrent pneumonias characterized 85% of affected patients with development of bronchiectasis in 60% of cases [5]. Viral infections, acute and/or chronic, were identified in almost 50% of affected patients [5,6]. Gastrointestinal involvement was present in 25–50% of affected patients [5,6]. Finally, benign lymphoproliferation was reported in more than two thirds of affected patients [5,6]. Of note, our index patient harbouring the novel P658L mutation in p110δ does not present any of the above mentioned hallmarks of the disease during a 20-year long follow-up, suggesting that other factors besides the hyperactivation of the PI3K pathway may be involved.

The effect of the gain of function mutation in p110δ in early B cell development has been studied in a very limited number of patients with variable results: while one study showed impairment in bone marrow early B cell development in APDS-1 patients ($N = 10$) [9], the second one did not confirm these findings ($N = 4$) [10]. The index patient showed progressive severe B cell lymphopenia with early B cell developmental impairment, further suggesting that possibly additional factors besides activating p110δ mutations influence bone marrow B cell maturation.

In conclusion, we report on a novel activating P658L mutation in p110δ resulting in “atypical” APDS-1 without the hallmarks of the disease, associated with early B cell developmental impairment, underlining how next generation sequencing may be a useful tool in defining the genetic basis of PIDs, even in the absence of clinical hallmarks of the disease, with evident implications in affected patients' management.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2019.01.003.

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Disclosure of conflicts of interest

The authors declare no conflict of interest.

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