PNAS
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Supplementary Information for

SAMD9L AUTOINFLAMMATORY OR ATAXIA PANCYTOPENIA DISEASE MUTATIONS ACTIVATE CELL-AUTONOMOUS TRANSLATIONAL REPRESSION

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Figures S1 and S2

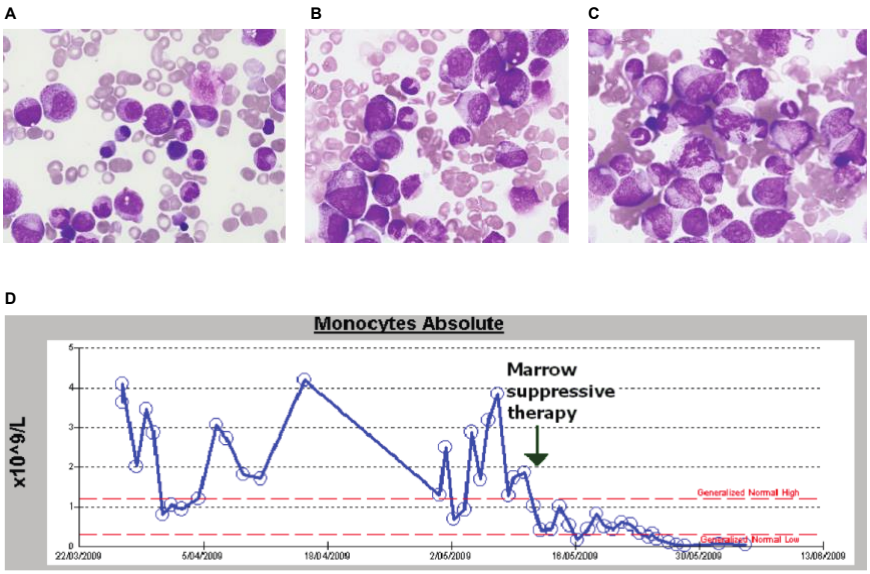

Fig. S1. ***Hematological and clinical details for Patient 1.***
P1 is the first child of non-consanguineous Chinese-Australian parents, and presented shortly after birth with a complex multi-system disease including fever and raised inflammatory markers (CRP =179, ESR = 90), hepatosplenomegaly, and the involvement of multiple organs, most notably skin, bone marrow and immune system. He developed erythematous plaques over the head, limbs and thorax which developed into deep ulcerative, scarring lesions. Skin biopsy showed extensive neutrophilic leukocytoclasis with panniculitis, consistent with Sweet's syndrome. He went on to have involvement of other organs, including non-infective epiglottitis and perforated bowel associated with neutrophilic infiltrates. He has calcification of the basal ganglia and learning delay.

Investigations revealed thrombocytopaenia (41 x 10^9) and anaemia requiring regular blood transfusions, but with neutrophilia (11 x 10^9). Bone marrow aspirate showed tri-lineage dysplasia with (A) dysplastic erythroid lineage cells, (B, C) dysplastic myeloid cells with excess of mitoses, and dysplastic megakaryocytes. There was a persistent peripheral blood monocytosis (D) until the child was treated with marrow suppressive therapy. No clonal cytogenetic abnormality (e.g. monosomy 7) or Juvenile Myelomonocytic Leukaemia (JMML) specific somatic mutation was identified. The most likely explanation was felt to be myelodysplastic syndrome with refractory anaemia.
Over the 1st year of life P1 presented a B-cell immunodeficiency with low IgG and absent IgA and IgM.

Unexpectedly, after the first year of life he began to produce platelets and red cells and no longer needs transfusions. Peripheral blood testing at aged 4 years demonstrated substantial recovery of mature B cells with a normal phenotype (CD45bright, CD10-, CD19+, CD20+, polyclonal light chain+) including 3.9% CD27+ memory and 1.7% class-switched (IgM- IgD-), although the absolute B-cell count was low (0.19 x 109/L (NR 0.7-13)) (Fig 7.8). At this time IgG = 5.75g/L (4.3-11.1) and IgA 0.32g/L (0.15-1.42) had normalized, with low IgM = 0.25g/L (0.42-1.61).

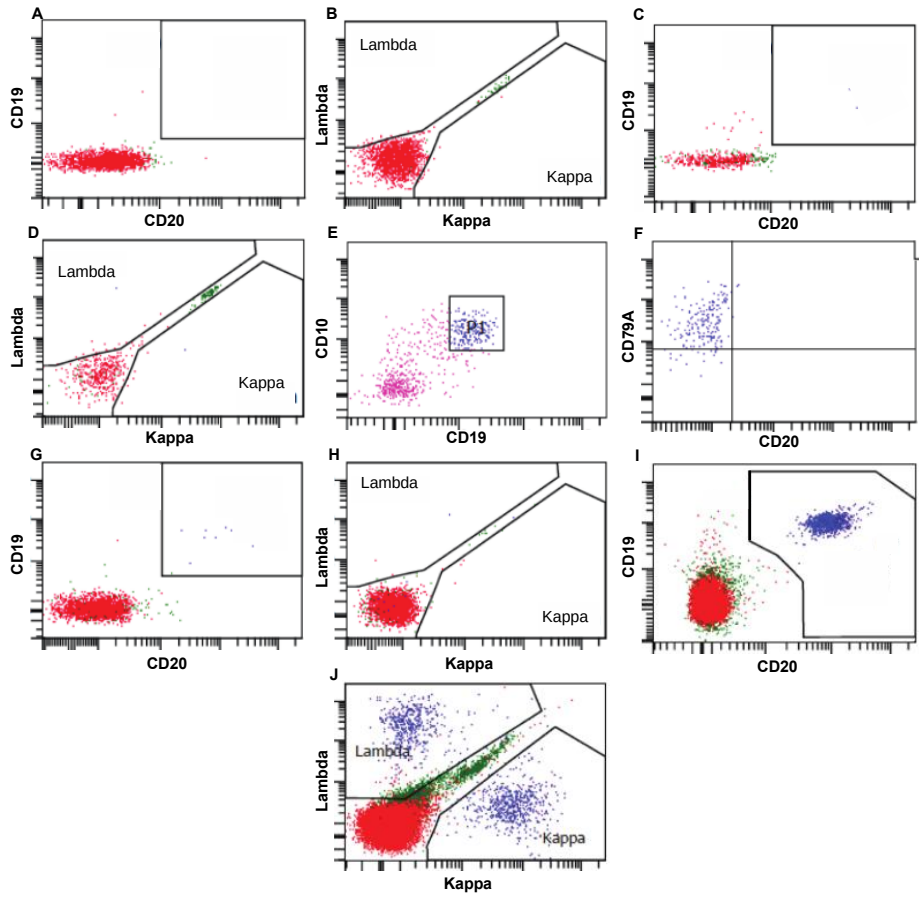

Fig. S2. ***Flow cytometric analysis of bone marrow and blood for Patient 1.***
(A-D) Absence of B-cells in blood (A, B) or bone marrow (C, D) at 1 month old. (E-G) Bone marrow at 4 mths old, showing a few B-lineage cells (0.2% of leukocytes), most of which were immature (CD45 dim+ CD10+ CD19+ CD20- CD79a+) and lacked surface light chain staining. A tiny group of more mature CD45bright, CD10+ CD19+ CD20+ cells (G), but these were also antigen receptor negative based on absence of light chain staining (H). (I, J) Peripheral blood at aged 4 years, demonstrating recovery of mature B cells with a normal phenotype of CD45bright, CD10-, CD19+, CD20+, polyclonal light chain+, including 3.9% CD27+ memory and 1.7% class-switched (IgM- IgD) memory B cells, although the absolute B-cell count was low (0.19 x 10^9/L (normal range 0.7-13).