## Supplemental data

1. Appendix

**Patient 1 description:** The patient is a female child of Albanian ethnicity with a disease onset at 4 years. Her parents are unrelated and there was no familial history. She was admitted with a clinical history of recurrent fevers associated with fatigue, polymorphous erythematosus skin rash and non-erosive arthritis of the hands and feet.

Laboratory investigations revealed a hemolytic anemia (Hb 7.5 g/dL; direct Coombs test positive), increased ESR and CRP (83 mm/h and 7,9 mg/L, respectively), elevated LDH (306 mg/dL) and low levels of C3 (569 mg/L) and C4 (40 mg/L). The titer of ANA antibodies was positive (1:640), as well as dsDNA antibodies but ANCA were not present. Blood parameters of renal and hepatic function were normal, but urine analysis revealed persistent proteinuria (664 mg/24h) and hematuria. Lupus nephritis was suspected but renal biopsy was not performed.

**Patient 2 description:** The second patient is a young girl from Arab descent. The disease started at 11 years with bilateral arthralgia associated with a chronic atypical urticaria. After few months of evolution, she presented a lupus like glomerulonephritis with increases in serum creatinine (88 µmol/L) and moderate proteinuria (1.28 g/L, 145 mg/mmol) and hematuria. A renal biopsy confirmed an immune complex glomerulonephritis. The titer of ANA was positive (1:320), as well as ANCA with anti-MPO specificity (5 IA). Both C3 and C4 levels were reduced (565mg/L and 117 mg/L respectively). CRP was normal but ESR was elevated (107). She was treated with corticosteroids, mycophenolate mofetil, hydroxychloroquine and tacrolimus, leading to remission two months later (negative proteinuria and ANA).

**Patient 3 description:** The third patient is a girl who was born to non-consanguineous Italian parents with no significant family medical history. From the age of 15 years-old, she presented with recurrent episodes of fever, accompanied by urticaria, arthralgia and myalgia. Then she presented with a significant anemia (4.5 g/dL) for which she underwent a blood transfusion. She had no renal involvement. Blood tests showed a pronounced elevation of inflammatory markers, *i.e.* ESR, CRP, SAA (111 mg/L). ANA was positive (1:160) and the value of ANCA was in the gray zone (0.7). Non-steroidal anti-inflammatory drugs was first used and was effective in

reducing pain but not on urticaria. She was then treated with steroids, hydroxychloroquine and azathioprine.

Patient 4 description: Pt 4 is a boy whose symptoms started at the age of 18 months with stomachache, vomiting and diarrhea. He also presented urticaria repeating 7-15 days along with macular rash and arthritis. Histopathology showed a chronic bowel inflammation with gut eosinophil infiltration. Corticosteroids and azathioprine treatment lead to an improvement but result in steroid dependency. Then, from the age of 5-6 years old, he presented marked systemic inflammation with febrile episodes improved by repeated courses of rituximab. Laboratory findings showed ANA with anti dsDNA as well as anti C1q antibodies. Gastrointestinal symptoms and skin rash were still occurring at the age of 10, and ANA were positive associated with high TNF-alpha and IL-6 and low levels of C3.

## 2. Methods

For patient 1, DNA was run on a custom-designed targeted exon panel covering 147 genes including proven SLE disease-associated as well as prospective candidate genes. Variants identified were confirmed by Sanger sequencing (Primers : EX3F gatgaacagtggcccttcca - EX3R aggcccctagttttgacagc), purified PCR amplification products were sequenced using BigDye™ terminator chemistry and an ABI 3130 DNA sequencer. To identify copy number variants, demultiplexing and sequence alignment of the sequence data, and variant calling using the Genome Analysis Tool kit, Pindel and ExomeDepth was undertaken. Copy number analysis was performed using the TaqMan Universal PCR Master Mix (Applied Biosystems). Copy number probes chosen were Hs01348573_cn and a custom designed probe within the exon 5 coding region of DNASE1L3. AG1778 PH was included as the calibrator sample, and copy number was assessed with the Applied Biosystems StepOne Software v2.1 and Applied Biosystems CopyCaller software V2.0. Sanger sequencing was used to study the single *DNASE1L3* gene in patient 2 (Family B) for which the clinical data strongly suggests a DNASE1L3 deficiency. PCR products sequencing (Primers : EX4F gaaagvvatgggaacctaca - EX4R tccttaatgggcrcatgctc )was carried out using BigDye™ terminator on a 3500 XL analyser. In patient 3, a panel of 41 key genes involved in autoimmunity has been studied using Illumina technology / The Nimblegen SeqCap Target Enrichment kit (Roche) on a Novaseq 6000 (Illumina). Finally, patient 4 genetic

analysis was carried out using the NGS TruSightOne Panel (Illumina) that target up to 6700 genes associated with human diseases.