A 40 year old female was referred for investigation of a possible primary immunodeficiency. She had an 18 month history of recurrent sino-pulmonary infections with underlying bronchiectasis and recurrent low virulence mycobacterial infections on a background of treated pulmonary tuberculosis as a young adult. She had chronic oral herpes simplex, shingles, oral and vaginal candidiasis, chronic hepatitis B on lamivudine, and prior peripartum *Listeria* sepsis. 6 years earlier, she had a splenectomy for refractory idiopathic thrombocytopaenia purpura and remained on penicillin prophylaxis. She was treated with sulfasalazine for psoriatic arthritis, which was stopped owing to profound thrombocytopaenia which did not resolve. A single dose of Romiplostim caused an impressive platelet response from <10 to 1300. Our patient migrated from Burma, was married with two well children and the youngest of 9 with short stature but no other dysmorphic features.

Initial assessment revealed hypogammaglobulinaemia (IgG 5.7g/L, IgA 0.43g/L, normal IgM), with suboptimal vaccine responses. She had a lymphocytosis (6.34x10^9) with reduced switched and unswitched memory B cells and increased CD21-lo cells placing her in the Freiberg IA category of common variable immunodeficiency with a predisposition to autoimmune presentations. She responded well to immunoglobulin replacement therapy. Whole exome sequencing identified a heterozygous missense mutation in signal transducer and activation of transcription (STAT) 3, resulting in a methionine-to-threonine substitution at position 394 (M394T) in the DNA binding domain.

STATs are important intracellular signaling molecules downstream of multiple cytokine receptors, and influence gene transcription. Mutations in the JAK-STAT pathway are associated with immunodeficiency phenotypes including STAT1 deficiency (viral and mycobacterial infections) and STAT3 loss of function (staphylococcal boils, candidiasis, eczema and dysmorphic features through loss of Th17 differentiation).

Activating mutations in STAT3 have only recently been described, first by Flanagan et al., who reported 4 different de novo germline mutations in highly conserved STAT3 domains in 5 patients with early onset autoimmune disease (diabetes, enteropathy, interstitial lung disease, juvenile arthritis, hypothyroidism), short stature and eczema. Muted STAT3 responses to IL-6 stimulation were noted relative to wild type, and regulatory T cells (Tregs) were reduced. Milner et al. identified 9 germline activating mutations in 13 patients with lymphadenopathy, autoimmune cytopenias, multiorgan autoimmunity, recurrent infections and short stature. Hypogammaglobulinaemia, T cell lymphopaenia, expansion of double negative T cells, reduced STAT1 and STAT5 phosphorylation on stimulation and a reduction in Tregs was noted. One patient was transplanted attaining complete remission, and another treated successfully with IL-1 blockade. Haapaniemi et al. described 3 patients with an immunodeficiency phenotype and multisystem autoimmunity, where the first reported case of the M394T mutation was reported. This patient had mild autoimmunity (lymphocytic colitis, ITP and eczema), recurrent respiratory tract infections, lymphopaenia, hypogammaglobulinaemia with a Freiberg IA phenotype, reduced Tregs and disseminated mycobacterial disease with intact IL-12-IFNy signaling.

In summary, germline activating mutations in STAT3 cause dysregulated cytokine signaling, a reduction in Tregs and altered Th17 cells resulting in autoimmunity and immunodeficiency as demonstrated by our case. The M394T mutation predisposes to mycobacterial infectious however the cause for this is not known. STAT signaling is complex, as demonstrated by STAT3 loss of function and activating mutations which do not cause opposing phenotypes. These findings have important implications for the understanding of lymphocyte tolerance and the pathogenesis of systemic autoimmunity.
References