A Copy Number Gain in NFKB2 in a Patient with Immune Dysregulation

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Background

- Pathogenic variants in the NFKB2 gene are strongly associated with B cell dysregulation and inborn errors of immunity (IEI)[1]. Recent data has suggested that copy number variants (CNVs) can also cause IEI.[2]

Case Description

- An 18-year-old male with chronic ITP controlled on eltrombopag and intermittent oral steroids for crises and without prior infectious history was admitted to the hospital with Streptococcus pneumoniae meningitis and bacteremia requiring intubation.
- Head imaging revealed extensive sinus disease, enhancement suggestive of bacterial meningitis, an incidental Chiari Type 1 malformation, and a sinus venous thrombosis in the superior sagittal sinus. He was treated with prolonged course of ceftriaxone and a bivalirudin drip, which was later transitioned to apixaban upon discharge.
- Additional history was significant for intermittent lymphadenopathy, prior LN biopsy demonstrating reactive lymphocytes at age 10, two bone marrow biopsies revealing hypocellular marrow, and a family history of autoimmune pancreatitis and vitiligo.

Diagnostic and Laboratory Evaluation

- IgG 466mg/dL, IgA <6.2 mg/dL, IgM 128 mg/dL
- CD27+ IgM-IgD- cells (2 cells/uL)
- Naive T cells (33 cells/uL)
- Cd21lo B cells (37 cells/uL)
- sIL2RA (3956 pg/mL)
- Absent titers to Tetanus, Diphtheria, Pneumococcus, Measles, Mumps, and Varicella
- PN23- 0/23 protective titers

- The laboratory results, shown above, demonstrate hypogammaglobulinemia, absent titers for tetanus, diphtheria, pneumococcal, measles, mumps, and varicella, low class switched memory B cells and naive T cells, and increased Cd21lo B cells and soluble IL-2 Receptor.
- Abdominal ultrasound revealed a spleen size at the upper limit of normal.
- IEI immunodeficiency and cytopenias panel showed a NFKB2 Gain (Entire coding sequence) copy number = 3 of uncertain significance.
- Further testing was conducted to evaluate for overexpression of NFKB2-p52 (Figure 2) and CXCL13 (Figure 3) which is normal (not expected).

Functional Testing

Reference Interval	Unstim	CD3/CD28 stimulation
Number of values	15	15
Minimum	0.07650	0.3015
25% Percentile	0.1750	0.4065
Median	0.2375	0.4665
75% Percentile	0.3335	0.5895
Maximum	0.4600	1.224
Range	0.3835	0.9220
5% Percentile	0.07650	0.3015
95% Percentile	0.4600	1.224
Mean	0.2527	0.5570
Std. Deviation	0.1089	0.2468
Std. Error of Mean	0.02813	0.06372

Patient	Unstim	CD3/CD28 stimulation
Frozen PBMCs	0.3550	0.6445

Figure 1: Reference interval vs. patient sample

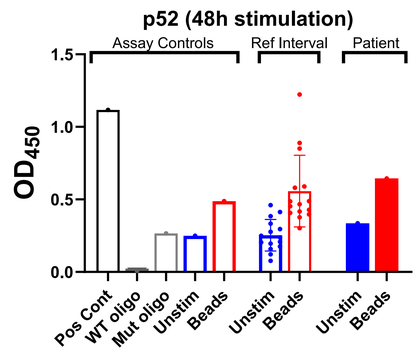

Figure 2: NFKB2- p52 transcriptional expression assay

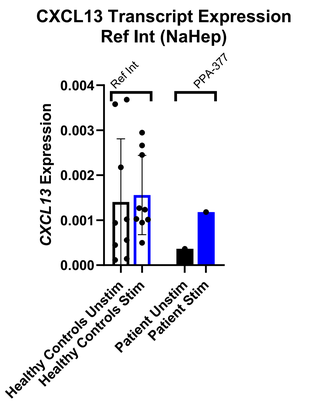

Figure 3: CXCL13 transcriptional expression assay

Conclusions

- Our patient was started on subcutaneous IgRT. He is being referred for a potential trial with leniolisib for treatment of CVID with complicated features. Additional functional studies are being pursued.
- Existing literature strongly underscores the role of NFKB2 in immune dysregulation, including cytopenias, CVID- like diagnoses, autoimmune alopecia, and ectodermal dysplasia.
- The patient's CNV (here a copy number gain) may overactivate NFKB2, leading to immune dysregulation, but its significance remains unknown, necessitating additional functional validity testing.
- Currently, a monogenic cause is found in less than 30% of patients with IEI, specifically in those with immune dysregulation[3]. Integrating CNV analysis into routine sequencing will aid in diagnosis and improve treatment options for patients.

References

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