Immunology as a window to understanding 22q11.2 issues

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The immune system was one of the central features in the original description of DiGeorge syndrome. He highlighted the recurrent severe infections. Today, we recognize that the immunodeficiency is as variable as the effects on any other tissue in 22q11.2 deletion syndrome. What is less understood is the downstream effects of the immunodeficiency. The immunodeficiency is thought to be primarily due to limitation of the thymic tissue required for maturation of T lymphocytes. This is manifested as low T cell counts in early infancy. Through an expansion of the existing T cells, the T cell counts become more normal over time. Direct downstream consequences of the limited thymic tissue and low T cells are functional defects in T cells related to homeostatic expansion. Infection is the most obvious consequence. T cells under homeostatic expansion also acquire features that support allergic responses and indeed, patients have an increased risk of atopy. Another direct effect with complex mechanisms is the predisposition to autoimmunity. Regulatory T cells, important for the prevention of clinical autoimmunity, are low, perhaps due to limited thymic niches for development and homeostatically expanded T cells are also enriched in auto-reactive T cells. These direct effects are reasonably well understood, however, what other clinical features in 22q11.2 deletion syndrome might be influenced by the abnormal immune system? Chronic inflammation is associated with increased depression and fatigue. Could persistent infections or dysregulated inflammation be responsible in part for depression and fatigue in 22q11.2 deletion? Today, we understand that the immune system regulates the development of the microbiome. Could that impact some of the gastrointestinal manifestations of 22q11.2 deletion syndrome? These are difficult questions to address but are tractable with large data sets and a dedication to looking at interactions.