

Letter to the Editor

Mutation of *TNFRSF13B* in a child with 22q11 deletion syndrome associated with granulomatous lymphoproliferation

To the Editor:

Immunodeficiency, secondary to 22q11.2 deletion syndrome with thymic dysplasia, is variable and does not correlate with other phenotypic features. Rarely, patients exhibit severe T lymphocytosis with severe combined immunodeficiency phenotype,¹ but most have mild to moderate lymphocytopenia, with associated partial humoral immunodeficiency, often clinically more severe in early life.

The most prevalent primary immunodeficiency (PID), common variable immunodeficiency (CVID), is a heterogeneous group of disorders² characterized by hypogammaglobulinemia and failure to mount protective antibody responses. Patients may develop autoimmunity, lymphoproliferation, and malignancy.² Transmembrane activator and calcium-modulating and cyclophilin ligand interactor (TACI), encoded by *TNFRSF13B*, is mutated in 10% cases of CVID.³ TACI is important in B-lymphocyte activation and plasma cell differentiation, and it plays an important role in central B-lymphocyte tolerance.⁴ TACI-deficient mice experience increased lymphomas and autoimmune phenomena including a lupuslike condition with autoantibody production.⁵ A number of *TNFRSF13B* mutations are described in patients with CVID, most commonly heterozygous p.C104R and p.A181E mutations, each found in 4% to 5% of the patients with CVID,^{6,7} who develop splenomegaly and autoimmune phenomena more frequently than do patients with other mutations, including CD8 lymphoproliferation described in a patient with a heterozygous p.104C>R *TNFRSF13B* mutation.⁸ We report a patient with 22q11 deletion and heterozygous p.104C>R *TNFRSF13B* mutation who developed granulomatous-lymphocytic interstitial lung disease (GLILD) and other widespread

granulomatous-lymphocytic disease, although no peripheral CD8 lymphoproliferation.

During infancy, developmental and speech delay and mild dysmorphic features were noted. Early childhood was complicated by frequent upper respiratory tract infections, hepatosplenomegaly, microcytic hypochromic anemia, and thrombocytopenia secondary to hypersplenism. Progressive lymphocytopenia developed, with absent class-switched memory B-lymphocytes (Table I) and hypogammaglobulinemia with no antibody response to pneumococcal polysaccharide antigen vaccination. Immune-mediated hemolysis requiring steroid therapy developed after pneumococcal vaccination. Computed tomography demonstrated mediastinal and paraaortic lymphadenopathy as well as right middle-lobe collapse, patchy consolidation, and bronchial wall thickening, with multiple small nodules throughout both lung fields.

A heterozygous 3.0Mb 22q11.2 deletion was detected during these events. The patient commenced antibiotic prophylaxis, and subsequently immunoglobulin replacement.

At age 11 years, massive splenomegaly was apparent (25 cm). A repeat chest radiograph showed deterioration despite immunoglobulin substitution. Computed tomography revealed extensive mediastinal, paratracheal, hilar, and subcarinal lymphadenopathy, diffusely abnormal lung parenchyma with nodules, predominantly in a peribronchovascular distribution, marked splenomegaly below the pelvic rim, and diffusely abnormal lung parenchyma, consistent with lymphoproliferative disease. Lymph node histology demonstrated paracortical T-lymphocyte expansion with reduced and indistinct B-lymphocyte follicles containing only occasional germinal centers. There were aggregates of macrophages within parenchyma and sinuses, but there was no evidence of lymphoma (Fig 1). Lung biopsy showed a patchy but prominent interstitial and nodular lymphoid infiltrate expanding the alveolar septa and becoming focally confluent.

TABLE I. Serial immunologic results from the patient

Cells/ μ L (normal range)	Age (y)				
	8	11.5	12	12.5	13.5
CD3	378 (1400-2000)	712 (800-3500)	380 (800-3500)	480 (800-3500)	432 (800-3500)
CD4	258 (700-1100)	561 (400-2100)	312 (400-2100)	353 (400-2100)	336 (400-2100)
CD8	109 (600-900)	64 (200-1200)	45 (200-1200)	80 (200-1200)	73 (200-1200)
NK	92 (200-300)	73 (70-1200)	45 (70-1200)	78 (70-1200)	33 (70-1200)
CD19	92 (300-500)	105 (200-600)	336 (200-600)	91 (200-600)	71 (200-600)
CD27 ⁺ IgM ⁺ (%)	—	—	—	—	2
CD27 ⁺ IgM ⁻ (%)	—	—	—	—	0
CD27 ⁻ IgM ⁻ (%)	—	—	—	—	87
IgG (g/L)	2.2 (3.6-15.2)	IVIG	IVIG	IVIG	IVIG
IgA (g/L)	<0.07 (0.54-2.48)	<0.07 (0.64-2.58)	<0.07 (0.64-2.58)	<0.07 (0.64-2.97)	<0.07 (0.64-2.97)
IgM (g/L)	0.19 (0.43-1.9)	0.24 (0.43-1.9)	0.28 (0.43-1.9)	0.26 (0.43-1.9)	0.2 (0.43-1.9)
PHA—Patient					
Background	880				
Counts	16461				
Stimulation index	19×				
PHA—Control					
Background	401				
Counts	99075				
Stimulation index	247×				

IVIG, Intravenous immunoglobulin; NK, natural killer.

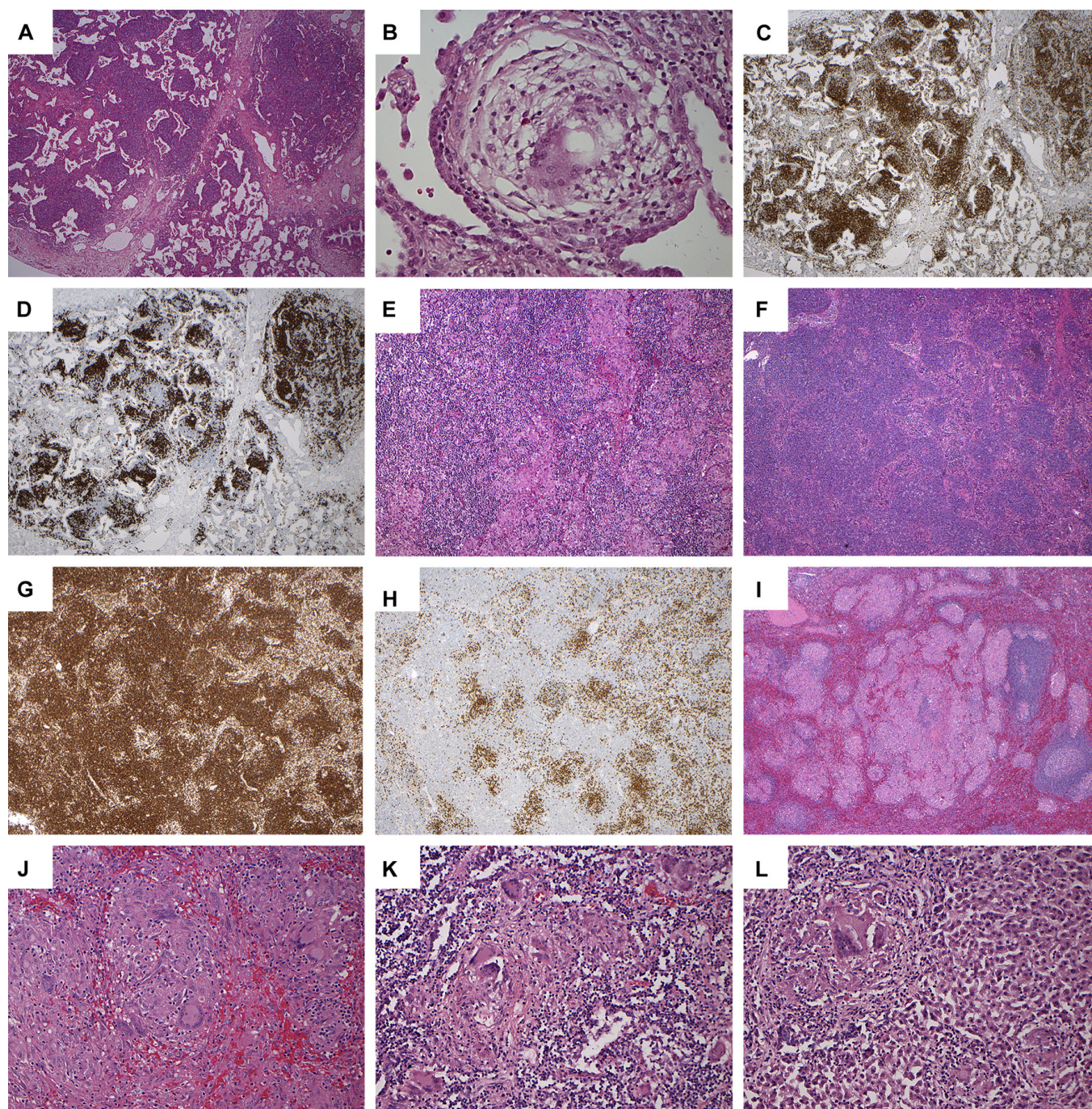


FIG 1. A-D, Lung. A, Interstitial lymphocytic infiltrate; B, Granuloma; C, CD3-positive T cells; D, CD20-positive B cells. E-H, Lymph node. E and F, T-cell-rich node with histiocytic infiltrate. G, CD3-positive T cells; H, CD79a-positive B cells. I and J, Spleen. I, Granulomatous infiltrate and variably active white pulp; J, Granulomas with multinucleate giant macrophages. K, Postmortem lung; florid lymphocytic and granulomatous infiltrate of GLILD. L, Postmortem liver; granulomatous hepatitis.

This was a mixture of T lymphocytes and B lymphocytes, the latter forming vague follicles containing occasional small germinal centers. Small nonnecrotising granulomas, including multinucleate giant cells, were scattered throughout. There was no evidence of lymphoma and no organisms, including HHV8 and EBV, were detected. The features were consistent with GLILD (Fig 1).

Despite treatment with systemic corticosteroids, high-dose immunoglobulin, hydroxychloroquine, and azathioprine, symptoms progressed. The patient died of early hemorrhagic postoperative complications following splenectomy. Splenic histology showed extensive parenchymal granulomatous inflammation, present as numerous small clusters of epithelioid macrophages and larger coalescent aggregates associated with

multinucleate giant cells and fibrosis but minimal necrosis. The red pulp was congested and activated with foci of incidental extramedullary erythropoiesis and Gamna-Gandy bodies. The white pulp was generally inactive, with only a few germinal centers evident. No organisms were identified, and no features suggested lymphoma (Fig 1). Histology of postmortem lung showed extensive interstitial lymphoid infiltrate with numerous granulomas. Granulomas were present in liver and occasional lymph nodes (Fig 1). Subsequent Sanger sequencing of genomic DNA identified a heterozygous p.104C>R TNFRSF13B mutation, not found in the mother or asymptomatic siblings.

The clinical presentation demonstrated features found in 22q11 deletion, and features most commonly associated with mutations in *TNFRSF13B*. Speech delay and typical facial gestalt indicate 22q11 deletion. Although autoimmunity is a feature of 22q11 deletion, the presenting clinical picture described was more consistent with CVID and GLILD, a clinical feature not previously described in 22q11 deletion.

Patients with CVID harboring *TNFRSF13B* mutations more frequently develop splenomegaly and autoimmune phenomena.⁷ Heterozygous p.104C>R alleles are associated with antibody deficiency, reduced CD19⁺CD27⁺IgM⁺IgD⁺ B lymphocytes, lymphoproliferation, and autoimmune complications.⁷ However, many individuals carrying a *TNFRSF13B* mutation do not develop CVID, because in many individuals, peripheral B-lymphocyte tolerance can be established despite a defective central B-lymphocyte tolerance checkpoint.⁴ Although one heterozygous *TNFRSF13B* mutation alone is insufficient to induce the development of CVID, the combination of another defect (22q11 deletion), associated with autoimmunity, may have been sufficient in our patient, either because some genes deleted in the 22q11 region, such as *TBX1* or *CRKL*, implicated in thymic development, act as a *TNFRSF13B* modifier, or the cellular immunodeficiency associated with 22q11 deletion acted in synergy with the defect caused by the *TNFRSF13B* mutation.⁴ The immunopathology of granulomatous disease in PID is unclear. Granulomata is described in diverse presentations including CVID, chronic granulomatous disease, hypomorphic recombination activating gene mutations, MHC class I deficiency, ataxia-telangiectasia, and cartilage hair hypoplasia. It has been suggested that profound lack of B-lymphocyte maturation in CVID, associated with an abnormal cellular or cytokine environment, supports subsequent granulomata formation.⁷ Furthermore, an expansion of CD8⁺ T lymphocytes and a lack of CD4⁺ T lymphocytes, with defective T-lymphocyte proliferative responses, have been associated with tissue granulomata in CVID.⁷ Although our patient had reduced lymphocyte proliferative responses and CD4 lymphocytopenia, CD8 lymphocytes were also reduced. Variable T lymphocytopenia is a frequent

finding in 22q11 deletion syndrome, whereas granulomatous lesions are rarely described.

This case illustrates the complexity in correlating clinical phenotype with genotype. Although many nonclassic phenotypes are associated with hypomorphic single-gene mutations, they may be due to simultaneous defects in more than 1 gene. Adoption of next generation sequencing as a routine diagnostic tool in patients with PID⁹ is likely to lead to the identification of such patients with increasing frequency, which may, in some cases, explain an overlapping or blended clinical immunopathological phenotype.

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2014.07.025>