Case 4

J.L. is a 30-year-old lawyer who presented to the hospital with fever, shaking chills and a cough productive of blood-tinged sputum. Past medical history included multiple prior hospital admissions for bacterial pneumonia that first became evident during the second year of life. By the age of 7 he was extensively evaluated to determine if he had an immunodeficiency. Pertinent immunologic findings included: normal delayed-type hypersensitivity (DTH)[1] skin test reactivity to mumps and *Candida* antigens; serum IgM levels of 450 mg/dl (high), markedly reduced levels of IgA (< 10 mg/dl) and IgG (< 50 mg/dl). Analysis of his peripheral blood lymphocytes by flow cytometry showed the cells to be 78% $CD2^+$, 60% $CD4^+$ and 26% $CD8^+$. Ten percent expressed surface membrane immunoglobulin (B-cell receptor for antigen; BCR). All B-cells expressed Class II MHC and CD21. Further workup revealed normal complement function (CH_{50}) and normal levels of the complement components C2, C3 and C4. The patient had normal expression of CD18 and CD11a, CD11b and CD11c on his leukocytes. Functional studies of the patient's lymphocytes revealed normal proliferative response and normal IL-2 secretion after triggering with anti-TCR (T-cell receptor for antigen) antibodies. The superoxide generation by the patient's monocytes was normal. The patient's lymphocytes produced 200 mg/ml of IgM, but no IgG, following stimulation with the B-cell activator, poke-weed mitogen (PWM); (normal lymphocytes produce greater than 210 mg/ml of IgM and 1000 mg/ml of IgG in response to PWM). To further evaluate the defect in IgG production by J.L.'s lymphocytes, his T- and B-cells were isolated. In addition, T- and B-cells were isolated from his normal MHC-identical sister. Co-culture of the indicated cell types were performed in either the presence or absence of PWM and Ig secretion was measured. The following results were obtained:

T-cells	B-cells	PWM	IgM (μg/ml)	IgG (μg/ml)
normal	normal	-	< 20	< 20
normal	normal	+	980	3,700
patient	patient	-	< 20	< 20
patient	patient	+	1,850	< 20
patient	normal	-	< 20	< 20
patient	normal	+	1,000	< 20
normal	patient	-	< 20	< 20
normal	patient	+	1,600	3,500

[1]DTH will be discussed in later cases; here, it was was used as an index of $CD4^+$ T-cell function.

Questions for Case 4

(1) What is your interpretation of the functional data depicted in the table above? What is the likely diagnosis in this case? How would you further evaluate the patient to confirm the diagnosis? What other (even rarer) disease might give identical clinical manifestations as the disease in this case?

(2) What genetic counseling would you provide the patient?

(3) In the evaluation of J.L. a number of immunodeficiency diseases were excluded. How were the following diseases excluded: (a) SCID; (b) X-linked agammaglobulinemia; (c) DiGeorge's

Syndrome; (d) C4 and C7 deficiency; (e) Leukocyte Adhesion Deficiency Disease; and (f) Chronic Granulomatous Disease (CGD).

(4) The defective molecule in this case is a member of a large family of ligands and receptors. What other members of this family play a role in death and survival of B cells?

(5) How would you treat J.L.?