forward to learning the answers to these questions.

Acknowledgments
The authors are supported in part by NIH grants R01DK56366, P30DK56336, and R01ES09912.

1. Strom, R. 2003. Increases in clinically severe obe-


2. National Institute of Diabetes & Digestive & Kid-

ney Diseases. Phenotyping obesity for human genetic


other/phenotyping/index.


cation in genetic association studies of obesity and dia-

5. Rosmond, R. 2003. Association studies of genet-
ic polymorphisms in central obesity: a critical
review. Int. J. Obes. Relat. Metab. Disord. 27:1141–1151.


obesity. In Obesity: mechanisms and clinical manage-

8. Segal, N., and Allison, D.B. 2002. Twins and vir-


12. Leibowitz, S.F., and Alexander, J.T. 1998. Hypo-
thalamic serotonin in control of eating behavior,


scans for human nutritional traits. What have we


human obesity genes reveals a major susceptibility


chromosome scan reveals a locus for fat distribu-


Genet. 70:1459–1468.

of complex traits: guidelines for interpreting and

18. Page, G.P., George, V., Go, R.C., Page, P.Z., and
when one has demonstrated specific genetic cau-
sation in complex diseases and quantitative traits.


20. Silventoinen, K., Kaprio, J., Lahelma, E., Viikari,
R.J., and Rose, R.J. 2003. Assortive mating by
body height and BMI: Finnish twins and their

quantitative-trait-locus effect in genome scans:
demonstration of the phenomenon and a
method-of-moments procedure for reducing bias.

Peeking under the peaks: following up genome-

Genes required for B cell development

Mary Ellen Conley1,2

1Department of Immunology, St. Jude Children’s Research Hospital, Memphis,
Tennessee, USA

2Department of Pediatrics, University of Tennessee College of Medicine, Memphis,
Tennessee, USA

Mutations in a variety of genes can cause congenital agammaglobuline-
mania and a failure of B cell development. The currently known genes encode components of the pre–B cell receptor or proteins that are acti-
vated by cross-linking of the pre–B cell receptor. Defects in these genes result in a block in B cell differentiation at the pro–B to pre-B cell tran-
sition. A patient with a translocation involving a previously unknown gene, LRRC8, demonstrated a block at exactly the same point in B cell
differentiation (see the related article beginning on page 1707). It will be
interesting to determine whether the protein encoded by this gene
interacts with the pre–B cell receptor signal transduction pathway or is
involved in a new pathway.


Address correspondence to: Mary Ellen Conley, University of Tennessee College of
Medicine, St. Jude Children’s Research Hospital, 332 North Lauderdale, Memphis,
Tennessee 38105, USA.

Phone: (901) 495-2576; Fax: (901) 495-3977; E-mail: maryellen.conley@stjude.org.

Conflict of interest: The author has declared
that no conflict of interest exists.

Nonstandard abbreviations used: X-linked agammaglobulinemia (XLA); B cell linker
(BLNK); leucine-rich repeat-containing 8 (LRRC8).

B cell maturation proceeds through a series of stages that can be defined by
the rearrangement status of the Ig genes, the expression of cell surface
markers, and the location of the cells within the bone marrow, the spleen, or
the lymph nodes (1–3). Patients with defects in early B cell maturation usu-
ally develop recurrent infections, caused by encapsulated bacteria, in the
first 2 years of life, and most are recog-
nized to have immunodeficiency when they are hospitalized for a dramatic
infection at less than 3 years of age (4).

Approximately 80% of patients with the early onset of recurrent infections,
hygammaglobulinemia, and marked-ly reduced or absent B cells have
X-linked agammaglobulinemia (XLA) (5). This disorder is caused by mutations in a hematopoietic-specific cyto-
plasmic tyrosine kinase, Btk (6, 7). Btk is expressed in myeloid cells, in plate-
lets, and at all stages of B cell development except plasma cells (8–10); how-
ever, it is important to note that patients with XLA have absent or markedly reduced numbers of B cells but do not have any clinical abnormalities in myeloid cells or in platelet
number or function. The earliest point in B cell differentiation at which Btk is required coincides with expression of the pre–B cell receptor at the pro–B to pre-B cell transition (11, 12). Therefore, it is not
surprising that defects in components of the pre–B cell receptor account for
an additional 7–10% of patients with congenital agammaglobulinemia. The
majority of these patients have mutations in the constant region of μ heavy
chain Ig (13), but a small number have defects in A5 (14), which is part of the
surrogate light chain, or in Igα (15), a transmembrane protein that binds to

The Journal of Clinical Investigation | December 2003 | Volume 112 | Number 11
The µ heavy chain and acts as part of the signal transduction module. Expression of these proteins is limited to the B cell lineage. Downstream targets of activation through the pre–B cell or B cell receptor complex include Btk and B cell linker (BLNK), a scaffold protein that binds Btk, PLCγ2, Grb2, Vav, and Nck. Two patients with agammaglobulinemia and defects in BLNK have been identified (ref. 16 and unpublished results). Patients with defects in components of the pre–B cell receptor, Btk, or BLNK all have a block in B cell differentiation at the pro–B to pre–B cell transition (17) (Figure 1).

The remaining 10–15% of patients with the early onset of infections, agammaglobulinemia, and absent B cells represent a heterogeneous group. Some of these patients have myelodysplasia, with hypogammaglobulinemia and reduced numbers of B cells being the first sign of their disease (18). Some patients have subtle T cell defects as well as more severe B cell defects; some have morphologic defects including failure to thrive, microcephaly, and/or abnormalities of the hands and feet (19–22); and some are clinically indistinguishable from patients with defects in µ heavy chain. A variety of approaches can be taken to identify the genes that are abnormal in these patients. Murine models of immunodeficiency resulting in decreased or absent B cells can provide some clues (23), but it is important to remember that mutations in the same gene may result in different phenotypes in mice and humans (17). Proteins belonging to the signal transduction pathways activated by cross-linking of the pre–B cell receptor are attractive candidates for analysis, particularly when the expression of the gene of interest is limited to hematopoietic cells. Careful evaluation of an unusual patient can be one of the most rewarding approaches.

In this issue of the JCI, Sawada et al. describe a 17-year-old girl with unusual facial features, agammaglobulinemia, and markedly reduced or absent B cells (24). Karyotype studies revealed a...
balanced translocation between chromosomes 9 and 20, resulting in the truncation of a novel gene, leucine-rich repeat-containing 8 (LRRC8), normally encoded on the long arm of chromosome 9. This unusual gene consists of only two exons, which encode an 810-amino acid protein with four transmembrane domains and an extra-cellular carboxy-terminal domain with nine leucine-rich repeats (Figure 2). The translocation occurred between the first and second exons and resulted in the loss of the last two-and-a-half leucine-rich regions and the addition of 35 amino acids from the intronic sequence. Using immunofluorescence staining and RT-PCR, the authors suggest that the gene is expressed in brain, heart, lung, liver, and kidney as well as T cells and B-lineage cells.

Based on the observation that there were no abnormalities in the other allele of LRRC8, and that protein from the normal and abnormal alleles were expressed in white blood cells from the patient, the authors interpret their results as indicating that the mutation had a dominant-suppressor effect on B cell development (24). It is interesting to speculate on how this dominant effect might occur and whether there might be other patients with agammaglobulinemia due to similar mutations. Several mechanisms can explain an autosomal dominant effect. For example, if the last two leucine-rich domains function as self-inhibitory domains, the loss of those domains might result in a constitutively active protein; or, if the protein is part of a multimeric complex that includes more than one copy of the LRRC8 protein, one abnormal allele could alter the function of a majority of complexes. Occasionally, an abnormal protein can change the stability or location of a binding partner and thereby inhibit the ability of the binding protein to function. By reconstituting lethally irradiated mice with bone marrow that had been transfected with a retroviral vector expressing the mutant protein, the authors showed that the mutant protein caused a block at the pro–B to pre–B cell transition (Figure 1). This brings up the possibility that LRRC8 might interact with the pre–B cell receptor in some way. Alternatively, the 35 amino acids derived from the intronic sequence at the carboxy-terminal portion of the mutant LRRC8 might confer on the protein a toxic function similar to that of the polyglutamine tract in trinucleotide repeat disorders.

At this time it is difficult to say whether there likely to be other patients with congenital immunodeficiency due to defects in LRRC8. The authors note that the gene is broadly expressed and that the gene product can be found on the surface of T cells. A detailed evaluation of T cell function might result in the detection of subtle findings that would allow one to identify similar patients. The authors also describe their patient as having mildly dysmorphic facial features. Because many otherwise normal people have mildly dysmorphic facial features, it is not clear at this time whether the unusual facial features of the individual examined by Sawada et al. (24) are secondary to the defect in LRRC8 or part of her familial inheritance. Finding an abnormal gene in a patient with immunodeficiency is only the first exciting step. The next steps should tell us how LRRC8 functions in the normal immune system.

---