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Genetics of Hypogammaglobulinemia: What do we really know?

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Summary

In the past, immunodeficiencies were categorized based on clinical and laboratory findings in the affected patient. Now we are more likely to define them based on the specific gene involved. One might expect this shift to increase the precision and clarity of diagnosis but in the last few years it has become increasingly clear that identification of a mutation in a specific gene may not tell the whole story. Some gene defects may reliably result in clinical disease, others may act as susceptibility factors that are more common in patients with immunodeficiency but can also be found in otherwise healthy individuals. Distinguishing between these two types of gene defects is essential for informative genetic counseling.

Introduction

Genetic analysis of patients with immunodeficiency has yielded remarkable insights into the development and function of the normal immune system. It has also made diagnosis and genetic counseling more specific. However, in recent years it has become increasingly clear that interpreting the consequences of alterations in DNA may be more complex than initially recognized. Disorders which have been considered single gene defects of the immune system, like X-linked agammaglobulinemia (XLA), can show striking variability in clinical phenotype due to modifying genetic factors. Several genetic defects that contribute to common variable immunodeficiency (CVID) have been identified, but in some ways this has complicated genetic counseling rather than simplified it.

For some genetic disorders, different mutations in the same gene can result in different modes of inheritance. For example, while most mutations in AICDA, a gene associated with hyper-IgM syndrome, result in an autosomal recessive disorder, others appear to be inherited in an autosomal dominant pattern [1]. Some changes in DNA sequence may decrease but not ablate the function of the protein encoded by the gene [2,3]. These hypomorphic mutations can provide valuable clues to the function of the normal protein. Further, different mutations in the same gene may result in very different phenotypes. For example, a small number of mutations in the gene responsible for Wiskott Aldrich syndrome are activating mutations rather than the more typical mutations that decrease or ablate the function of the protein. These activating mutations are associated with severe congenital neutropenia [4,5,6]. A combination of careful clinical and laboratory studies, and in vitro functional assays may help clarify the consequences

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of unusual mutations and isolate the effect of the specific mutation from other modifying factors. In this review I will touch on some of these complex issues with reference to defects in early B cell development and CVID.

Defects in Early B Cell Development

Patients with XLA, patients with mutations in the cytoplasmic tyrosine kinase Btk, account for approximately 85% of patients with the early onset of infections, profound hypogammaglobulinemia and markedly reduced or absent B cells in the peripheral circulation [7]. Of the remaining 15% of patients, approximately half have defects in components of the B cell antigen receptor or the downstream scaffold protein BLNK [8,9,10,11] (Fig. 1). In 5-8% of patients who have failure of B cell development but no other medical problems, the genetic defect remains unknown. This figure excludes patients with myelodysplasia, which can masquerade as a B cell specific defect [12] and more broadly expressed disorders that include decreased numbers of B cells [13,14,15].

XLA is a leaky defect in B cell development and most patients do have a small amount of serum IgG and a few B cells in the peripheral circulation. More than 600 different mutations in Btk have been reported [16] and no single mutation accounts for more than 3% of patients. With so many different mutations, it is difficult to ascribe mild or severe disease to any single mutation. However, by dividing mutations into null mutations, for example premature stop codons and frameshift mutations, and those that could be expected to generate some Btk, for example amino acid substitutions and splice defects that involve sites in the splice consensus sequence that are conserved but not invariant, our group and others have shown that amino acid substitutions and milder splice defects are more likely to be associated with later age at diagnosis, higher serum concentrations of IgM and more B cells in the peripheral circulation [17,18,19].

Obviously, not all amino acid substitutions are associated with milder disease. Some amino acid substitutions occur at sites that are critically important for the function of the protein. Others affect the stability of the protein. Screening for the presence of the protein of interest by flow cytometry or western blot analysis is often the first step in the functional analysis. Mutations that result in normal amounts of the mutant protein are often, but not always, associated with milder disease [8].

The amino acid sequence of Btk is remarkably well conserved. Human and murine Btk are identical at 98% of the amino acids, and there are no common polymorphisms that change the amino acid sequence of Btk. Recently Perez de Diego et al described a family in which a male with immunodeficiency had two alterations in Btk sequence [20]. One alteration was a previously described mutation in the kinase domain (R641H), the other caused an amino acid substitution in the SH3 domain (A230V). Although the patient and his mother were the only family members who carried the R641H mutation, the A230V amino acid substitution was seen in multiple family members, including a healthy male maternal cousin with 13% B cells, indicating that this change is unlikely to affect B cell development.

We identified another family in which a boy with typical signs and symptoms of XLA had 2 alterations in Btk, a premature stop codon in the kinase domain (K625X), and an amino acid substitution in the ATP binding site, Y418H [3]. Both changes were seen in the patient's mother and his 3 year old brother, who had hypogammaglobulinemia and low B cell numbers. The maternal grandfather and aunts of the boy all had the Y418H change but not the premature stop codon. The Y418H alteration has been reported in a patient with severe hypogammaglobulinemia and early onset immunodeficiency; however, the 58 year old maternal grandfather had no unusual history of infections. His serum immunoglobulins were borderline low but he had normal titers to tetanus toxoid and multiple pneumococcal serotypes.

On laboratory evaluation, the affected boy had 0.03% CD19+ B cells and his grandfather had 0.85% B cells (normal 4-18%). By FACS analysis we showed that the monocytes from the boy were negative for Btk whereas those from the grandfather were positive. The decreased number of B cells in the grandfather suggested, but did not prove, that the Y418H alteration had an adverse effect on Btk development. A functional assay was used to help answer this question.

A Btk- chicken B cell line was transfected with wild type or Y418H Btk and the ability of the cells to respond to cross linking of the surface immunoglobulin was examined. Cells containing the altered Btk consistently showed a 15-20% decrease in calcium flux and IP3 production at early time points, providing strong support for the contention that the Y418H altered Btk function [3]. The difference in clinical outcomes in the maternal grandfather compared to the other reported patient with the Y418H alteration could be explained by modifying genetic factors that ameliorated the findings in the grandfather or amplified the severity of disease in the other patient. Our functional assay suggests that the latter is more likely.

Graziani et al have also reported a family with an amino acid substitution in Btk (T316A) in a patient with an immunodeficiency that would be very atypical of XLA [21]. The patient had the onset of recurrent infections in infancy and multiple medical problems, but he had 8% B cells at 12 years of age. At 28 years of age the percentage of B cells had decreased to 2%. Western blot analysis showed normal amounts of Btk in an EBV transformed B cell line, and phosphorylation of Btk in the cell line from the patient appeared to be normal or increased. Is it possible that this patient had an unusual type of mutation, perhaps an activating mutation? Activating mutations in the PH domain of Btk have been described [22]. The fact that the patient's mother and aunts, carriers of the T316A alteration, had pulmonary emphysema increases this possibility. Could the mutation enhance binding to the scaffold protein BLNK? Functional assays might help clarify the question. Understanding the consequences of the T316A alteration in this family, or the Y418H amino acid substitution described above, has obvious implications for genetic counseling.

Despite their clear value, functional assays can sometimes be misleading. Several years ago we identified a patient with a defect in B cell development who had a homozygous amino acid substitution in Ig β (G137S), a signal transduction molecule that is a component of the B cell antigen receptor. Several findings suggested that this alteration was the cause of her immunodeficiency: 1) the amino acid substitution was not seen in 100 normal controls; 2) it was in a region of the molecule that was highly conserved; 3) and we could postulate a functional effect of the change. The amino acid substitution was immediately downstream of the cysteine required for the disulfide bridge between Ig α and Ig β . We assumed that this change would result in the failure of Ig α and Ig β to assemble and escort the μ heavy chain to the cell surface. However, in transient transfection assays, in which fibroblasts were transfected with expression vectors that produced all of the components of a BCR: μ heavy chain, λ light chain, Ig α and either wild type or G137S mutant Ig β , the G137 Ig β was able to bring the B cell receptor to the cell surface as well as the wild type sequence.

Transient transfection can result in over expression of the proteins of interest, making the interpretation of results more difficult. Therefore we developed a system in which Jurkat T cells were stably transduced with retroviral vectors producing GFP (green fluorescent protein) as well as μ heavy chain and λ light chain and vectors producing YFP (yellow fluorescent protein) plus Ig α and either wild type or G137S Ig β . Three to six weeks after transduction, the intensity of surface IgM expression was evaluated in cells that were equally positive for GFP and YFP. Cells containing G137S Ig β consistently demonstrated reduced expression of surface IgM [2]. This sensitive assay revealed differences that were not detected in the transient transfection assay.

Gene Defects in CVID

CVID is a term used to describe a heterogeneous group of disorders characterized by recurrent infections and failure to make antibody to vaccine antigens. Affected patients have a high incidence of autoimmunity, gastrointestinal disease, and lymphoproliferation, as well as upper and lower respiratory infections. CVID is a diagnosis of exclusion. When the diagnosis is made in a child less than 10 years old, other diagnostic possibilities should be considered at each clinic visit. Some of these younger patients may have a constitutive delay in immunoglobulin production or a single gene defect of the immune system.

Over the years there have been several attempts to subdivide patients with CVID into groups based on clinical or laboratory findings [23,24] but on the whole, these classifications have not been helpful in determining the genetic etiology of CVID. About 10% of patients with CVID have a family history of immunodeficiency or immune dysfunction [25] (Fig. 2), but this figure may depend on how intensively one searches for immunodeficiency and the criteria used to define immunodeficiency. Individuals who are identified as having immunodeficiency by laboratory screening rather than an evaluation because of recurrent or unusual infections might be considered to have “laboratory immunodeficiency” rather than “clinical immunodeficiency”. Although individuals with “laboratory immunodeficiency” are instructive, it may not be appropriate to treat them the same, or give them the same type of genetic counseling as patients with “clinical immunodeficiency”.

It has been recognized for many years that certain MHC haplotypes are more common in CVID [26,27]. Because there are many genes that influence the immune system in the MHC locus, including the cytokines TNF and lymphotoxin, the antigen processing proteins TAP1 and TAP2 and complement factors C2 and C4, as well as the antigen presenting MHC Class I and Class II proteins, it has been difficult to sort out which specific genes act as susceptibility factors. There are data that suggest that certain polymorphisms in the gene for TNF are more common in CVID [28,29]. In recent studies Sekine et al. suggested that polymorphic variants in the mismatch repair gene, Msh5, which is encoded in the MHC locus, might contribute to IgA deficiency and CVID [30]. However, the frequency of these variants in controls is only slightly lower than it is in CVID patients, suggesting that these variants do not play a strong role.

Two rare autosomal recessive disorders that result in a clinical picture similar to CVID have been reported. Grimbacher et al. have described 9 patients with the same homozygous deletion in the gene encoding the T cell activation marker, ICOS [31,32]. Haplotype analysis indicated that the patients, all of whom were German, shared a common ancestor. The patients ranged from 3 to 28 years of age at the time of diagnosis and all but the youngest two patients had decreased numbers of circulating B cells.

Mutations in the gene encoding CD19 also cause an immunodeficiency that could be mistaken for CVID. Van Zelm et al. described 4 patients from two unrelated families, a Turkish family and a Colombian family, who had normal numbers of B cells when CD20 was used as the B cell specific marker, but had no CD19+ B cells [33]. All 4 patients had the onset of recurrent infections at less than 10 years of age; however the 3 Colombian siblings were not recognized to have immunodeficiency until they were over 30 years of age. Both families had frameshift mutations in the intracytoplasmic domain of CD19, one in exon 6 and the other in exon 11. Kanegane et al. described a Japanese boy with two different mutations in CD19, a large deletion encompassing the entire gene on one allele and a splice defect on the other allele [34]. This child was given the diagnosis of CVID at 5 years of age. We identified a 6th patient with CD19 deficiency, a Turkish girl who began having infections in the first year of life and was evaluated

for immunodeficiency when she was 11 years old. She had a homozygous C deletion in codon 488 in exon 12, resulting in a frameshift (Conley and Casanova, unpublished results).

It is likely that CD19 deficiency would be detected during a routine evaluation for immunodeficiency, as CD19 is the standard marker used to identify B cells. ICOS deficiency would be more difficult to identify because it would require T cell activation and staining with an antibody that is not part of the typical evaluation. However, a substantial number of patients with CVID have been screened for mutations in ICOS and defects have been found only in the patients listed above. It is not clear that screening for mutations in ICOS would alter treatment or genetic counseling for adults. The gene defect is so rare that there is a very low probability that the spouse of the patient would carry a mutant allele.

The situation is more complex when we consider TACI mutations. As many as 10% of patients with CVID have heterozygous or homozygous alterations in TACI [25,35,36,37], a member of the TNF receptor family that is expressed on B cells. In contrast to Btk, TACI is highly polymorphic and a variety of amino acid substitutions have been described in healthy controls [37,38,39]. Although some of the mutations described in patients are null mutations, the majority are amino acid substitutions. Patients who carry mutations in TACI appear to have a higher incidence of autoimmune disease and splenomegaly [36,37]. However, the clinical severity and B cell phenotype of patients with TACI alterations are quite variable. Even some of the individuals who have alterations on both alleles of TACI have only mildly decreased serum immunoglobulins. Some of these people might be considered to have “laboratory immunodeficiency”.

Salzer et al have suggested that heterozygous mutations in TACI act as susceptibility factors for CVID, but biallelic alterations in this gene predictably cause disease [37]. Examination of the data does not support this contention. Large populations studies have shown that 1-2% of normal controls carry the same heterozygous amino acid substitutions as seen in patients [37, 38,39]. Using the lower estimate of 1%, one can calculate, based on Hardy-Weinburg calculation (0.01×0.01), that the incidence of individuals who are homozygous for alterations in TACI is 1/10,000. Since the prevalence of CVID is about 1/25,000 and only 10% of patients with CVID have alterations in TACI, one must assume that 90% of individuals who are homozygous for alterations in TACI die before they are recognized to have immunodeficiency or they do not have infections that are sufficiently unusual to elicit an evaluation of the immune system. In the absence of a frequent history of early deaths in families with alterations in TACI, I would favor the second possibility.

Additional research needs to be done to determine how alterations in TACI affect the immune system, and which pathways compensate for TACI defects. However, screening for mutations for TACI to predict prognosis or help in genetic counseling is unlikely to be useful. The phenotype of patients with the same mutation is highly variable. For many years it has generally been stated that patients with CVID have approximately 10% risk of having children with immunodeficiency. Identification of a TACI alteration would not change that figure.

Conclusions

The identification of genes and pathways involved in hypogammaglobulinemia has generated considerable interest. Defects in many of the genes that cause immunodeficiency result in a phenotype that is different from that seen in mice with mutations in the same genes [31,40]. This emphasizes the importance of studies done in the human model and gives us an idea about the alternative pathways that can be used to generate a normal antibody response.

In the next few years, I expect that there will be additional information about modifying genetic factors that influence the severity of hypogammaglobulinemia. Are there a limited number of

genes that play a dominant role or are there hundreds of genes, each of which could make a small contribution? As we learn more about the genetics of immunodeficiency, it will be increasingly important to think about how we intend to use the information. Screening for genetic disorders that act as susceptibility factors will not help us treat patients or provide genetic counseling.

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Defects in B Cell Development

Fig. 1.

The pie diagram shows the percentage of patients with early defects in B cell development who have mutations in each of the genes shown. These are patients with the early onset of recurrent infections, severe hypogammaglobulinemia and absent or markedly reduced numbers of circulating B cells, but no other medical problems.

CVID

Fig. 2.

This pie diagram shows the percentage of patients with CVID who have a family history of immunodeficiency or who have a known genetic defect.