

# Immunogenetics: changing the face of immunodeficiency

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Primary immunodeficiency is increasingly recognised in both children and adults. Although clearly defined disorders are individually rare, collectively they form a significant group. The molecular basis of several disorders has been known for over a decade, but in the past 10 years there has been a massive increase in the definition of defects underlying many immunodeficiencies.

Management of immunodeficiency has historically consisted of supportive treatment, including antibiotics, immunoglobulin (Ig) replacement, and in some cases, immunomodulation and immunosuppression. Bone marrow transplantation has been standard treatment for the past 20 years, but only for clearly defined cases of severe combined immunodeficiency (SCID) and a few other disorders known to have a very poor outlook without bone marrow transplantation. Accumulating worldwide experience is now providing evidence for poor long term prognoses in many other situations, even with optimal medical treatment. Bone marrow transplantation is therefore being considered for increasing numbers of children affected by these disorders, and, in parallel with this, there is a pressing need to define individual disorders as accurately and as early as possible.

The recent increase in knowledge of the molecular defects underlying many immunodeficiencies has led to several improvements in diagnosis and management.

First, precise molecular diagnosis is now possible in many cases, allowing earlier decisions to be made about the most appropriate management. This is particularly applicable in children who have evidence of combined (cellular and humoral) immunodeficiency, but with "milder" clinical phenotypes than infants with classical SCID. Some of these children are found to have identical molecular defects to those causing SCID, and in these cases the long term outlook is now known to be poor enough to justify bone marrow transplantation at an early stage.

Second, accurate carrier detection and first trimester prenatal diagnosis are possible in any family where the precise mutation has been defined. In some cases prenatal diagnosis of an affected fetus may not lead to termination of pregnancy, but can allow preparation for bone marrow transplantation early in the neonatal period, or even in utero in selected cases. Earlier bone marrow transplantation is associated with a greater chance of a successful outcome.

Third, knowledge of the molecular basis of immunodeficiencies allows further research into the mechanisms of the immune defects, with the possibility of designing more rational

treatment in some cases, and for developing strategies for somatic gene therapy.

## Specific disorders

Those immunodeficiencies for which the underlying molecular defects have been defined are summarised in tables 1 and 2. In several of these disorders, knowledge of the molecular basis has led to the improvements in management outlined above. In other cases ongoing research is continuing to add to our understanding of the molecular mechanisms of immune function. It is not within the scope of this review to go into detail for every disorder, so several illustrative diseases will be discussed.

## X linked agammaglobulinaemia (XLA)

X linked agammaglobulinaemia is the archetypal humoral immunodeficiency, presenting in its classical form with susceptibility to bacterial infection, absent or low circulating mature B cells, and absence of all immunoglobulin isotypes.<sup>1</sup> Standard treatment is with life long immunoglobulin replacement. The outlook is good provided that adequate IgG levels are maintained and infections are promptly treated. There is, however, a significant risk of enteroviral infection, and chronic meningoencephalitis can develop despite immunoglobulin replacement therapy.<sup>2</sup> The diagnosis of XLA has been made on lack of peripheral B lymphocytes, absence of immunoglobulin production, and in some cases an X linked pedigree. However, girls with congenital agammaglobulinaemia and absent B cells<sup>3</sup> and boys with a similar immunological profile but from an autosomal pedigree have also been reported, suggesting that the same immunophenotype can arise from a number of molecular defects.

In 1993, two groups identified the gene defective in XLA, one using a positional cloning strategy and another using a reverse genetic approach.<sup>4,5</sup> Subsequently designated Btk (Bruton's tyrosine kinase), the gene is a non-receptor tyrosine kinase expressed in the B and myelomonocytic cell lineages but not in T cells. Btk is activated following stimulation of several cell surface receptors including most importantly the B cell receptor.<sup>6</sup> In addition, interaction of Btk with a variety of intracellular signalling molecules including PIP<sub>3</sub> (phosphatidylinositol-3,4,5-trisphosphate) and PLC $\gamma$ 1 (phospholipase C $\gamma$ 1) is crucial for regulation of the sustained calcium signal in response to BCR engagement (reviewed in<sup>7</sup>). However, despite the large volume of experimental data, it is still unclear precisely how defects in Btk lead to the arrest in B cell maturation seen in XLA.

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The identification of the Btk gene defect allows unambiguous assignment of a molecular diagnosis to individuals with XLA and to female carriers. This is particularly important as defects in  $\mu$  heavy chain and  $\lambda 5/14.1$  surrogate light chain (components of the pre-B cell receptor) have also been shown to give rise to congenital agammaglobulinaemia.<sup>8,9</sup> Furthermore, screening of individuals with atypical or less severe XLA phenotypes, including those previously labelled as common variable immunodeficiency or immunoglobulin subclass deficiency, has shown that some of these individuals may also have Btk defects.<sup>10</sup>

Mutation detection in XLA has traditionally been carried out by initial screening of the 19 exons of the Btk gene by single stranded conformation polymorphism (SSCP) analysis and subsequent direct sequencing of the affected exon. This is a time consuming technique that may take months to complete, and has a sensitivity of only 90%. More recently generation of specific anti-Btk antibodies has allowed development of more rapid methods of diagnosis. Analysis of Btk protein expression in peripheral blood mononuclear cells of XLA patients by intracellular fluorescence activated cell sorter (FACS) or western blot analysis shows that over 90% lack Btk expression.<sup>11,12</sup> These techniques have also been useful in determining carrier status. In obligate carriers of XLA, intracellular FACS staining of monocytes shows a dual population of Btk expressing and Btk non-expressing cells since monocytes are randomly X inactivated in these women.<sup>11</sup> Similarly, if an XLA patient expresses a Btk protein of abnormal size, western blot analysis of monocytes from carrier females shows expression of an abnormal and normal sized band, thereby confirming carrier status.

#### CD40 ligand deficiency

X linked hyper IgM syndrome (XHM) has been recognised since 1966,<sup>13</sup> its characteristic immunological phenotype including very low IgG and IgA levels, normal or raised IgM, nor-

mal lymphocyte subpopulations, and apparently normal T cell function. The clinical phenotype is one of susceptibility to bacterial infection, but for many years before the responsible gene was identified it was known that boys affected by XHM were susceptible to opportunistic infection with organisms such as *Pneumocystis carinii*.<sup>14</sup> More recently, particular susceptibility to *Cryptosporidium parvum* has also been recognised. It was therefore not surprising when the gene responsible for XHM was identified in 1993 as that coding for CD40 ligand (CD40L), a surface molecule present on activated T cells.<sup>15-17</sup> CD40L is essential for immunoglobulin isotype switching through its interaction with CD40 on the surface of B cells, but it also plays an as yet undefined role in T cell function. T cell proliferative responses to a range of antigens have been shown to be defective in CD40L deficiency.<sup>18</sup> CD40L is also expressed on the surface of biliary epithelial cells, and CD40/CD40L interaction here is thought to be involved in control of intracellular pathogens such as *C parvum*.

A further problem in CD40L deficiency is that of susceptibility to liver disease and liver/gastrointestinal malignancy, with a possible link between chronic cryptosporidial infection and sclerosing cholangitis.<sup>19</sup> The European Society for Immunodeficiency database for CD40L deficiency currently contains clinical and molecular data from 113 affected males. The actuarial survival at 25 years is only 25%, and the incidence of liver disease by the age of 20 years is 80%.<sup>20</sup> There is so far little apparent genotype/phenotype correlation, and there is considerable intrafamilial variation in clinical phenotype, so predictions of severity or likelihood of liver disease are not possible.

Knowledge of the molecular basis of XHM allows accurate diagnosis not only in boys who have a typical phenotype or a positive family history but also in some cases of previously undefined hypogammaglobulinaemia. Several adult males diagnosed as affected by common variable immunodeficiency (CVID) have recently been found to have CD40L deficiency.

Table 1 X linked immunodeficiencies

Disorder (year of definition of molecular basis)	Chromosomal location	Gene	Function/defect	Diagnostic tests
X linked chronic granulomatous disease (1986)	Xp21	gp91 $phox$	Component of phagocytic NADPH oxidase-phagocytic respiratory burst	Nitroblue tetrazolium test gp91 $phox$ by immunoblotting Mutation analysis
X linked agammaglobulinaemia (1993)	Xq22	Bruton's tyrosine kinase (Btk)	Intracellular signalling pathways essential for pre-B cell maturation	Btk by immunoblotting or FACS analysis Mutation analysis
X linked severe combined immunodeficiency (1993)	Xq13	Common $\gamma$ chain ( $\gamma c$ )	Component of IL-2, 4, 7, 9, 15 cytokine receptors; T and NK cell development, T and B cell function	CD154 expression on activated T cells by FACS analysis Mutation analysis
X linked hyper-IgM syndrome (CD40 ligand deficiency) (1993)	Xq26	CD40 ligand (CD154)	Isotype switching, T cell function	CD145 expression on activated T cells by FACS analysis Mutation analysis
Wiskott-Aldrich syndrome (1994)	Xp11	WASP	Cytoskeletal architecture formation; immune cell motility and trafficking	WASP expression by immunoblotting Mutation analysis
X linked lymphoproliferative (Duncan's) syndrome (1998)	Xq25	SAP	Regulation of T cell responses to EBV and ? other viral infections	Mutation analysis ?SAP expression—under development
Properdin deficiency (1992)	Xp21	Properdin	Terminal complement component	Properdin levels

FACS, fluorescence activated cell sorting; IL, interleukin; NK, natural killer cell.

Although these individuals may not develop the life threatening complications of CD40 ligand deficiency, other affected family members could have a more severe phenotype. Carrier detection and prenatal or early diagnosis is therefore important for relatives at risk. Any affected male who has a matched family donor is now recommended for bone marrow transplantation, and, where possible, unrelated donor bone marrow transplantation is offered to affected boys who have any evidence of liver disease or other complications.

### Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome (WAS) is a rare X linked recessive disease characterised by immune dysregulation and microthrombocytopenia.<sup>21</sup> Clinical manifestations of the immune dis-

order include susceptibility to pyogenic, viral, and opportunistic infection, and eczema. There is usually progressive loss of T lymphocytes during childhood, with defects in proliferative and delayed type hypersensitivity responses, and deficient production of antibodies to both polysaccharide and protein antigens. Conventional supportive treatment for WAS includes prophylactic antibiotics and immunoglobulin, splenectomy for thrombocytopenia, and platelet transfusion in circumstances of life threatening haemorrhage.<sup>22 23</sup> Currently only allogeneic bone marrow transplantation can offer curative treatment for WAS.<sup>24</sup> Like many other primary immunodeficiencies, there is considerable heterogeneity in the severity of clinical manifestations. In mildly affected individuals, diagnosis based on clinical criteria has proved difficult.

Table 2 Autosomal recessive immunodeficiencies

Disorder (year of definition of molecular basis)	Chromosomal localisation	Gene	Function/defect	Diagnostic test(s)
<b>I. Severe combined immunodeficiency</b>				
Adenosine deaminase (ADA) deficiency (1983)	20q12-13	Adenosine deaminase	Enzyme in purine salvage pathway; accumulation of toxic metabolites	Red cell ADA levels and metabolites Mutation analysis
Purine nucleoside phosphorylase (PNP) deficiency (1987)	14q11	Purine nucleoside phosphorylase	Enzyme in purine salvage pathway; accumulation of toxic metabolites	Red cell PNP levels and metabolites Mutation analysis
Recombinase activating gene (RAG 1 and 2) deficiency (1996) Omenn's syndrome	11p13	RAG1 and RAG2	Defective DNA recombination affecting immunoglobulin and T cell receptor gene	RAG1 and RAG2 mutation analysis
T cell receptor deficiencies (1987)	11q23	CD3 $\gamma$ /CD3 $\epsilon$	T cell receptor function and signalling	CD3 fluorescence intensity Mutation analysis
Zap70 deficiency (1994)	2q12	ZAP70	T cell function; selection of CD8+ cells during thymocyte development	ZAP70 expression and activation Mutation analysis
JAK3 deficiency (T-B+NK- SCID) (1995)	19p13	JAK3	IL-2, -4, -7, -9, -15 receptor signalling; T and NK cell development; T and B cell function	JAK3 expression/activation Mutation analysis
IL-7 receptor deficiency (1998)	5p13	IL-7 receptor $\alpha$	Essential role in T cell development and function	IL-7 $\alpha$ FACs expression Mutation analysis
<b>II. Non-SCID</b>				
Leucocyte adhesion deficiency type 1 (1987)	21q22	CD11/CD18	Defective leucocyte adhesion and migration	CD11/CD18 expression by FACS analysis Mutation analysis
Chronic granulomatous disease (1990) (1990) (1988)	7q11 1q25 16p24	p47phox p67phox p22phox	Defective respiratory burst and phagocytic intracellular killing	p47phox, p67phox, p22phox expression by immunoblotting Mutation analysis
Chediak Higashi syndrome (1996)	1q42	LYST	Abnormalities in microtubule mediated lysosomal protein trafficking	Giant inclusions in granulocytes Mutation analysis
MHC class II deficiency (1993) (1998) (1995) (1997)	16p13 19p12 1q21 13q13	CIITA (MHC2TA) RFXANK RFX5 RFXAP	Defective transcriptional regulation of MHCII molecule expression	HLA-DR expression Mutation analysis
MHC class I deficiency (1994) (1999)	6p21 6p21	TAP2 TAP1	Defective peptide loading and presentation of HLA class I molecules	HLA class I expression
Autoimmune lymphoproliferative syndrome (ALPS) (1995)	10q24	APT1 (Fas)	Defective apoptosis of lymphocytes	Fas expression Apoptosis assays Mutation analysis
Ataxia telangiectasia (1995)	11q22	ATM	Cell cycle control and DNA damage responses	DNA radiation sensitivity Mutation analysis
Inherited mycobacterial susceptibility (1996) (1998) (1998)	6q23 5q31 19p13	Interferon $\gamma$ receptor IL-12 p40 IL-12 receptor $\beta$ 1	Defective $\gamma$ interferon production and signalling function	Interferon $\gamma$ receptor expression IL-12 expression IL-12 receptor expression Mutation analysis

FACS, fluorescence activated cell sorting analysis; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer cell; SCID, severe combined immune deficiency.

However, the identification of WASP (Wiskott-Aldrich syndrome protein), the gene defective in WAS, now allows definitive molecular diagnosis. To illustrate this, the clinical syndrome of microthrombocytopenia in X linked pedigrees (X linked thrombocytopenia or XLT) was originally thought to be a distinct genetic entity, but it has now also been shown to arise from WASP defects.<sup>25</sup> Furthermore, in parallel with the development of protein based assays for XLA, similar tests are now available for the rapid detection of WASP abnormalities using immunoblotting and FACS analysis.<sup>26 27</sup>

From a more basic perspective, the identification of the gene defect has allowed a greater understanding of the molecular pathogenesis of the WAS phenotype. The WASP gene encodes a 502 amino acid intracellular protein expressed exclusively in haematopoietic cells,<sup>28</sup> which belongs to a recently defined family of more widely expressed proteins involved in transduction of signals from receptors on the cell surface to the actin cytoskeleton. The WASP family proteins are organised into modular domains defined by sequence homology and binding interactions with other signalling molecules (reviewed in<sup>29</sup>). Experimental data suggest that there are intrinsic defects in cytoskeletal architecture organisation and WAS immune cell motility and trafficking that may explain the variety of immunological abnormalities. Recent studies have shown WASP to cluster physically with polymerised actin and to act as a direct effector molecule for the small GTPase protein Cdc 42, which is critical for regulation of cytoskeletal structures.<sup>30 31</sup> Studies directly visualising WAS cells have shown that both WAS dendritic cells and macrophages have major abnormalities in the distribution of peripheral filamentous actin and fail to develop polarised filopodial extensions in response to chemotactic attractants.<sup>32 33</sup> T cells from WAS patients show abnormalities of antigen receptor (CD3) stimulated proliferation (but not allostimulation), and both T and B lymphocytes have similar defects in the distribution of filamentous actin to those seen in dendritic cells and macrophages.<sup>34 35</sup> These data suggest that a major component of the WAS immunophenotype may be abnormal initiation and regulation of immune responses owing to defective immune cell trafficking and motility.

#### **X linked lymphoproliferative disease (Duncan's syndrome)**

X linked lymphoproliferative disease (XLP) is a rare disorder characterised by a dysregulated immune response to Epstein-Barr virus (EBV). First recognised over 25 years ago,<sup>36 37</sup> more than 80 kindreds have now been identified worldwide. The most usual presentation is with fulminant, often fatal acute EBV infection, but its phenotypic expression is highly variable. Other presentations include acquired hypogammaglobulinaemia, B cell lymphoma, aplastic anaemia, vasculitis, and lymphomatoid granulomatosis.<sup>38</sup> In addition, this same study reports that 27 of 272 individuals (10%) manifested an XLP phenotype without serological

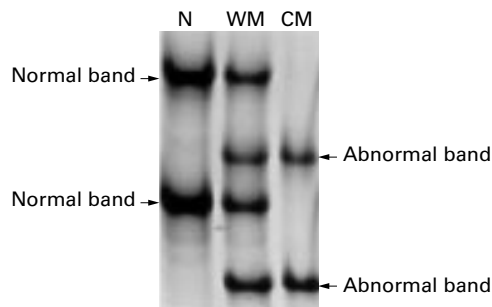
and in some cases genomic evidence of EBV infection. This, together with the variability in the clinical phenotype and the lack of a reliable diagnostic test, has made firm diagnosis of XLP extremely difficult. Historically, the diagnosis was based on a typical history with a suggestive pedigree, and sometimes the finding of raised anti-EBV antibody levels in obligate female carriers. In families where XLP has been considered likely, boys have been treated with long term immunoglobulin replacement in an attempt to protect them against EBV infection. However, this was not effective in at least one boy, who developed a haemophagocytic lymphohistiocytosis-like syndrome while receiving adequate doses of immunoglobulin.

The gene responsible for XLP was localised to Xq25 in 1990 by demonstration of an Xq25 deletion in an affected family,<sup>39</sup> but it was not until 1998 that the gene was finally identified as that coding for SAP (signalling lymphocyte activating molecule associated protein).<sup>40 41</sup> Signalling lymphocyte activating molecule (SLAM) is a B and T cell surface marker which forms a receptor-ligand pair, triggering of which coactivates B and T lymphocyte responses. SAP is a 15 kDa protein that is primarily expressed in T cells and acts as a negative regulator of SLAM interactions. Mutations of SAP in XLP patients are postulated to dysregulate interactions between SLAM molecules on the surfaces of T and B cells, and result in uncontrolled B cell proliferation. Mutations in the SAP gene have so far been demonstrated in 13 males affected by XLP. However, there are still several families thought to carry XLP in whom no SAP mutations have been found, and the possibility remains that a second gene is involved.

Identification of the gene responsible for XLP allows accurate diagnosis by mutation detection, so that boys found to be affected can be recommended for bone marrow transplantation before the onset of progressive EBV disease or other complications. As the gene consists of only four exons, SSCP analysis (fig 1) or direct sequencing of genomic or cDNA should be relatively straightforward. It is also likely that use of an SAP antibody will allow the development of a rapid protein based diagnostic assay. Unfortunately, lack of an identifiable mutation cannot at present exclude a diagnosis of XLP because of the uncertainty concerning a possible second genetic locus.

#### **Defects in the common $\gamma$ chain and JAK3 proteins**

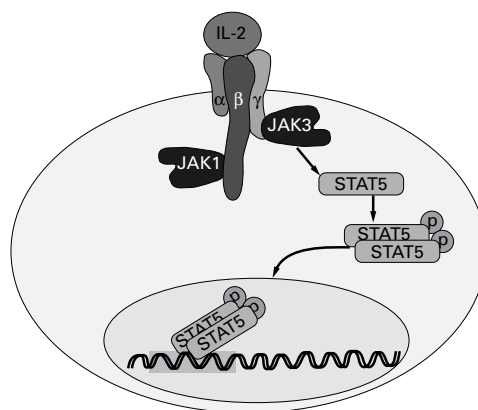
Of the different molecular defects that result in SCID (tables 1 and 2), the most common is X linked severe combined immunodeficiency (X-SCID) which arises from defects in the common  $\gamma$  chain ( $\gamma$ c).<sup>42</sup> The characteristic immunophenotype in X-SCID consists of absence of T and NK (natural killer) cell development, but normal B cell numbers, although these are dysfunctional (T-B+NK-SCID). A similar, though much rarer, clinical and immunological phenotype arises from an autosomal defect in the gene encoding the tyrosine kinase JAK3 (Janus associated



**Figure 1** Single stranded conformational polymorphism (SSCP) analysis of the *SAP* gene in a family with XLP shows that the affected boy (CM) has a band shift in exon 2 in comparison with a normal control (N). Subsequent sequencing of exon 2 in CM identified a C to G change at codon 54 which resulted in a tyrosine being replaced by a stop codon (Y54X) thus confirming the diagnosis of XLP. The boy's mother (WM) shows presence of both normal and abnormal bands by SSCP and is a carrier of the Y54X mutation.

kinase-3).<sup>43-44</sup> Details of the  $\gamma$ c/JAK3 signalling pathway are illustrated in fig 2. Data from in vitro studies and from "knockout" mice models have shown that functional interleukin (IL)-7/IL-7R and IL-15/IL-15R mediated signalling pathways are essential for normal T and NK cell development, respectively, thus explaining the lineage specific development defects present in X-SCID and JAK3 deficient patients. Abnormalities in IL-2 and IL-4 signalling may further explain the functional B cell defects.

Identification of  $\gamma$ c and JAK3 has had profound effects on the diagnosis and management of these conditions. Approximately two thirds of children with X-SCID have abnormal expression of  $\gamma$ c on the surface of mononuclear cells,<sup>45</sup> allowing confirmation of the molecular diagnosis by FACs analysis of peripheral blood mononuclear cells. In infants affected by T-B+NK- SCID who have normal  $\gamma$ c expression, further dissection of the signalling pathway can now be undertaken. IL-2 stimulation of mononuclear cells results in tyrosine phos-



**Figure 2**  $\gamma$ c is an essential component of the high affinity cytokine receptors for interleukin (IL)-2, -4, -7, -9 and -15. Upon activation of these receptor complexes by cytokine, the JAK3 molecule, which binds selectively to  $\gamma$ c, is itself activated and subsequently phosphorylates STAT5 (Signal Transducer and Activators of Transcription). Phosphorylated STAT5 dimerises and then translocates to the nucleus where it binds to specific sites to initiate transcriptional events.

phorylation of JAK3 at specific tyrosine based motifs. A monoclonal antibody directed against phosphotyrosine residues can be used to demonstrate JAK3 activation, so abnormalities in this signalling pathway can be detected at a protein level before genetic analysis. The variability in clinical presentation in these forms of SCID and especially in JAK3 deficiency again underlines the need to identify the molecular defect so that earlier referral for bone marrow transplantation can be made.

The ability to make a molecular diagnosis in utero in known carriers has also changed the treatment options for these types of SCID. Tissue typing can be carried out on DNA obtained from a CVS sample and used to identify potential donors. If a genotypically identical HLA match is available, transplantation can be undertaken almost immediately after birth before the onset of any infectious complications. If no related or unrelated donors are available, parental haplo-identical transplantation in utero may be an option. This has been attempted in a small number of SCID patients worldwide, with promising results.<sup>46-47</sup> Finally, establishment of the molecular defect opens up the possibility for treatment by somatic gene therapy. SCID caused by ADA deficiency was the first human disease to be treated in this way, although the results of initial trials were disappointing.<sup>48-51</sup> Advances in vector technology and stem cell transduction have now led to another wave of clinical gene therapy trials, and the first study of gene therapy for X-SCID is currently under way in Europe. Furthermore, correction of the immunological abnormalities by gene transfer in a JAK3 deficient mouse model<sup>52</sup> suggests that gene therapy for JAK3 deficiency may also be possible.

## Summary

Tables 1 and 2 highlight the enormous advances that have been made in the definition of the molecular defects underlying primary immunodeficiencies in the past decade. The identification of *SAP* as the gene defective in XLP now completes the molecular bases of all the recognised X linked syndromes. Of the autosomally inherited syndromes, only the genes for DiGeorge syndrome, hyper-IgE, and perhaps most importantly, common variable immunodeficiency remain to be elucidated.

The major clinical benefits of this information have primarily been in offering more accurate and rapid molecular diagnoses. The ability to make a molecular diagnosis also increases the options for earlier definitive treatments such as bone marrow transplantation and somatic gene therapy. Finally, as illustrated by the studies on the functions of WASP and the  $\gamma$ c/JAK-3 pathway, identification of the gene defect is the first step to understanding the molecular pathogenesis of the immunological abnormalities.

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