**Lec (2) Immunological disease**

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Major Categories of Antibody Deficiency

These are summarized in Table 1

ANTIBODY DEFICIENCY ASSOCIATED WITH ABSENT B CELLS

B-cell maturation beyond the pre-B-cell stage found in the bone marrow, requires signals received through the pre-B-cell receptor complex. The pre-B-cell receptor is composed of the µ chains, surrogate light chains (heterodimers of  constant region with V pre-), and the signal-transducing components Ig and Ig. The activities of the protein BTK (Bruton’s tyrosine kinase) and BLNK (B-cell linker protein) are also essential for the transduction of signals received via the B-cell (and pre-B-cell) receptors. Therefore, it is not surprising that mutations in each of these elements causes early-onset antibody deficiency associated with lack of circulating B cells.

Ninety percent of all such cases occur in boys due to mutation of the *BTK* gene, which maps to the X chromosome.

**Table1: Major Antibody and/or T-cell Deficiencies**

|  |  |  |
| --- | --- | --- |
| **Antibody Deficiency Diseases** | **Mutated Gene/Pathogenesis** | **Associated Features** |
| X-linked | *BTK* | Antibody deficiency and |
| agammaglobulinemia |  | B lymphopenia |
| Autosomal recessive | Mutations in genes for , Ig, Ig, | Antibody deficiency and |
| agammaglobulinemia | 5, or BLNK | B lymphopenia |
| X-linked hyper IgM | CD40 ligand | Lack of CD40 ligand on |
| syndrome |  | activated T cells. Failure |
|  |  | of Ig class-switching and |
|  |  | affinity maturation; low IgG/ |
|  |  | IgA, raised or normal IgM; |
|  |  | may develop neutropenia, |
|  |  | autoimmune cytopenias, |
|  |  | opportunistic infections, and |
|  |  | gastrointestinal and liver |
|  |  | pathologies |
| CD40 deficiency (a | *CD40* | Lack of CD40 expression |
| type of autosomal |  | on B cells. Other features |
| recessive hyper IgM |  | similar to CD40L deficiency |
| syndrome) |  |  |
| Hyper-IgM syndrome | *UNG* or *AID* | Low IgG and IgA, raised |
| (autosomal recessive) |  | IgM |
| Common variable | Unknown in most; *TACI* in  10%*,* | Antibody deficiency; |
| immunodeficiency | rarely *ICOS, CD19*, or *BAFFR* | may have autoimmunity, |
|  |  | lymphoproliferation, |
|  |  | systemic granulomata |
| Selective IgA deficiency | Most unknown; few due to *TACI* | Most remain healthy; |
|  | mutations | increase in autoimmunity, |
|  |  | atopy, celiac disease |
| IgG subclass deficiency | Unknown | If associated with specific |
|  |  | antibody deficiency, (see |
|  |  | text) may have recurrent |
|  |  | sinopulmonary infections |
| **T- and B-cell Immunodeficiencies** | **Mutated Gene/Pathogenesis** | **Associated Features** |
| Severe combined | See Table 5.6 for details | Lymphopenia, low serum |
| immunodeficiency |  | Igs, failure to thrive, severe |
| (SCID) |  | recurrent infections by |
|  |  | viruses, bacteria, and |
|  |  | parasites; fatal without bone |
|  |  | marrow transplant (BMT) |
| Omenn’s syndrome | Hypomorphic mutation of *RAG1,* | Variant of SCID; some T |
|  | *RAG2, Artemis, or IL7Ra* | and B cells may develop |
|  |  | but are oligoclonal. Features |
|  |  | include erythroderma, |
|  |  | lymphadenopathy, |
|  |  | hepatosplenomegaly, |
|  |  | eosinophilia. Outcome poor |
|  |  | without BMT |

*(continued)*

|  |  |  |
| --- | --- | --- |
| **Antibody Deficiency Diseases** | **Mutated Gene/Pathogenesis** | **Associated Features** |
| MHC class II deficiency | *MHC2TA, RFXANK, RFX5, RFXAP* :  SCID due to defective MHC class II transcription | Lack of MHC class II expression resulting in CD4 lymphopenia and severe failure of T-cell and B-cell function |
| MHC class I deficiency | *TAP1 or TAP2* | Lack of MHC class I expression on cells; CD8 Lymphopenia; present with bronchiectasis or vasculitis |

(Xp22). This condition is called X-linked agammaglobulinemia, which was the first immunodeficiency to be described in 1952 by Colonel Ogden Bruton. Mutations in the genes, encoding  5, Ig, Ig, and BLNK cause rare autosomal recessive forms of early-onset antibody deficiency with severe B lymphopenia.

ANTIBODY DEFICIENCY DUE TO DEFECT IN IMMUNOGLOBULIN ISOTOPE SWITCHING

During primary antibody responses, B cells initially produce IgM and later on in the response switch to the production of IgG, IgA, and IgE.

During the so-called immunoglobulin class-switching process, the heavy chain constant region changes while antigen specificity is maintained. Immunoglobulin class switch takes place within germinal centers contained within B-cell follicles of the secondary lymphoid organs. Another process that occurs within germinal centers is somatic hypermutation, which results in the sequential accumulation of point muta- tions in the Ig variable region gene. If the point mutation(s) result in increased bind- ing affinity to the inducing antigen, the B- cell blasts (centrocytes) survive, proliferate, and eventually give rise to memory B cells and plasma cells that secrete high-affinity

antibody (this process is called affinity maturation). Through these processes, memory B cells are generated within germina centers.

Defects in genes encoding molecules required for the above processes, which operate within germinal centers, result in a form of antibody deficiency with elevated (or normal) IgM levels but lack- ing IgG, IgA, and IgE. These conditions are called hyper-IgM (HIGM) syndromes. A key requirement for germinal center formation and function is the interaction of CD40 (belonging to the TNF-receptor superfamily) found on the surface of B cells with an “activation induced,” CD40- ligand (CD40L) protein expressed on the surface of CD4 lymphocytes. Mutations in the *CD40L* gene or the *CD40* gene result in X-linked (relatively common) and autoso- mal recessive (rare) HIGM, respectively. Patients with the CD40L deficiency suffer from recurrent bacterial infections typical of antibody deficiency. However, because CD40L function is required for optimal T-cell immunity, they also suffer from opportunistic infections characteristic of T-cell deficiency. About a third of patients with CD40L deficiency develop *Pneumocys- tis pneumonia*. Infections with cryptosporio- dosis, toxoplasmosis, and nontuberculous

mycobacteria also occur in this condition. These opportunistic infections can be ex- plained on the basis that the interaction of CD40L on activated T cells with CD40 ex- pressed on the surface of macrophages and dendritic cells, which in turn undergo matu- ration and activation, is required for the opti- mum expression of antimicrobial immunity. A high proportion of CD40L-deficient patients develop progressive liver dam- age (sclerosing cholangitis), probably the result of cryptosporidial infection of the

bile ducts.

Defects in the RNA-editing enzymes, activation-induced cytidine deaminase (AID), and uracil-DNA glycosylase (UNG) result in two further types of HIGM syn- dromes, which are defective class switch- ing and affinity maturation.

Signaling through CD40, which belongs to the TNF-receptor superfamily, depends on the activation of the inhibitor of  kinase (IKK) complex, resulting in the induction of NFB. Hypomorphic mutations of the gamma subunit of the IKK complex, which is called *NEMO* (NFB essential modu- lator), impairs NFB activation. Patients with mutations in *NEMO* develop a com- plex immunodeficiency, which includes features of the HIGM syndrome.

COMMON VARIABLE IMMUNE DEFICIENCY

Most patients with primary antibody deficiency are collected under the heading “common variable immune deficiency,” which is a condition characterized by low serum IgG and IgA and a variable decrease in IgM and the impaired production of specific antibodies following natural microbial exposure or immunization. The estimated prevalence of CVID is between 1 in 10,000 and 1 in 50,000. Clinically, CVID is dominated by the effects of antibody deficiency. About 20 percent of patients

with CVID develop autoimmune disor- ders (arthritis, cytopenias, endocrinopa- thies). Some patients with CVID develop noncaseating sarcoidlike granulomata infiltrating various organs (lungs, liver, spleen, skin). The mechanisms underlying autoimmunity and granulomatous disease in CVID are unknown.

The immunological phenotype of CVID is heterogeneous with documented defects in B-cell survival, generation of B memory cells, and in vitro B- and T-cell activation. About 10 percent of cases of CVID are familial, with a predominance of autosomal dominant or autosomal reces- sive inheritance. CVID or selective IgA deficiency can affect different members of the same kindred. Recently, a number of gene defects have been identified in CVID patients, accounting for about 10–15 per- cent of the total patient pool.

The commonest defect (in approxi- mately 10% of CVID patients) is a mutation of the gene *TACI* (transmembrane activator and calcium modulator and cyclophilin ligand interacter). *TACI*, which belongs to the TNF-receptor superfamily, is a ligand for the cytokines, BAFF (B-cell-activat- ing factor of the TNF family) and APRIL (a proliferation-induced ligand), which induce immunoglobulin class-switch recombination.

Mice deficient in BAFF or its recep- tor have impaired B-cell development and antibody deficiency. TACI−/− mice have reduced serum IgA and IgM levels, reduced antibody responses to T-cell- independent antigens, and tend to develop autoimmunity and B lymphoprolifera- tion. Mutations in *TACI* have been found in CVID patients and their relatives, with selective IgA deficiency, indicating variable penetrance of this gene defect. In the majority of currently documented

patients, *TACI* mutations affect only one allele, indicating a dominant negative effect of the mutated gene. A possible explana- tion is that *TACI*, like other members of the TNF-receptor family, undergoes ligand- independent preassociation and function as multimeric units. Thus, incorporation of a mutated *TACI* chain in this multimeric complex may disrupt ligand binding or signal-transducing capacity. Recent stud- ies have found that family members of CVID patients possessing heterozygous *TACI* mutations may have completely nor- mal serum immunoglobulin levels and “in vitro” B-cell function. This leads to the con- clusion that the development of antibody deficiency in those carrying heterozygous *TACI* mutations may depend on modifier genes or environmental factors.

ICOS (inducible co-stimulating recep- tor) is a co-stimulatory T-cell molecule that induces cytokines required for sup- porting class-switch recombination, Ig production and terminal B-cell differentia- tion. ICOS−/− and ICOS ligand−/− mice exhibit defective germinal center formation and antibody production. Mutations in the *ICOS* gene account for about 1 percent of CVID patients.

A single CVID patient was identified to have a mutation on the gene encoding the BAFF receptor, a finding that could be pre- dicted from observations in BAFF−/− mice.

Finally, CD19 deficiency has been described in two families with CVID. CD19 is a B-cell accessory molecule that is required for B-cell activation, proliferation, and hence B-cell development. CD19−/− mice exhibit hypogammaglobulinemia and poor antibody responses to protein antigens.

In the case of the large majority of patients with CVID, the underlying molec- ular defect is unknown.

IgA DEFICIENCY

IgA deficiency is characterized by reduced (<0.07 g/L) or absent serum IgA levels. IgA deficiency is the commonest form of primary antibody deficiency and affects about 1 in 700 Caucasians. IgA deficiency is rare in some racial groups (Japanese, Africans). The majority of IgA- deficient individuals remain free of infec- tion due to the ability of IgG and IgM to compensate for the lack of IgA. Long-term studies have shown that a small propor- tion of IgA-deficient patients develop recurrent sinopulmonary or gastroin- testinal infections. Most infection-prone IgA-deficient patients have concomitant IgG2 subclass deficiency and a selective inability to produce antibodies against bacterial capsular polysaccharides. IgA deficiency is associated with an increased incidence of atopy, celiac disease, and a range of autoimmune diseases, including arthritis, “lupus-like” syndrome, autoim- mune endocrinopathies, and autoimmune cytopenias.

IgA-deficient patients with serum lev- els below 0.07 g/L are at the risk of devel- oping anti-IgA antibodies after receiving blood products. Such individuals are at risk of developing anaphylaxis on receiv- ing blood products.

IgA deficiency and CVID can differ- entially affect members of the same kin- dred. Rarely, IgA deficiency can precede the development of CVID. Therefore, in some instances, the molecular mechanisms underlying CVID and IgA deficiency may be identical. TACI deficiency can cause IgA deficiency in some family members while others develop CVID. However, the molec- ular basis of IgA deficiency in most cases is largely unknown.

Genetic analysis of kindred with CVID and IgA deficiency have highlighted the

**Table 2:** Causes of T-Cell Deficiency

Primary (inherited) See Table 3 and text

Secondary

1. Viral-induced HIV

Measles (transient)

1. Iatrogenic Irradiation

BMT until engraftment is complete

Chemotherapy for malignancy

Immunosuppressive therapy

1. Thymoma
2. Lymphoma
3. Severe renal or liver failure

Idiopathic CD4 cell deficiency (cause unknown Idiopathic

T-cell deficiency. These viruses are not a problem in adults as they have residual protective antibody responses generated by primary infection or immunization. Adults with T-cell deficiency are typically affected by the reactivation of latent viruses (e.g., cyto- megalovirus, *Herpes simplex*), which can produce life-threatening disseminated infections.

1. Fungal infections: T-cell-deficient pa- tients are typically susceptible to fungal infections.
   1. *Pneumocystis giroveci* causes intersti- tial pneumonia, which is pathogno- monic for T-cell deficiency;
   2. Mucocutaneous infection with

*Candida*;

* 1. Systemic infections with filamentous fungi (e.g., *Aspergillus fumigatus*);
  2. Meningitis or systemic infection caused by *Cryptococcus neoformans.*

Intracellular bacterial infection is a particular problem in T-cell-deficient patients. These patients are highly susceptible to infection with *M. tuberculosis* or reactivation of latent tuberculosis. They are also suscep tible to disseminated infections with poorly pathogenic mycobacteria (e.g., non tuberculous mycobacteria, BCG).

1. Infants with T-cell deficiency are usually lymphopenic and fail to thrive (i.e., fail to maintain normal rates of growth in height and weight).
2. Infants with SCID may develop der- matitis and hepatosplenomegaly due to graft-versus-host disease caused by maternal lymphocytes that have crossed the placenta.
3. Malignancies: T-cell-deficient indi viduals are prone to develop a range of malignancies where viral infection acts as a co-factor (e.g., Epstein-Barr virus [EBV-] induced non-Hodgkin’s lymphoma, Kaposi’s sarcoma where human herpes virus 8 is a co-factor). There is also an increase in cutaneous malignancies occurring in an individ- ual exposed to significant amounts of ultraviolet light (basal-cell carcinoma and squamous carcinoma).

**Major Categories of Combined Immunodeficiency**

SEVERE COMBINED IMMUNODEFICIENCY

SCID comprises a group of inherited diseases characterized by a severe deficit in T-cell development and function with variable defects in B-cell and natural killer or NK cell development. SCID leads to death within the first two years of life, unless patients are rescued by hematopoietic stem cell transplantation (HSCT). These are rare disorders with an estimated frequency between 1 in 50,000 and 1 in 100,000 live births.

Table3: Classification of SCID

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of SCID** | **Relative Frequency (%)** | **Inheritance** | **Cells Affected** | **Defective Gene** |
| Reticular | <1 | AR | T, B, NK, | ? |
| dysgenesis |  |  | Leucocytes, |  |
|  |  |  | platelets |  |
| T − B − SCID | 10 | AR | T, B | *RAG1/2* |
|  | 10 | AR | T, B | *Artemis* |
| T − B  SCID | 50 | XL | T, NK | *IL2R6* |
|  | 10 | AR | T, NK | *JAK3* |
|  | 1 | AR | T, NK | *IL7RA* |
|  | <1 | AR | T | *CD45* |
|  | <1 | AR | T | *CD36,CD3E* |
| T − B − NK − SCID | 20 | AR | T, B, NK | *ADA* |
| AR, antosomal recessive; XL, X-linked | | | | |

Classification of SCID

The classification of SCID, based on immunological and genetic criteria, is summarized in Table 5.6.

SCID: Clinical Features

These patients typically present in the first year of life with failure to thrive and recurrent infections caused by bacterial, viral, and fungal pathogens. Infections typically affect the respiratory and gastrointestinal systems. The infections may be caused by common pathogens (adenovirus, respiratory syncytial virus, parainfluenza virus), as well as by opportunistic organisms of low-grade virulence (*Candida*, *Pneumocystis carinii*, cytomegalovirus). Live vaccines such as BCG can lead to disseminated life-threatening infections. The persistent infections developing in SCID patients rapidly lead to malnutrition, growth impairment, and early death. Because of the patient’s inability to reject allogeneic cells, graft- versus-host disease (GvHD) can be caused by transplacentally acquired maternal lymphocytes or by allogeneic

cells following blood transfusion. GvHD manifests as skin rashes or hepatosplenomegaly and lymphadenopathy.

The absence of tonsils or other lymphatic tissue may be evident and radiographic studies may reveal thymic-hypoplasia. Lymphopenia (absolute lymphocyte count

 3 × 109/L in the first year of life) is a characteristic feature seen in over 80 percent of patients with SCID. (Therefore, SCID needs to be excluded in any infant with unexplained lymphopenia.)

**Immunological and Molecular Classification of SCID**

SCID can be classified in two groups based on the blood lymphocyte phenotype.

* Patients lacking T cells with normal or increased B cells: T−B+ SCID
* Patients lacking T and B cells: T−B−SCID

Defects in one of four functionally related genes causes T−B + SCID. X-linked SCID, which is the commonest form, is due to a mutation of the gene encoding the IL-2 receptor  chain, which is the signal-transducing chain common to the receptors for six cytokines (IL-2, IL-4, IL- 7, IL-9, IL-15, and IL-21). The absence of responses to these cytokines causes defects in a broad range of T- and B-cell functions. IL-7 is required for early stages of T-cell development. Lack of response to this cytokine results in T lymphopenia. IL-15 is required for NK-cell development and its lack results in the failure of NK-cell development. Signal transduction through the aforementioned cytokine receptors involves the interaction of the common  chain with the tyrosine kinase JAK3. This explains why mutations of the *JAK3* gene result in an autosomal recessive form of SCID, with a phenotype similar to X-linked SCID. Mutations of the α chain of IL-2 or IL-7 receptors result in two rare forms of SCID.

T- and B-cell receptors consist of invariant signal-transducing elements combined with elements that make up the variable regions, which contribute to the antigen- binding portion of the receptor. The gene recombination required for generating these receptors requires the function of the product of recombination activating genes 1 and 2 and a number of proteins that are required for DNA repair (DNA-PKcs, KU70, KU80, XRLC4, and DNA-IV). In

mice, mutations in any one of these genes produces analogues of SCID.

In humans, T−B−SCID is most common (50 percent of total) caused by mutations of the recombinase-activating genes, *RAG1* or *RAG2*. RAG1 and RAG2 are enzymes responsible for introducing double- stranded DNA breaks, which initiate V(D)J gene rearrangements, required for generating T- and B-cell receptors for antigen. Without normal RAG1 and RAG2 function, T- and B-cell development is arrested early in ontogeny, producing T−B−SCID.

Hypomorphic mutations of *RAG1* or *RAG2* result in a leaky form of SCID called Omenn’s syndrome. In Omenn’s syn drome, a few T- and B-cell clones may be generated but the full T- and B-cell repertoire fails to develop. The few T- and B- cell clones that leak through may undergo secondary expansion. As a result, patients with Omenn’s syndrome may not be markedly lymphopenic but the lymphocyte repertoire is oligoclonal and severe immuno- deficiency is the outcome.

T- and B-cell antigen receptors are assembled from the recombination of variable region V(D)J and constant region genes. A protein called ARTEMIS is required for DNA repair, including the repair of DNA breaks generated during V(D)J recombination. Mutation of the gene encoding ARTEMIS results in a rare form of T−B−SCID. These patients also exhibit increased sensitivity to ionizing radiation. About 15 percent of SCID cases are caused by deficiency of adenosine deaminase (ADA), an enzyme required for the salvage of nucleotides within lymphoid cells. The lack of ADA causes the accumulation of toxic metabolites of adenosine (deoxy- adenosine and deoxy-ATP) within lymphoid cells, resulting in their demise. ADA deficiency results in profound lymphopenia affecting T cells, B cells, and NK cells. Rarely, mutations of ADA causing milder forms of enzyme deficiency lead to a milder form of combined immunodeficiency presenting at a later stage in life. Purine nucleoside phosphorylase (PNP) is an enzyme required for purine salvage within lymphocytes, and PNP deficiency causes a milder phenotype of SCID than seen in ADA deficiency. SCID due to PNP deficiency not treated with

HSCT is fatal in childhood.

Mutations in proteins required for normal functioning and signal transduction through the T-cell receptor (TCR) cause rare forms of SCID. Mutations of the tyrosine phosphatase, CD45, which helps to initiate signaling by the TCR, results in T−B+ SCID in humans. Mutation of components of CD3-complex (CD3 , , and ) result in a SCID phenotype. During signal transduction via TCRs, the protein tyrosine kinases Lck and ZAP70 are required for phosphorylation of ITAMs on the intracytoplasmic segment of the TCR. Deficiency of either of these kinases results in rare forms of SCID.

TCRs of CD8 cells recognize antigenic peptides that are complexed to MHC class I antigens, and TCR of CD4 cells recognize antigen bound to MHC class II on the surface of antigen-presenting cells. Cell- surface expression of MHC class I molecules fails if either of the two transport ers of antigenic peptides (TAP1 or TAP2) is lacking. TAP1 and TAP2 help to transfer peptides from the cytosol into the endoplasmic reticulum, for subsequent loading onto newly synthesized MHC class I mol ecules. In the absence of peptide loading, MHC class I molecules are degraded before reaching the cell surface. In the absence of MHC class I antigen expression, CD8 cell function is deficient, and these cells are not generated within the thymus. The result- ing immunodeficiency is milder than SCID and often presents in later life. Paradoxically, viral infections are not a problem in these patients. Some MHC class I deficient patients develop progressive bronchiectasis, while others develop vasculitis affecting the face and upper respiratory tract. It has been postulated that vasculitis seen in these patients may be due to self-destruction of vascular endothelial cells by the unrestrained cytotoxicity of NK cells.

In contrast, MHC class II deficiency results in a profound failure of CD4 cell

functions. Lack of thymic CD4+ CD8− cell selection for survival results in peripheral CD4 lymphopenia. Because CD4 function is required for normal cell-mediated immunity, as well as antibody production, MHC class II deficiency results in a severe form of SCID with a fatal outcome. MHC class II deficiency is due to a mutation in one of four transcription factors (RFXAP, CIITA, RFX5, RFXANK), which regulate MHC class II expression.

TREATMENT OF SCID

**Hematopoietic Stem Cell Transplantation**

**Untreated SCID is invariably fatal in** early infancy. Once a diagnosis of SCID is confirmed, irrespective of the molecular diagnosis, HSCT from a human leucocyte antigen (HLA-) identical or haplo-identical family donor is the treatment of choice. Treatment of SCID with HSCT before 3.5 months of age results in good immune reconstitution and 95 percent survive long term. Delay in treatment, or the occurrence of infection, impairs outcome. Infection and GvHD are the main complications follow- ing HSCT. North American and European data indicate that long-term survival after transplants from HLA-matched unrelated donors was close to 60 percent. Review of European data between 1968 and 1999 indicates the progressive improvement of outcome, which is mainly because of better prevention of GvHD and the treatment of infection. Analysis of the outcome of European and U.S. bone marrow transplant programs for the treatment of SCID is ongoing and will be regularly reported.

Gene Therapy for SCID

Long-term immune reconstitution has been achieved in patients with SCID caused by the common -chain deficiency or ADA deficiency, using gene therapy This was achieved by ex vivo gene transfer to hematopoietic stem cells isolated from the patient’s bone marrow. These gene- reconstituted stem cells were retransfused into the patient. To date, gene therapy has been restricted to patients without an HLA- matched family donor.

Several cases of leukemia have occurred among -chain-deficient patients who received gene therapy. In these cases, the retroviral vector had integrated close to the LMO2 proto-oncogene in the leukemia clone, leading to aberrant transcription and expression of LMO2. Because of this setback, clinical trials of gene therapy for SCID are being carefully evaluated, and more experience is required before the definitive role of gene therapy in SCID is established.

**DiGeorge’s Syndrome (Thymic Aplasia)**

DiGeorge’s syndrome (DGS) is secondary to a hemizygous deletion of the short arm of chromosome 22 (DEL 22q. 11.2). This chromosomal defect causes a complex inherited syndrome characterized by cardiac malformations, thymic hypoplasia, palatopharyngeal abnormalities with associated velopharyngeal dysfunction, hypoparathyroidism, and facial dysmorphism. The 22q deletion has an incidence of approximately 1 in 2,500 live births. The associated clinical phenotype is highly variable. About 20 percent of individu- als with 22q deletion have thymic aplasia, resulting in T lymphopenia and impaired CMI. In most such cases, the degree of T lymphopenia is modest (partial DGS) and almost complete restitution of the T-cell repertoire and function occurs by two years of age. Therefore, infections characteristic of T-cell deficiency are rare in these indviduals. A minority of infected individuals

(<1 percent) exhibit profound T lympho- penia, associated with opportunistic infec- tions and a poor outlook unless rescued with fetal thymic transplant.

The cardiac, velopharyngeal, thymic, and parathyroid abnormalities are due to the defective development of third and fourth pharyngeal arches during ontogeny. The 22q. 11.2 region contains the *TBX1* gene, which belongs to the T-BOX fam- ily of genes that incorporate proteins that regulate embryonic development. Patients with mutations in the *TBX1* genes also develop the clinical features seen in 22q.

11.2 deletion syndrome, suggesting that haplo-insufficiency of the *TBX1* gene may be responsible for the clinical features seen in those with a deletion of the 22q. 11.2 region.

**PHAGOCYTE DEFICIENCIES**

Neutrophils are the principal circulating phagocyte. During inflammation, neutrophils become activated and migrate into the tissues where they ingest, kill, and digest invading bacteria and fungi. Neutrophil function can be deficient because of a reduction in the number of circulating neutrophils (neutropenia) or due to inherited defects in neutrophil function, which are rare disorders.