Primary Immunodeficiency Disease

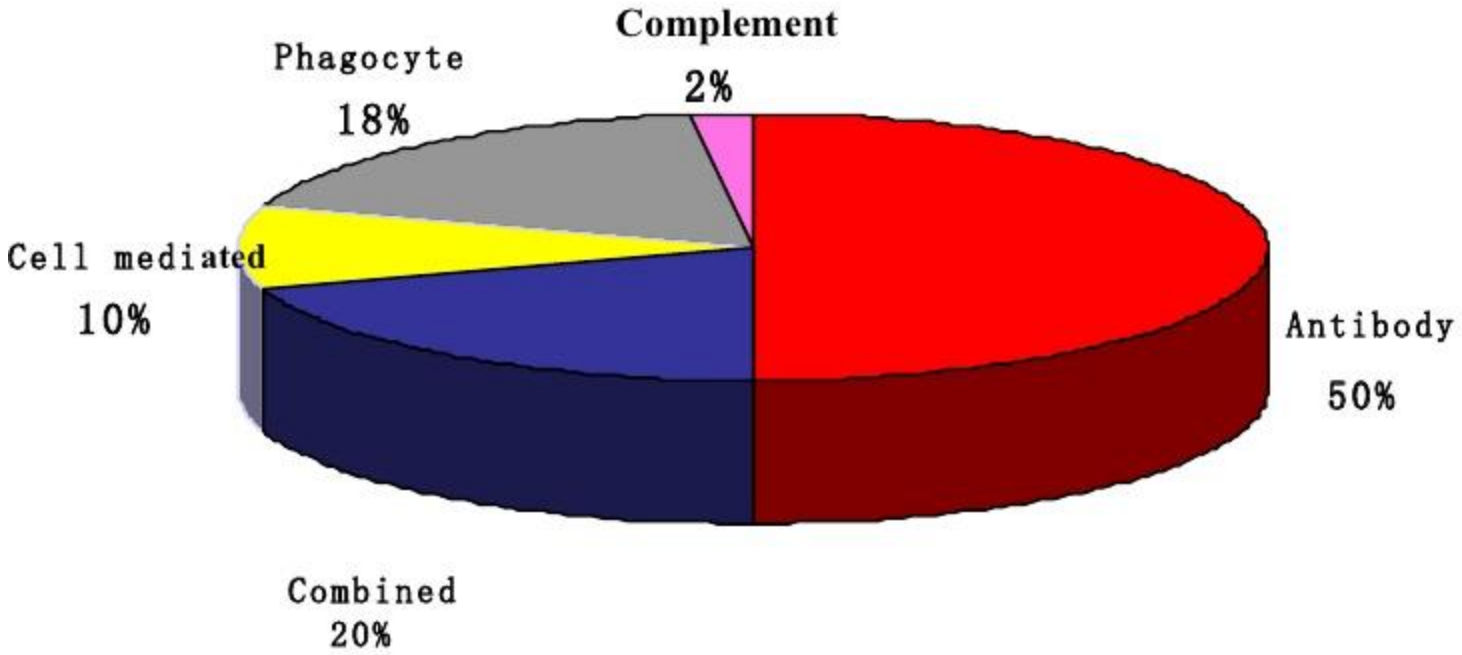
- A group of disorders characterized by an impaired ability to produce normal immune response. Most of these disorders are caused by mutations in genes involved in the development and function of immune organs, cells, and molecules.

- Clinical features ： Recurrent infection, high risk of autoimmune diseases, allergy and malignancy

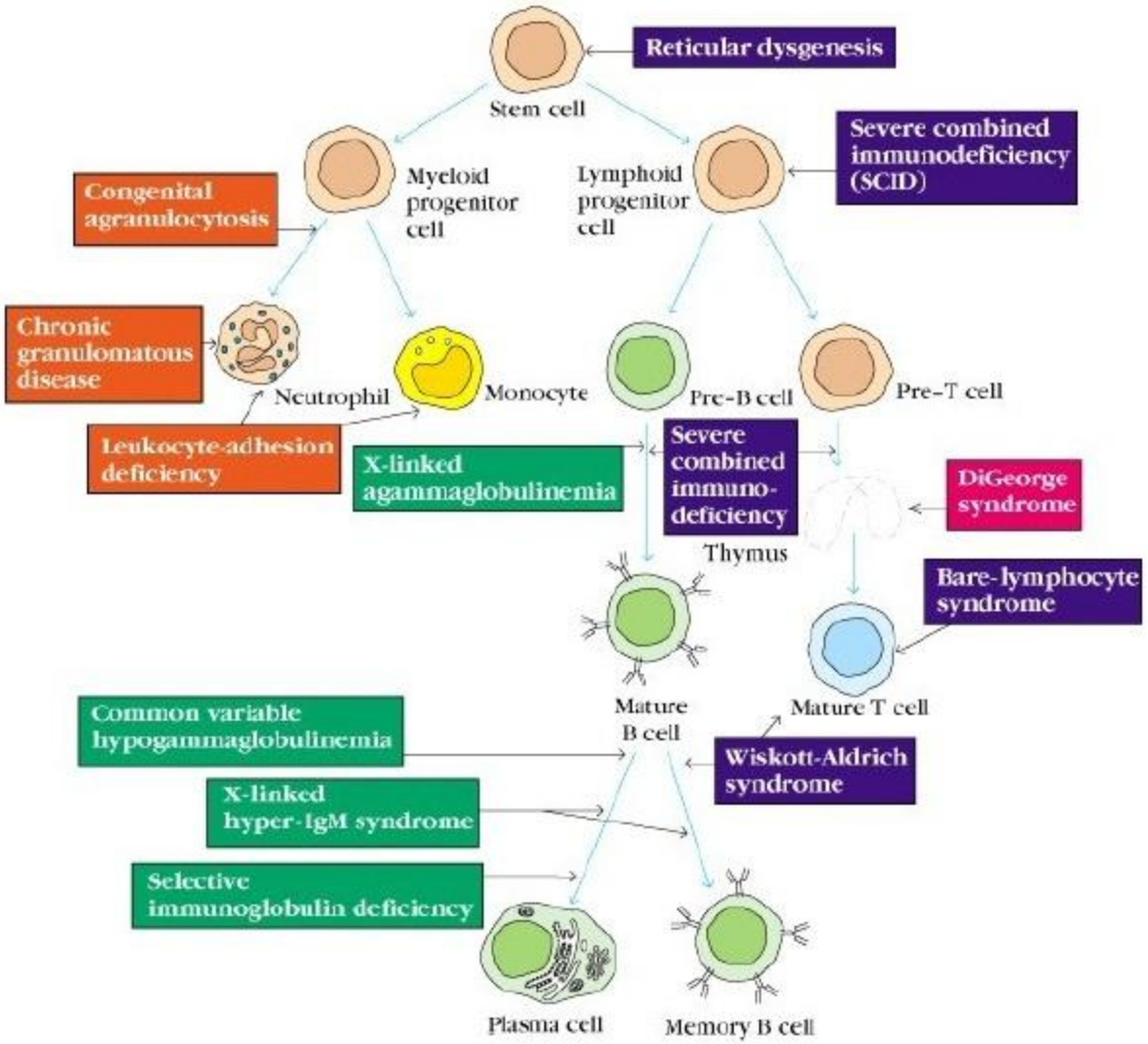
Prevalence

- **Most children with recurrent infections don't have primary immunodeficiency**
  - **90% have secondary cause**

Up to 2007 more then 200 kinds of PID reported



Distribution of PID


Reticular dysgenesis
Stem cell
Severe combined immunodeficiency (SCID)
Myeloid progenitor cell
Lymphoid progenitor cell
Congenital agranulocytosis
Chronic granulomatous disease
Neutrophil
Monocyte
Pre-B cell
Pre-T cell
Leukocyte-adhesion deficiency
X-linked agammaglobulinemia
Severe combined immuno-deficiency
DiGeorge syndrome
Thymus
Bare-lymphocyte syndrome
Mature B cell
Mature T cell
Common variable hypogammaglobulinemia
Wiskott-Aldrich syndrome
X-linked hyper-IgM syndrome
Selective immunoglobulin deficiency
Plasma cell
Memory B cell

Classification(new)

- **Combined Immunodeficiency (B and T cells)**
- **Predominantly antibody deficiency (B cells and Ab)**
- **Predominantly T-cell deficiency (T cells)**
- **Immunodeficiency syndromes**

- **Phagocyte deficiency (PMN's)**
- **Complement deficiency**
- **Others**

Note:-- **There is significant overlap among syndromes.**
--Great variability in expression of disorders for all categories from mild to severe/fatal.

Combined immunodeficiencies （ 1 ）

1. Severe combined immunodeficiency （ SCID ）

- X-linked (γc deficiency)
- Autosomal recessive (Jak3 deficiency)

T⁻B⁺

- RAG1/RAG2 deficiency
- Adenosine deaminase (ADA) deficiency
- Reticular dysgenesis

T⁻B⁻

Combined immunodeficiencies

(2)

2. Hyper-IgM syndrome

3. Purine nucleoside phosphorylase (PNP) deficiency

4. MHC class II deficiency

Clinical features of combined immunodeficiency

- Onset age at early infants(4 - 5 months)
- Recurrent infection with fungi, virus, bacteria, mycobacterium, protozoa
- Opportunistic infections
- Poor prognosis, early infant deaths
- Severe infection after live virus vaccine and BCG
- GVHD after blood transfusion
- High risk of malignancy

Common clinical manifestations PID

- **Infection recurrent**
  - ▼**Age >50 % younger than 3 yrs**
  - ▼**Location respiratory tract , GI tract…**
  - ▼**Pathogen**
  - ▼**Course**
- **Malignancy and autoimmune disease**
- **Tendency of inheritance <15yrs 80 % male**
- **Others**

Table 1. Characteristic infections of the primary immunodeficiencies			
component	primary pathogen	primary site	clinical example
T-cells	intracellular, bacteria viruses, protozoa, fungi,	non-specific	SCID, DiGeorge
B-cells	pneumococcus, streptococcus, haemophilus	lung, skin, CNS	IgG, IgM deficiency IgG, IgM deficiency
	enteric bacteria and viruses	GI, nasal, eye	IgA deficiency
phagocytes	Staphylococcal, Klebsiella Pseudomonas,	lung, skin, regional lymph node	Chronic granulomatous disease (CGD)
complement	neisseria, Haemophilus, pneumococcus, streptococcus	CNS lung skin	C3, Factors I and H, late C omponents

Predominantly antibody defects

- **Panhypogammaglobulinemia**

  X-linked agammaglobulinaemia（ Bruton disease ）

  Common variable immunodeficiency（ CVID ）

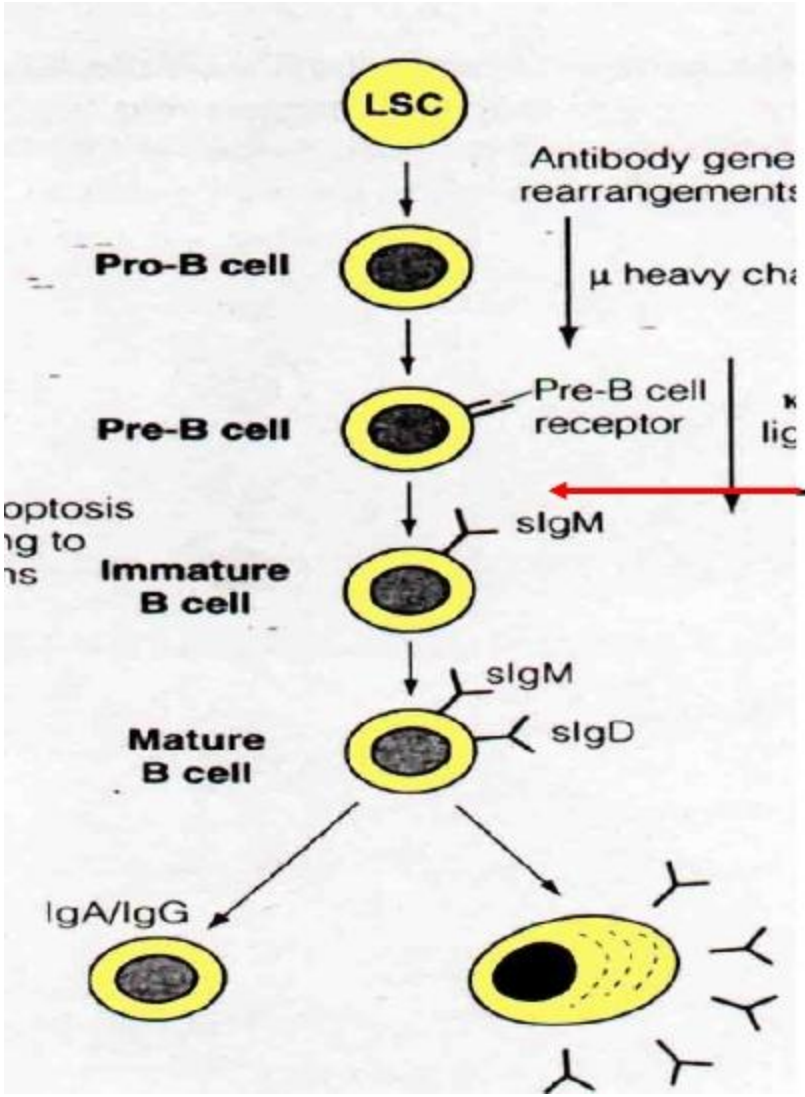
  Transient hypogammaglobulinaemia of infancy (ITHG)

- **Selective Ig deficiency**

  Ig heavy chain deficiency

  IgA deficiency

  Selective IgG subclass deficiency



—**Bruton disease**

— **mutations in btk**

—**maturation disorder**

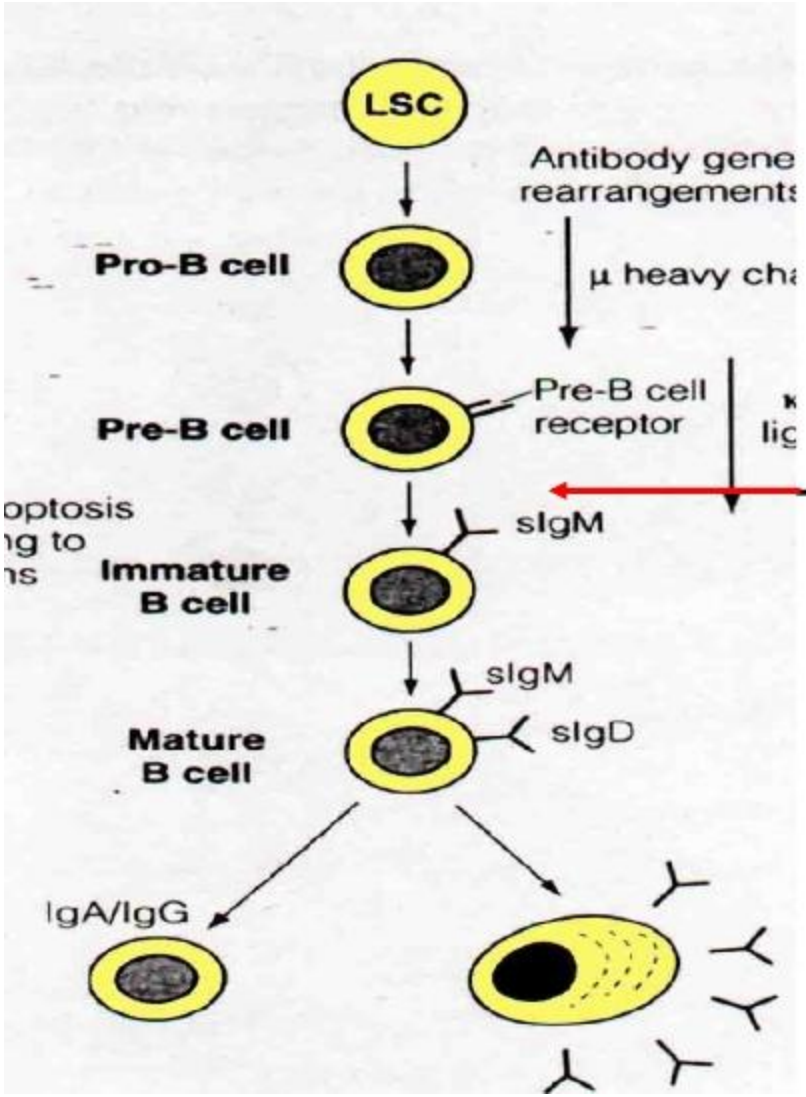
of pre-B cell

Predominantly antibody defects

Common clinical manifestations:

- **Recurrent bacterial infections (sepsis and meningitis)**
- **Viral ,fungal or protozoan infections rare**
- **Lymphatic system hypoplasia- tonsils, lymph node**

  （ except CVID ）
- **Autoimmune disease**



—Bruton disease

— mutations in btk

—maturation disorder

of pre-B cell

Predominantly antibody defects

Common clinical manifestations:

- **Recurrent bacterial infections (sepsis and meningitis)**
- **Viral ,fungal or protozoan infections rare**
- **Lymphatic system hypoplasia- tonsils, lymph node**

  （ except CVID ）
- **Autoimmune disease**

Predominantly antibody defects

Laboratory test

- **Serum Ig ↓ (< 3 ~ 4g/L)**
- **Natural antibody ↓ （hemagglutinin titers < 1:4）**
- **Common antibody ↓ , > 2 A , ASO < 1 :10**
- **Antibody responses to vaccine antigens ↓**
- **Circulating B cell （ CD_{19}^{+}、 CD_{20}^{+}）↓ ,**

  bearing Ig cell ↓

Immunodeficiency syndrome

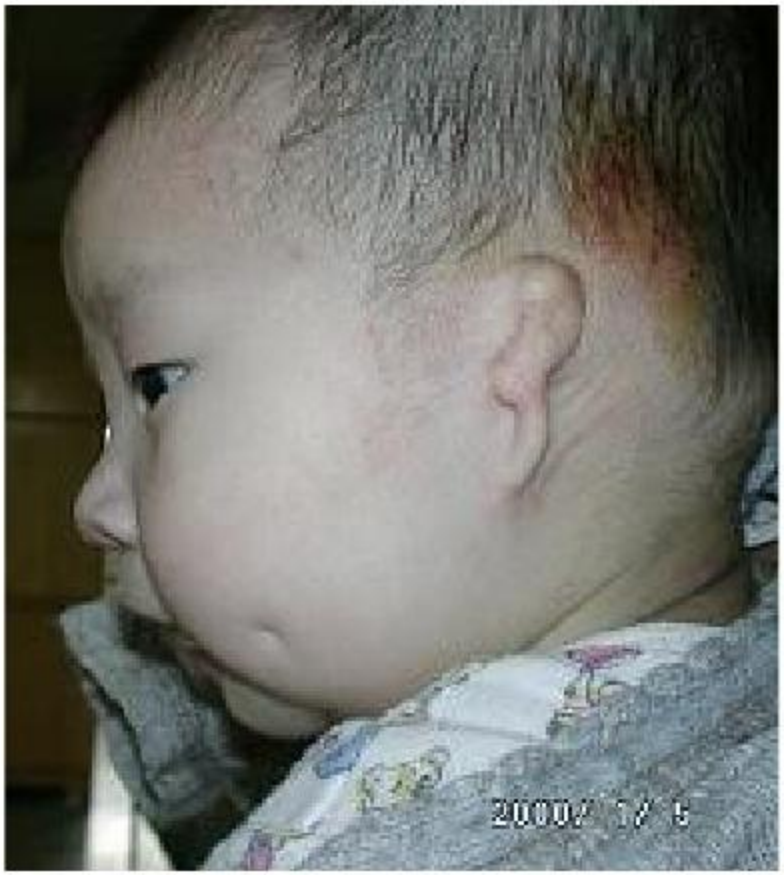
	deficiencies				
Destination	serum Ig	B-cells	T-cells	genetic defect	clinical findings
• Wiskott-Aldrich Syn	IgM↓	Normal	Progressive↓	XL Mutation in WAS	Thrombocytopenia eczema lymphoma
• Ataxia-Telangiectasia	IgA, E, G↓ IgM ↑	Normal	↓	ATM	Ataxia, telangiectasia
• DiGeorge Syn	Normal or ↓	Normal	↓or normal	Deletion of chromosome 22q11.2-pter	Hypoparathyroidism conotruncal defect abnormal facies

DiGeorge Syndrome

- **Deletion of chromosome 22q11.2**
  - **Defective development of 3rd and 4th pharyngeal pouches**
- **Absence of Thymus**
  - **Therefore low or absent T cells**
  - **No B cell abnormalities except in more severe forms.**
- **Associated Anomalies**
  - **Conotruncal Cardiac Defects**
    - **VSD**
    - **Tetralogy of Fallot**
    - **Interrupted Aortic Arch**
  - **Parathyroid Hypoplasia**
    - **Low Calcium**
    - **Tetany**

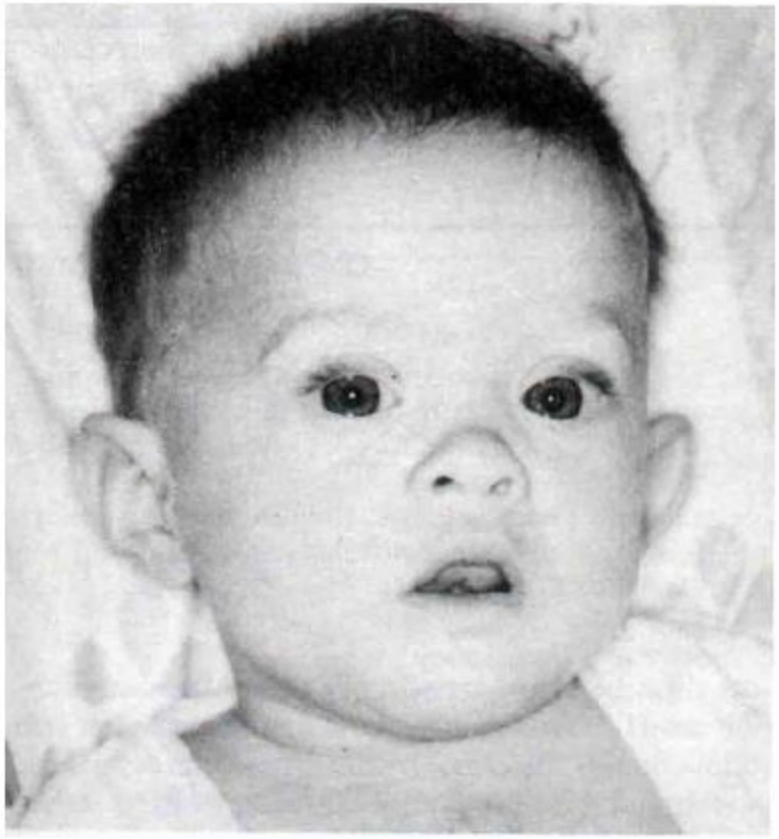
DiGeorge Syndrome

- **Other Anomalies**
  - **Cleft Palate**
  - **Velocardiofacial Syndrome**
  - **Esophageal abnormalities**
  - **Ocular anomalies**
  - **Renal anomalies**
  - **Increased incidence of Autoimmune disease**
- **Diagnosis – FISH**
  - **Will often have decreased CD3 T cells**
- **Treatment**
  - **IVIG and antibiotic prophylaxis**
  - **Should be on TMP/SFA for PCP prophylaxis**
  - **Thymic transplant or Bone marrow transplant**



DiGeorge anormaly

Facial features of children with DiGeorge syndrome



Hypertelorism

hooded eyelids

short philtrum with

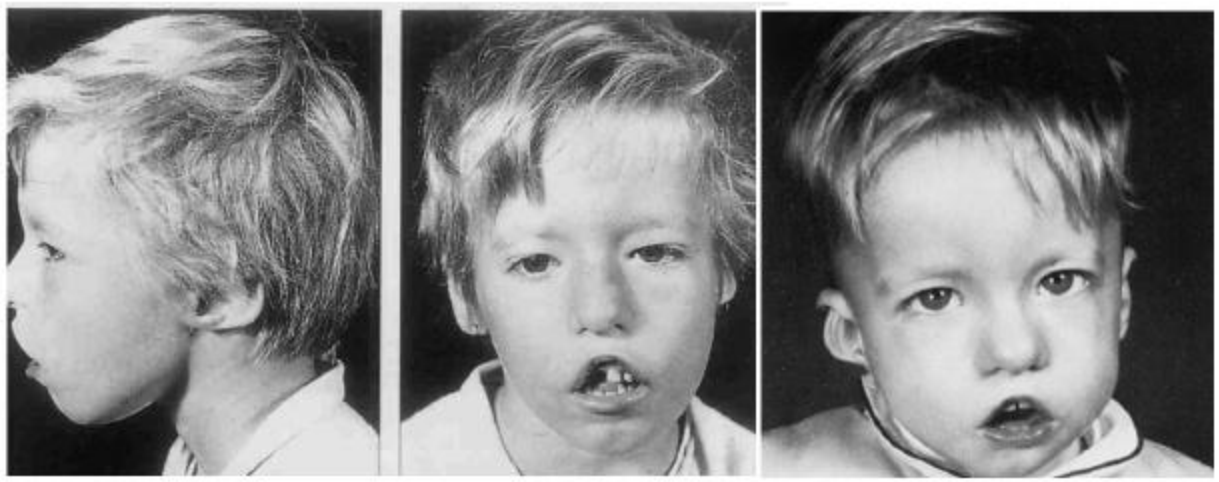
fish-mouth appearance ,

micrognathia

Low set ears

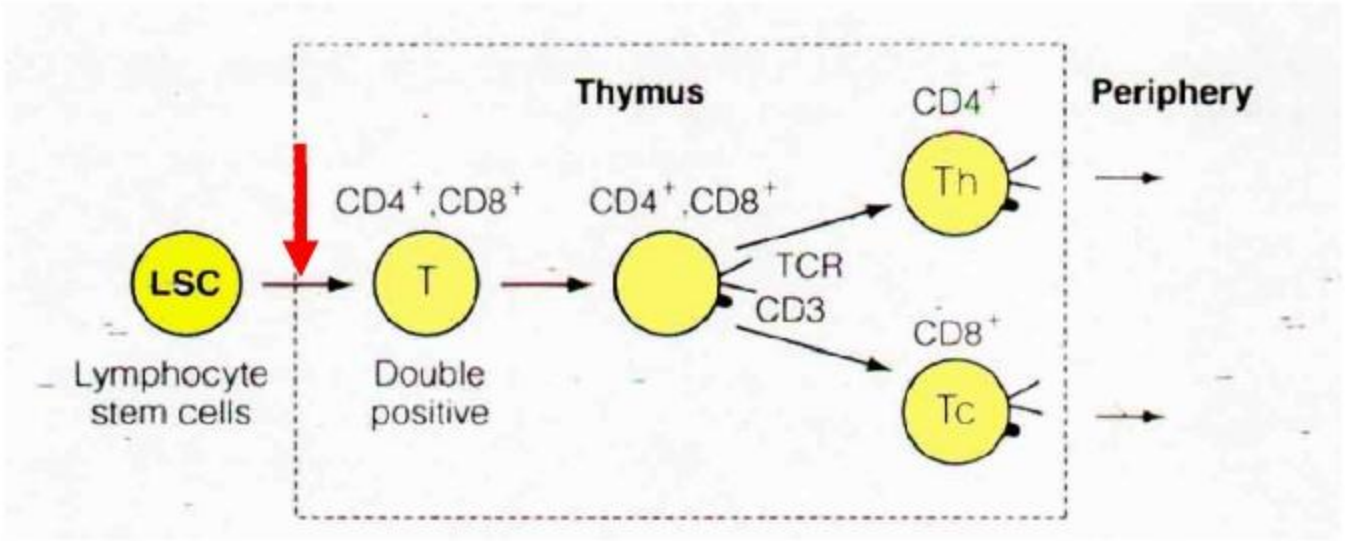
telecanthus with short

palpebral fissures



DiGeorge syndrome

DiGeorge Syndrome



The parents of D. George are very concerned. They wonder is there something wrong with him.

- **Is it normal to have so many infections?**
- **Could there be something wrong with his immune system?**
- **How are you going to figure this out?**
- **Does he need testing?**

Questions

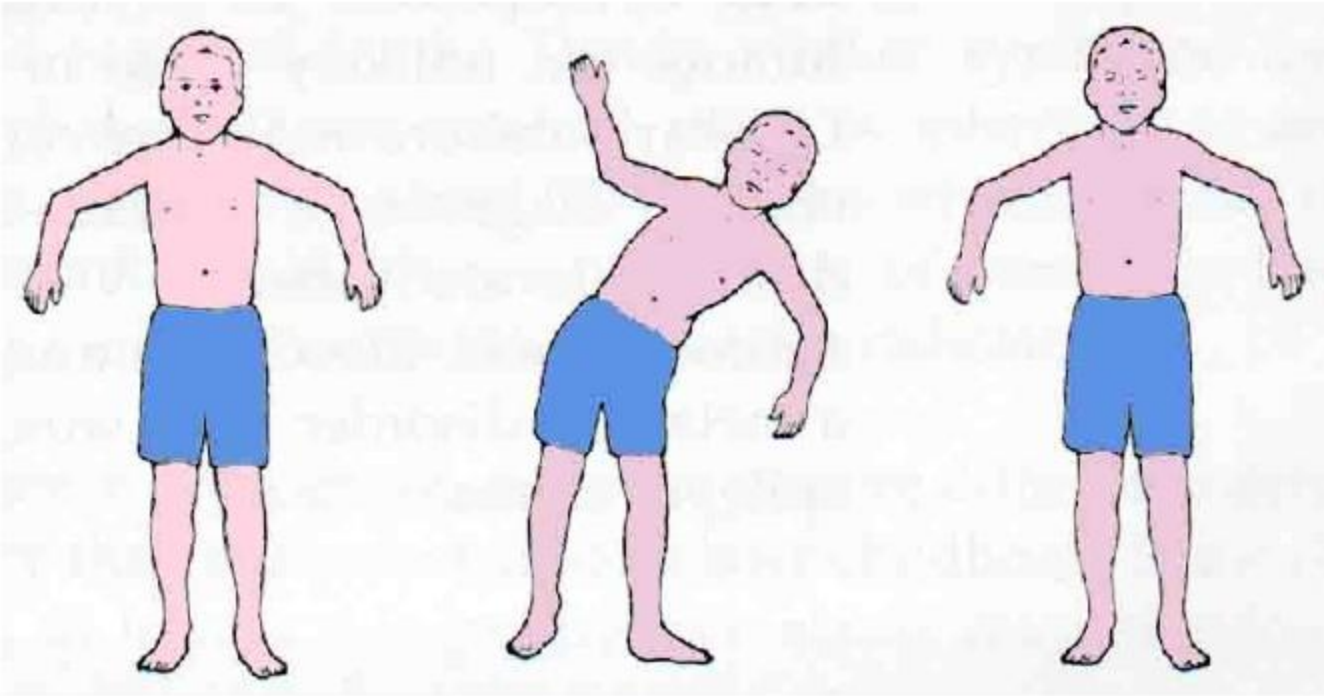
- What other information should we try to get from D. George and the family?
- Are there clues we could be missing in the history?
- Are there clues in the physical?

Wiskott-Aldrich Syndrome

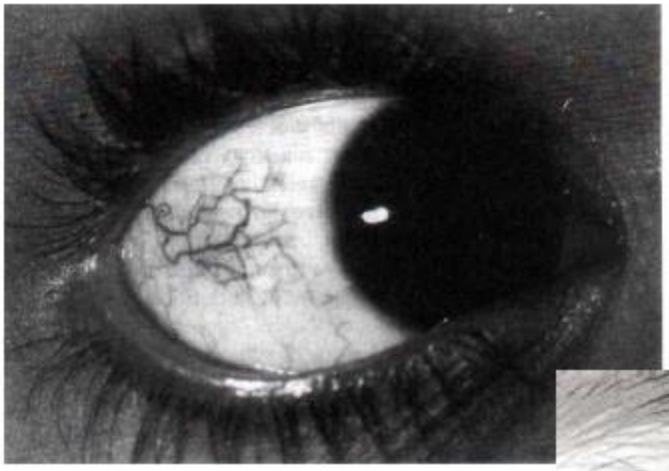
- X-linked Recessive
- Gene defect of WAS protein
- B and T cell dysfunction
- Triad of
  - Thrombocytopenia
  - Eczema
  - Recurrent pyogenic infections
- Treatment – Stem cell or Bone Marrow transplant
- Prognosis - Average life expectancy 11 years

Ataxia-Telangiectasia

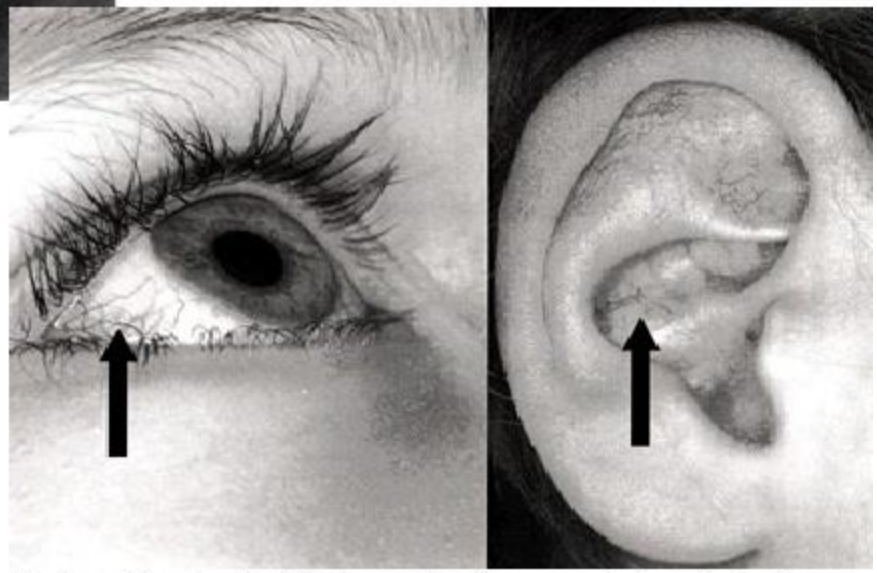
- Autosomal Recessive
- Have both B and T cell dysfunction
  - more characteristics of B cell dysfunction
- Associated Symptoms
  - Ataxia from early age – progressive
  - Telangiectasia develop after 2 yrs
  - High risk for various malignancies
  - Endocrine abnormalities – many with Diabetes
  - Liver Dysfunction
- Treatment – supportive
- Prognosis – death often in early childhood



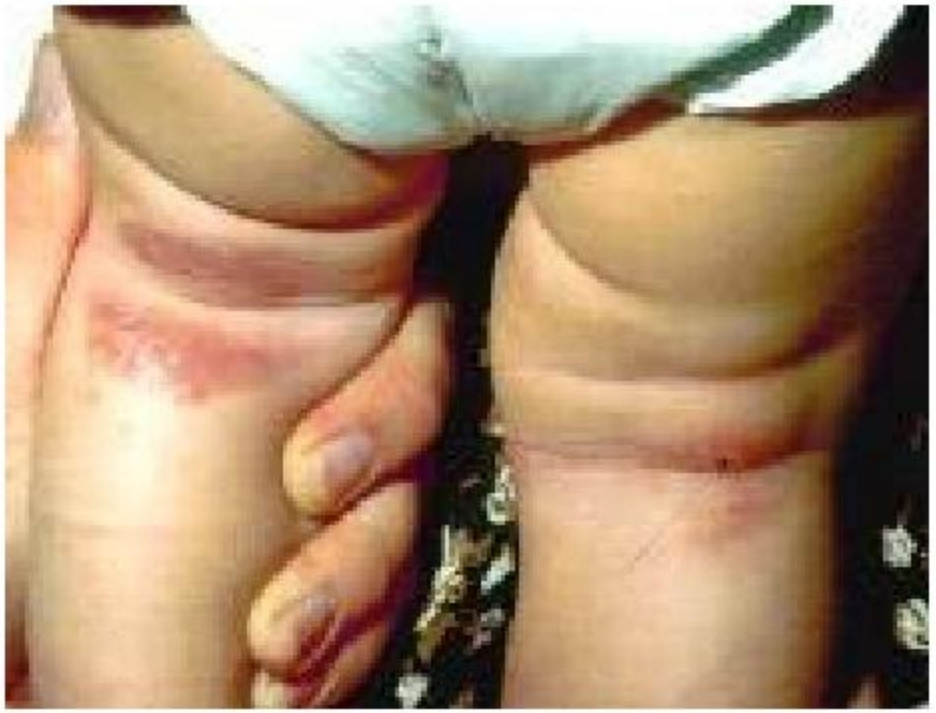
Ataxia



telangiectasi



Telangiectasia Ocular and cutaneous telangiectasias (arrows) in a child with Ataxia-telangiectasia. Courtesy of Douglas J Barrett, MD.

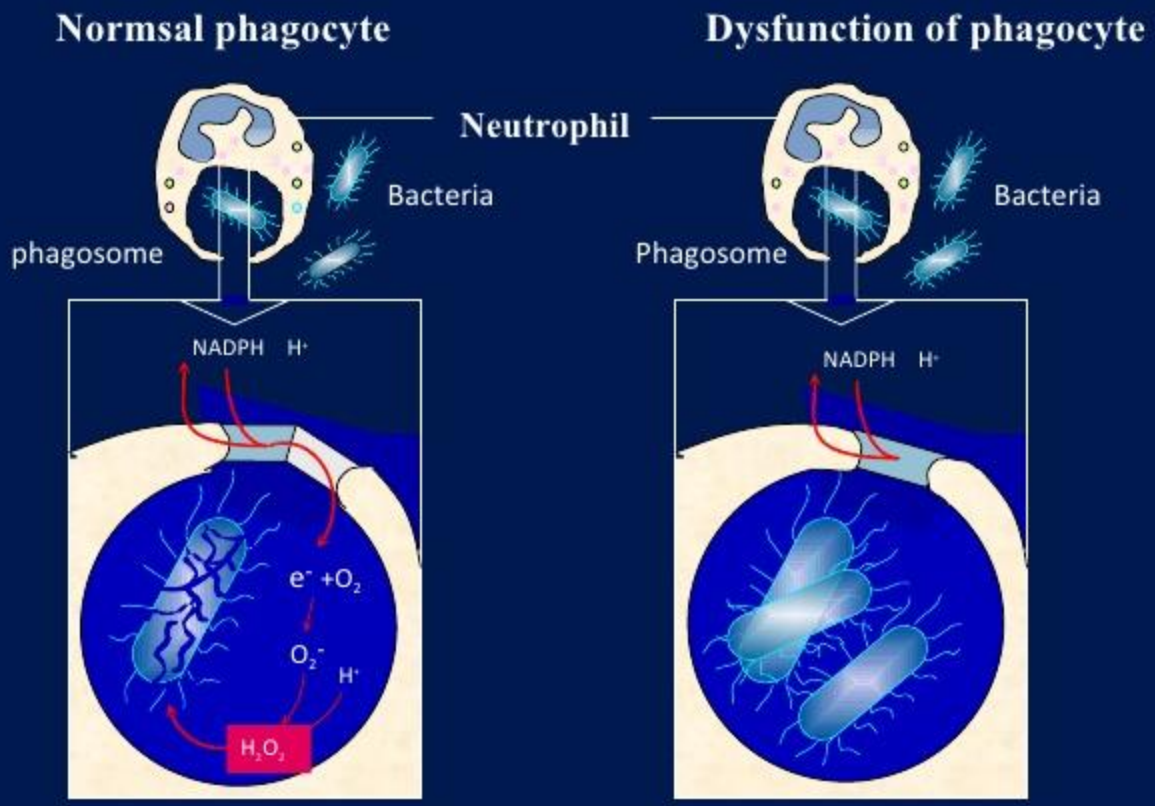


(eczema
)

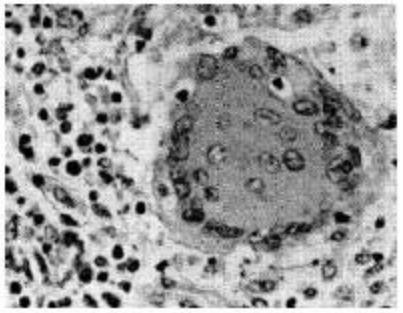
Congenital defects of phagocytic number and/or function

- Sever congenital neutropenia
  （ SCN ， Kostmann syndrome ）
- Chronic granulomatous disease
- Chediak-Hiashi syndrome

Chronic granulomatous disease



Chronic Granulomatous Disease



- Rare – 20 cases/year in the US
- Genetics
  - 70 % X-linked recessive
  - Defect in NADPH oxidase
  - Can't form reactive oxygen species to destroy micro-organisms
- Symptoms
  - Pneumonia, Abscesses, Adenitis, Osteomyelitis
  - Uniquely susceptible to Aspergillosis

Chronic Granulomatous Disease

- **Associated Symptoms**
  - **Severe Acne**
  - **Excessive Granulomata – often in GI tract**
  - **Lupus**
  - **Chorioretinitis**
- **Diagnosis – Nitroblue Tetrazolium Test (NBT)**
- **Treatment**
  - **Antibacterial and antifungal prophylaxis**
  - **Interferon Gamma**
  - **Stem cell or Bone Marrow Transplant**

Complement deficiency

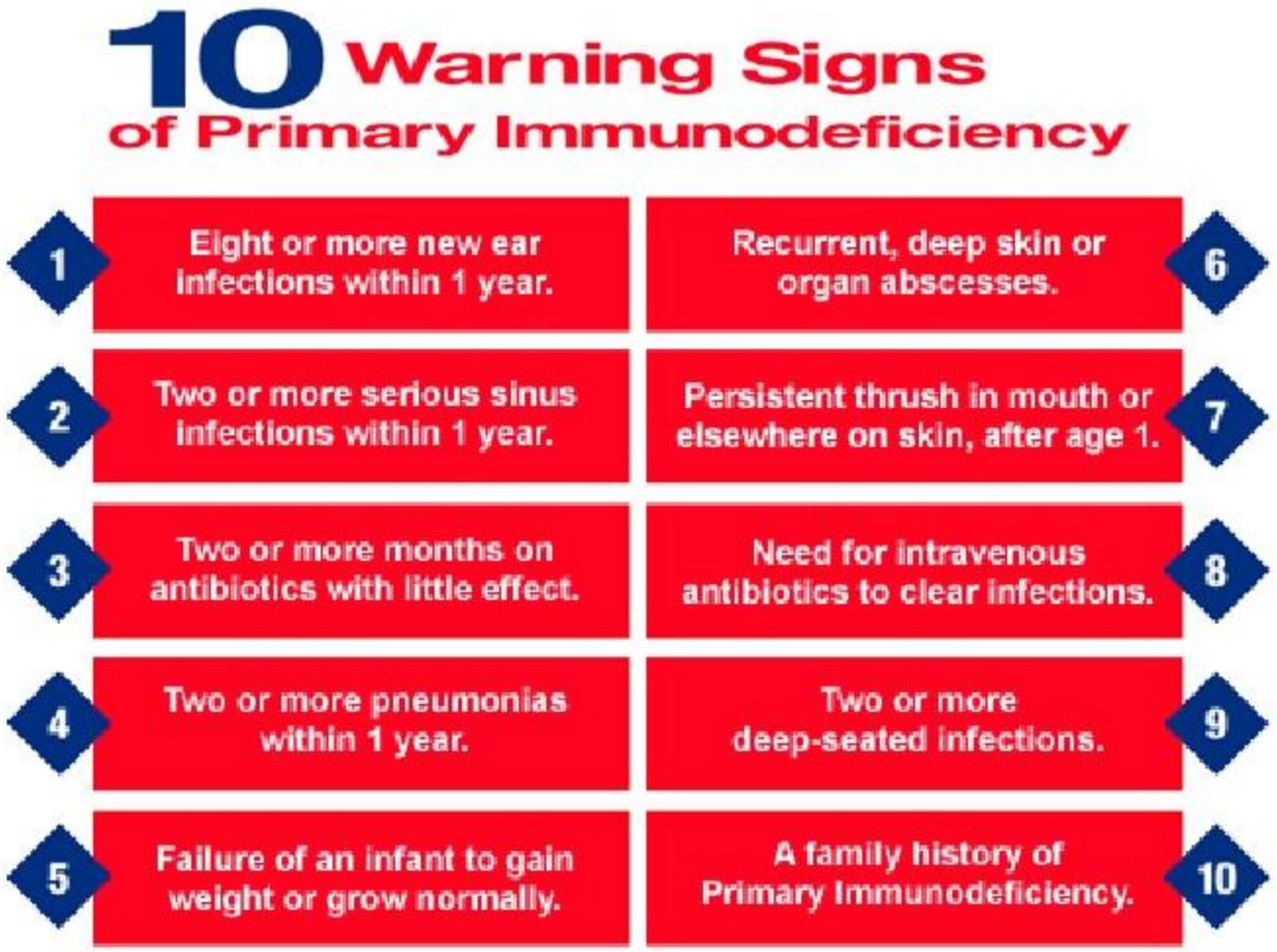
Defects	Inheritance	Clinical findings
• Classical pathway		Infections ,
(C1q 、 r 、 s 、 C_2 、 C_4)	AR	Autoimmune disease
C_1 inhibitor	AD	Hereditary angioedema
• Alternaive pathway		Recurrent pyogenic infection
(C_3 、 Factorl 、 FactorH)	AR	
• Others		Neisseria infection
(C_{5-8} 、 properdin 、 factor D)	AR	Lupus-link syndrome
C_9	AR	Asymptomatic

Approach to the patients with suspected immunodeficiency

- The medical history in immunodeficiency
- Physical examination
- Laboratory investigation

Initial and advanced laboratory tests for immunodeficiency

Disorder	Initial tests	Advanced tests
B cell deficiency	IgG,IgM,IgA,IgE levels	B cell phenotyping using flow cytometry
	Isohemagglutinin titers	IgG subclass levels
	Antibody response to vaccine antigens	Lymph node biopsy
		Mutation analysis
T cell deficiency	Lymphocyte count	Tcell phenotyping using flow cytometry
	Delayed hypersensitivity skin tests	T cell proliferative response to mitogens
	Chest X-ray for sive of thymus in infant only	Detection of Ag(MHC)
	T cell count subset analysis	T cell receptor and signal transduction
		ADA and RNP levels in RBC
		CK synthesis
		Mutation analysis
Phagocytic cell defects	Phagocytic cell count and morphology	Flow cytometric respiratory burst assay
		Chemotaxis assay
		Mutation analysis
Complement deficiency	C3,C4 levels, CH50 activity	Specific component assays



From INFO4PI.ORG

4 Stages of Immunologic Testing when Primary Immunodeficiency is Suspected

1

- History and physical examination, height and weight
- CBC and differential
- Quantitative Immunoglobulin levels IgG, IgM, IgA (related to age)

2

- Specific antibody responses (tetanus, diphtheria)
- Response to pneumococcal vaccine (pre/post)(for ages 3 and up)
- IgG subclass analysis

3

- Candida and Tetanus skin tests
- Lymphocyte surface markers CD3/CD4/CD8/CD19/CD16/CD56
- Mononuclear lymphocyte proliferation studies (using mitogen and antigen stimulation)
- Neutrophil oxidation burst (if indicated)

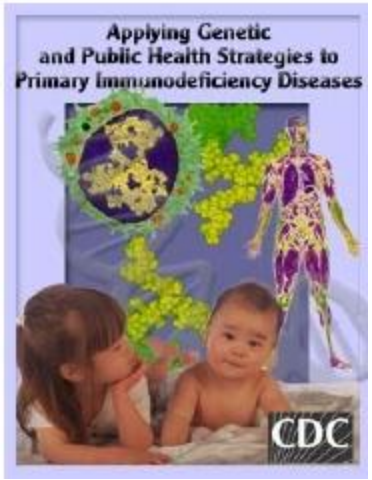
4

- Complement screening CH50, C3, C4
- Enzyme measurements (adenosine deaminase, purine nucleotide phosphorylase)
- Phagocyte studies (surface glycoproteins, mobility, phagocytosis)
- NK cytotoxicity studies
- Further complement studies AH50
- Neo antigen to test antibody production
- Other surface/cytoplasmic molecules
- Cytokine receptor studies
- Family/genetic studies

From INFO4PI.ORG

Management of PID

- General treatment
- Replacement therapy
- Immune reconstruction
- Gene therapy



General management of PID

- Diet
- Avoidance of pathogens ("germ-free" care)
- Antibiotics
  - Use in acute illness
  - Prophylactic
- Avoid whole blood transfusion in combined immunodeficiency disorder(GVHR)
- Avoid live virus vaccines and BCG