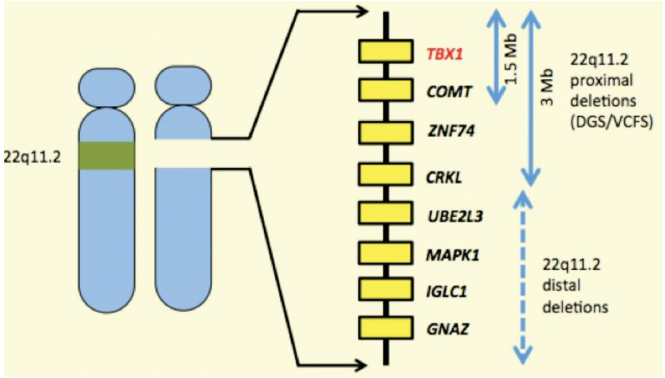
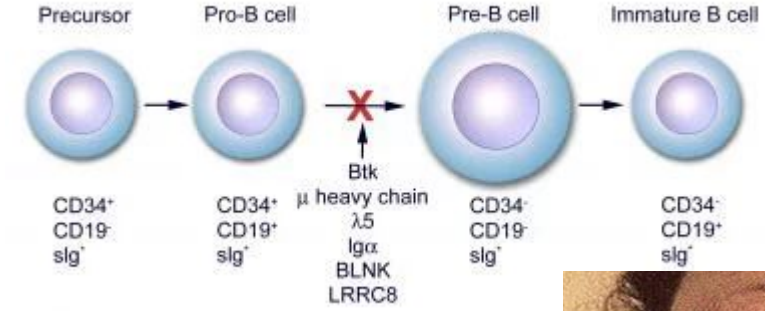
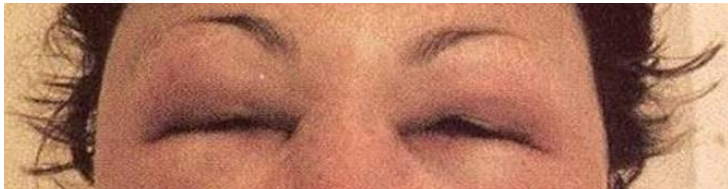
Primary Immunodeficiency

- DiGeorge Syndrome
- Severe Combined Immunodeficiency “SCID”
- X-Linked Agammaglobulinemia
- Common variable immunodeficiency (CVID)
- IgA deficiency
- Hyper- IgM Syndrome
- Wiskott-Aldrich syndrome
- Complement deficiencies

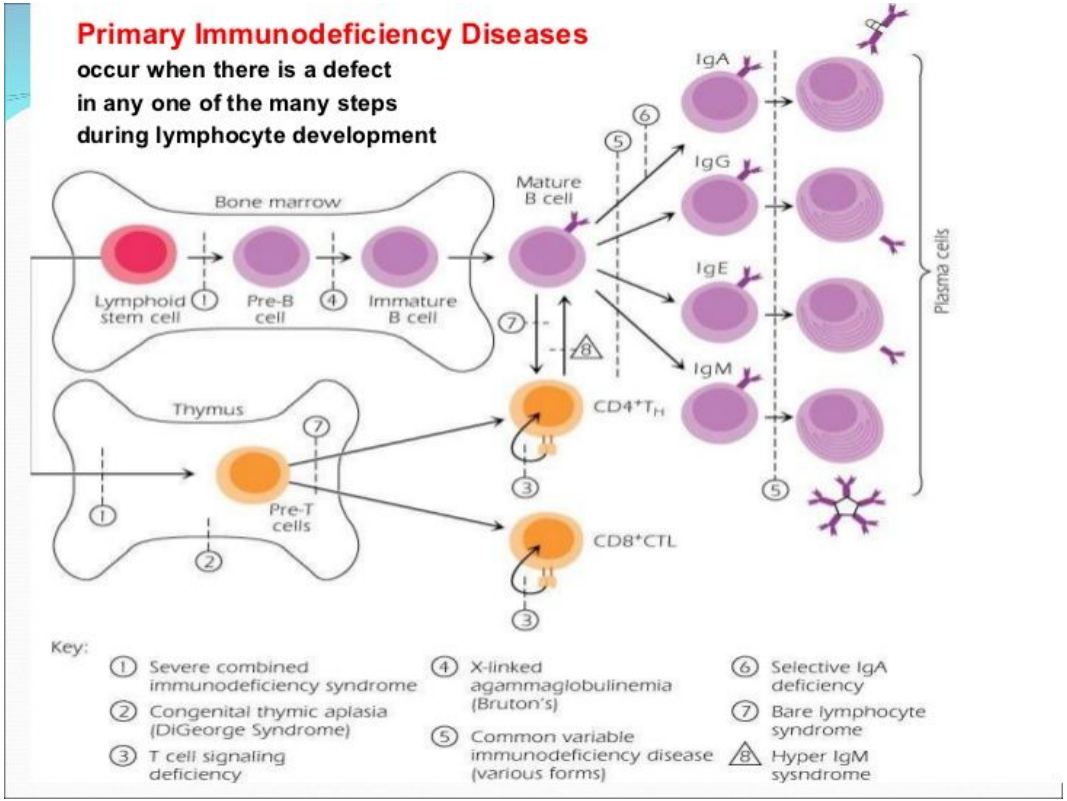






Immunodeficiency (or immune deficiency): is a state in which the immune system's ability to fight infectious disease and cancer is compromised or entirely absent.

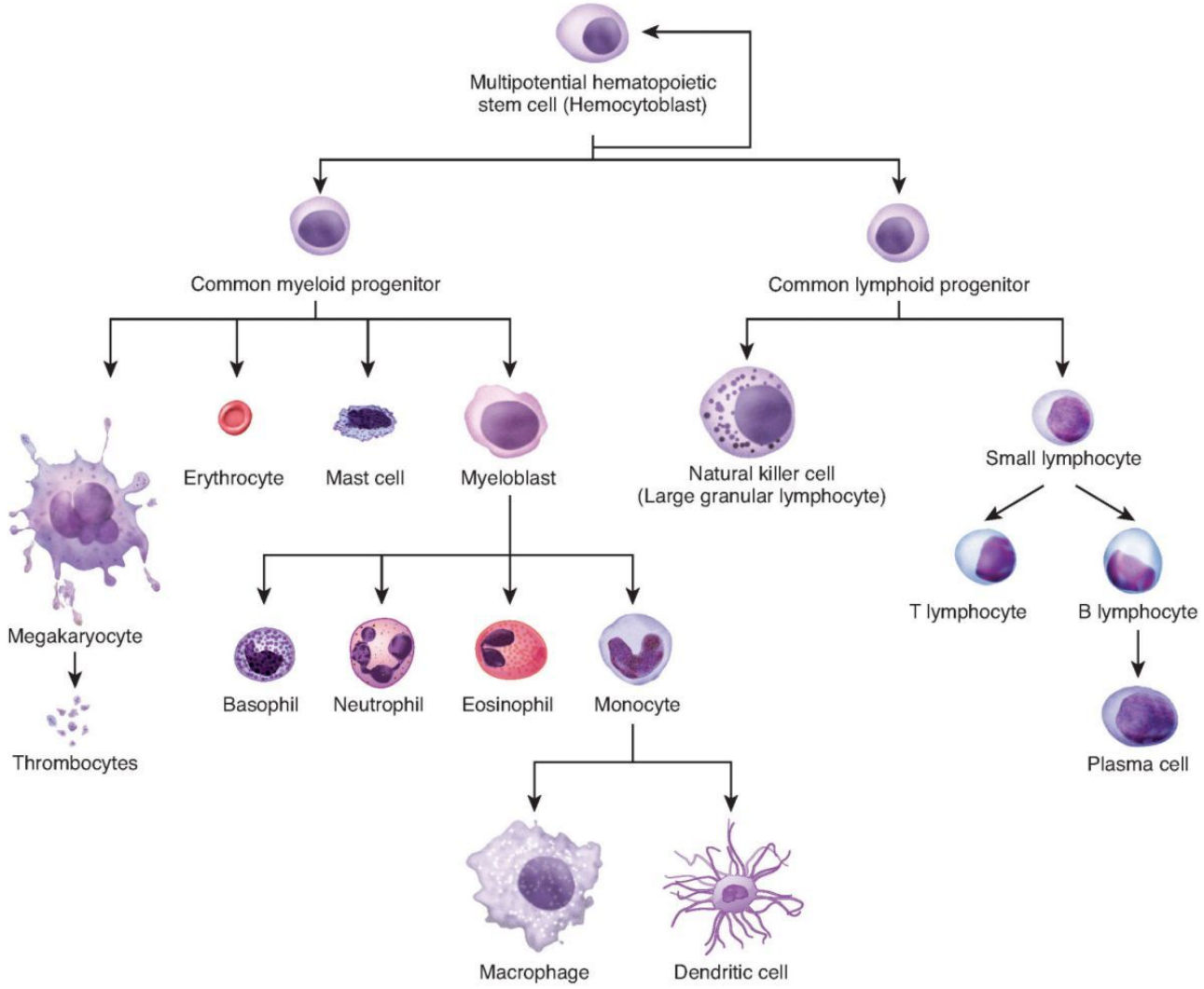
There are two types of immunodeficiency disorders: those you are born with (primary), and those that are acquired (secondary).



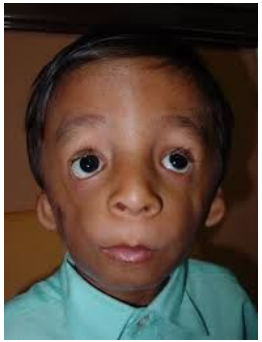
A group of disorders characterized by an impaired ability to produce normal immune response.

Most of these disorders are caused by mutations in genes involved in the development and function in immune organs, cells and molecules

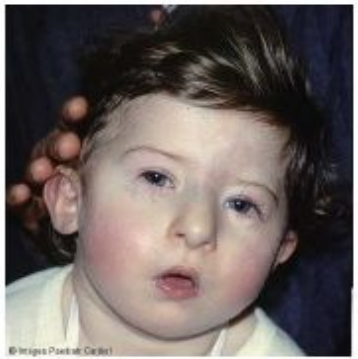
Clinical features: recurrent infections, high risk of autoimmune diseases, allergy and malignancies


Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Erythrocyte
Mast cell
Myeloblast
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
Megakaryocyte
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Plasma cell
Macrophage
Dendritic cell

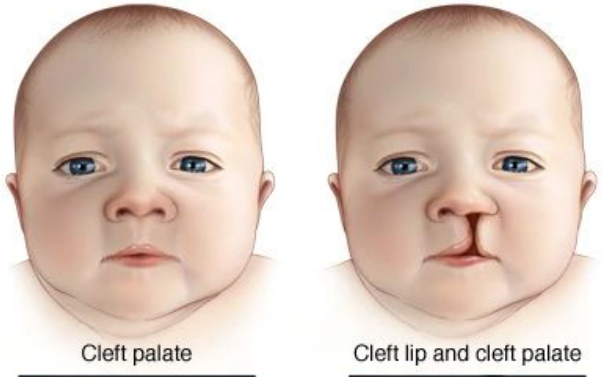
DiGeorge syndrome

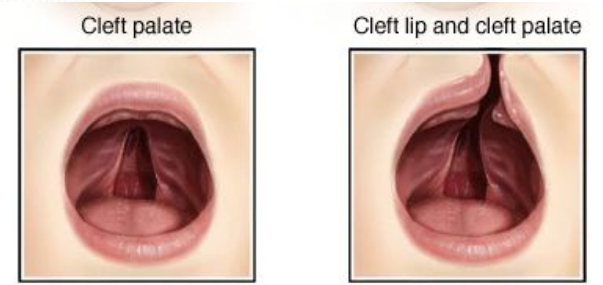


- More frequent cleft lip/palate
- Small jaw
- Small upper lip/mouth
- Eyes slanted upward or downward
- Low-set and/or abnormal folding of ears
- Short stature, mild to moderate learning difficulties
- Underdeveloped parathyroid and thymus
- Cardiac malformations

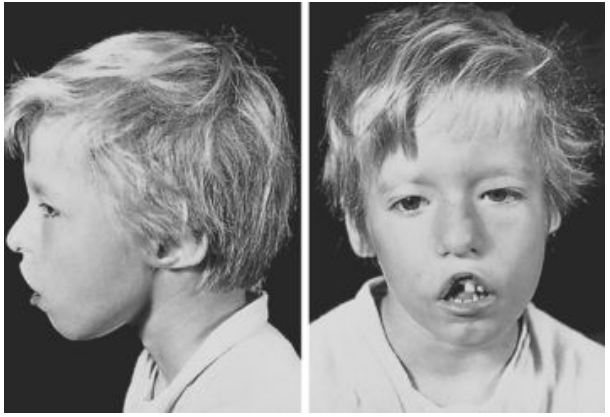


Digilio et



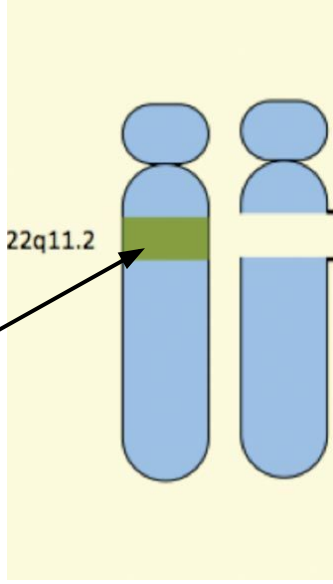


DiGeorge syndrome



- Due to 22q11 microdeletion

- Developmental failure of the third and fourth pharyngeal pouches.

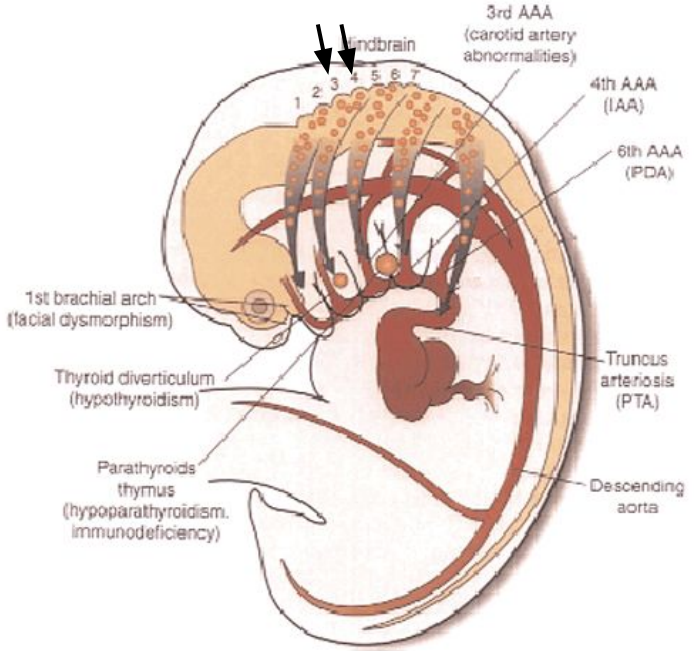


The deletion occurs in this region.

DIGEORGE SYNDROME - EMBRYOLOGICAL DEVELOPMENT

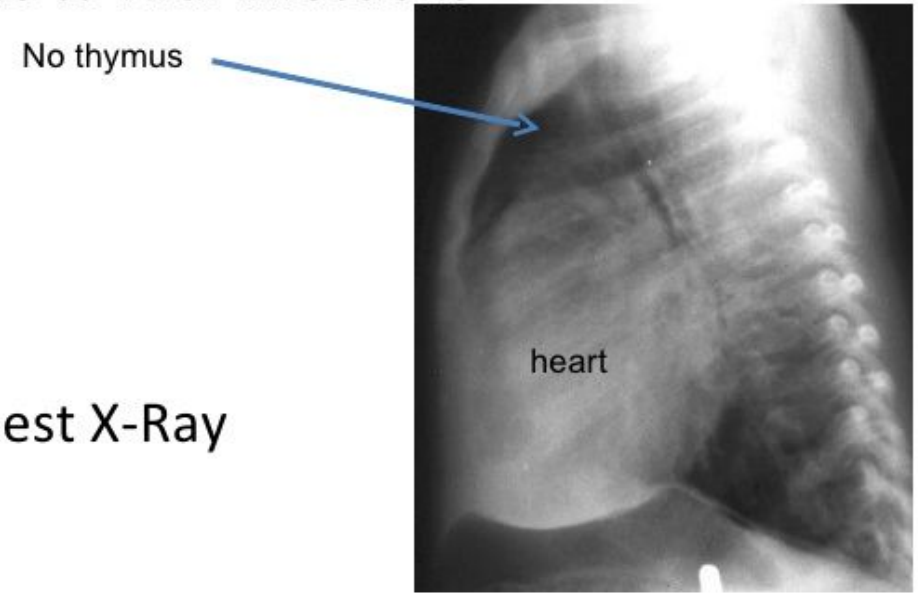
- Many of the structures primarily affected are derivatives of the brachial arch/pharyngeal pouch system
  - Face – 1st branchial arch
  - Heart – branchial arch arteries – 1st-4th arches
  - Thymus – 3rd pharyngeal pouch
  - Parathyroid – 3rd & 4th pharyngeal pouch

So, if there are a failure in the development of the 3rd and 4th pharyngeal pouch, there will be a lack in the thymus and in the parathyroid.



DiGeorge Syndrome

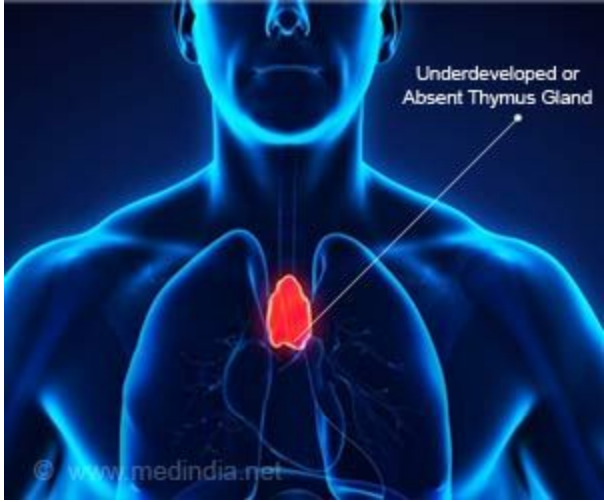
- Thymus – underdeveloped or absent
- Susceptible to viral infections



- Lateral Chest X-Ray

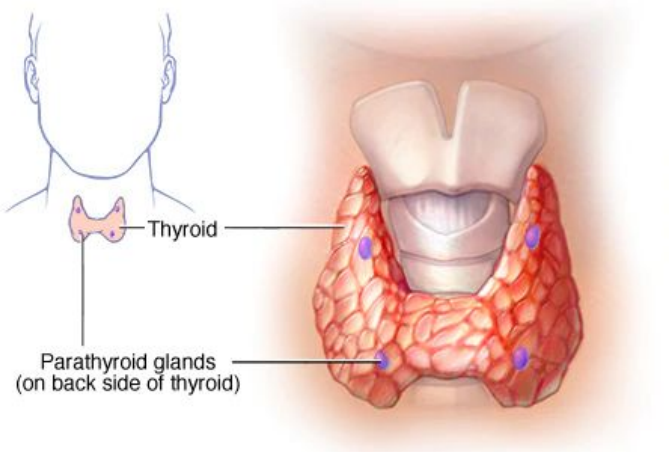
Presents with

- T-cell deficiency; due to the lack of thymus. So, patients have problem fighting viruses and fungal infection.



- Hypocalcemia; due to the lack of parathyroids.

- Abnormalities of heart, great vessels and face.



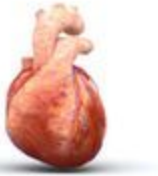
DiGeorge Syndrome

CATCH-22

Cardiac abnormalities
Abnormal facies
Thymic absence/abnormality, **T** cell abnormality
Cleft palate
Hypocalcemia
Chromosome **22**

Microdeletion in chromosome 22

Thymic hypoplasia → **Hypocalcemia** → Neonatal Seizure or Tetany



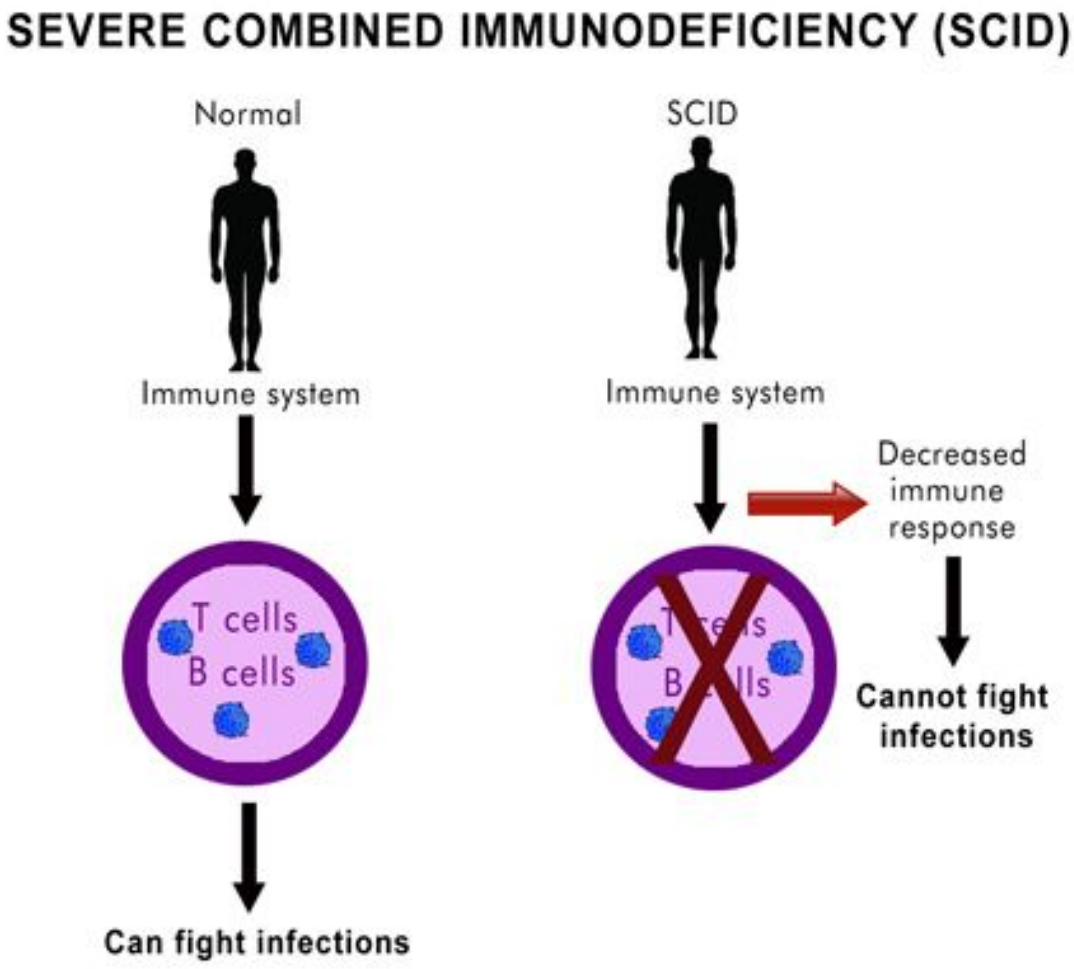
Congenital heart defect | Abnormal facies | Cleft palate

Defective:

cell-mediated i.e. T cells

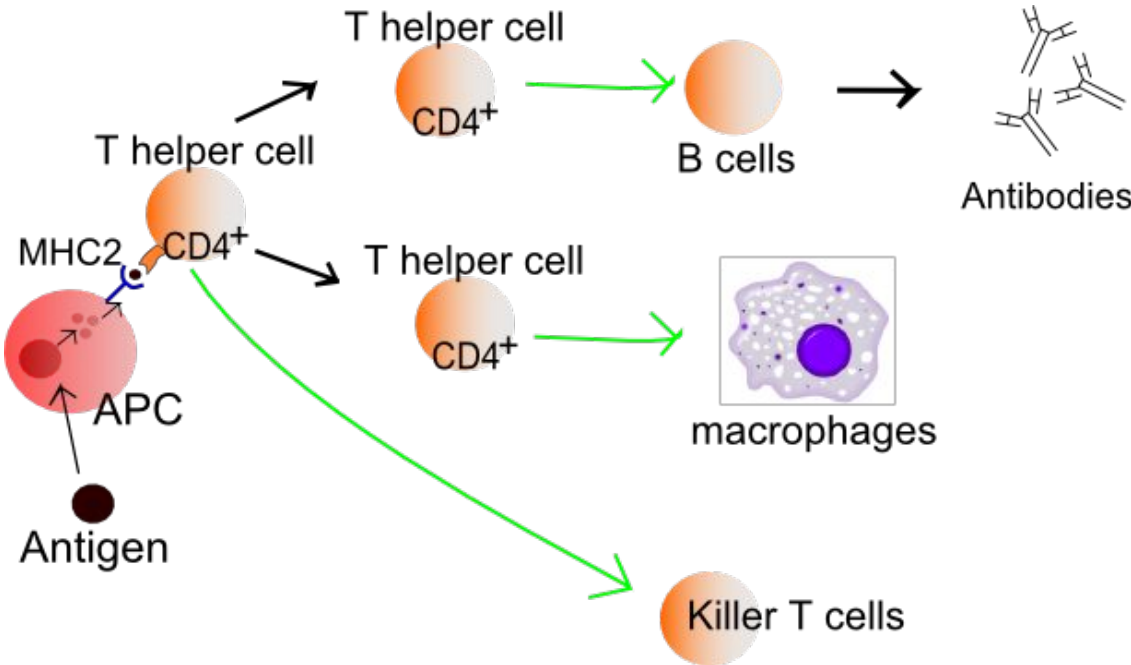
and

humoral immunity i.e. B cells



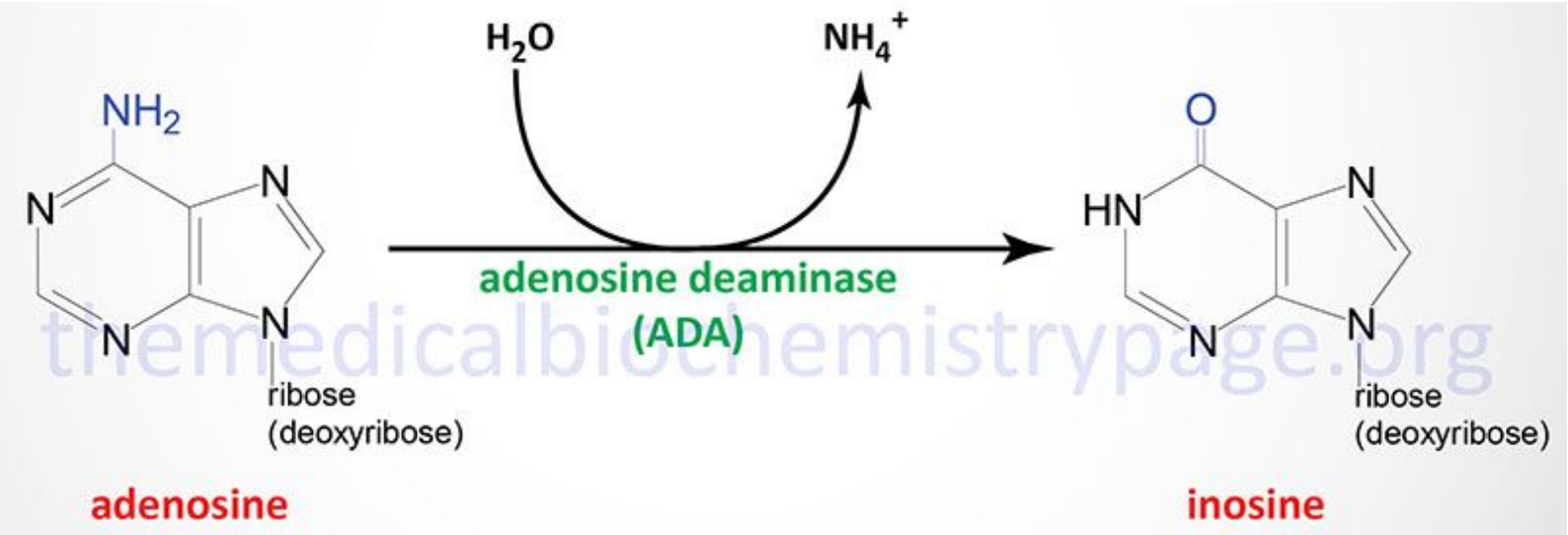
Etiologies (causation of a disease)
You can get SCID through:

- Cytokine receptor defects – cytokine signaling is necessary for proliferation and maturation of B and T cells.
  - E.g. cytokines produced by Helper T cells help B cells and Cytotoxic T cells to mature



Etiologies (causation of a disease)
You can get SCID through:

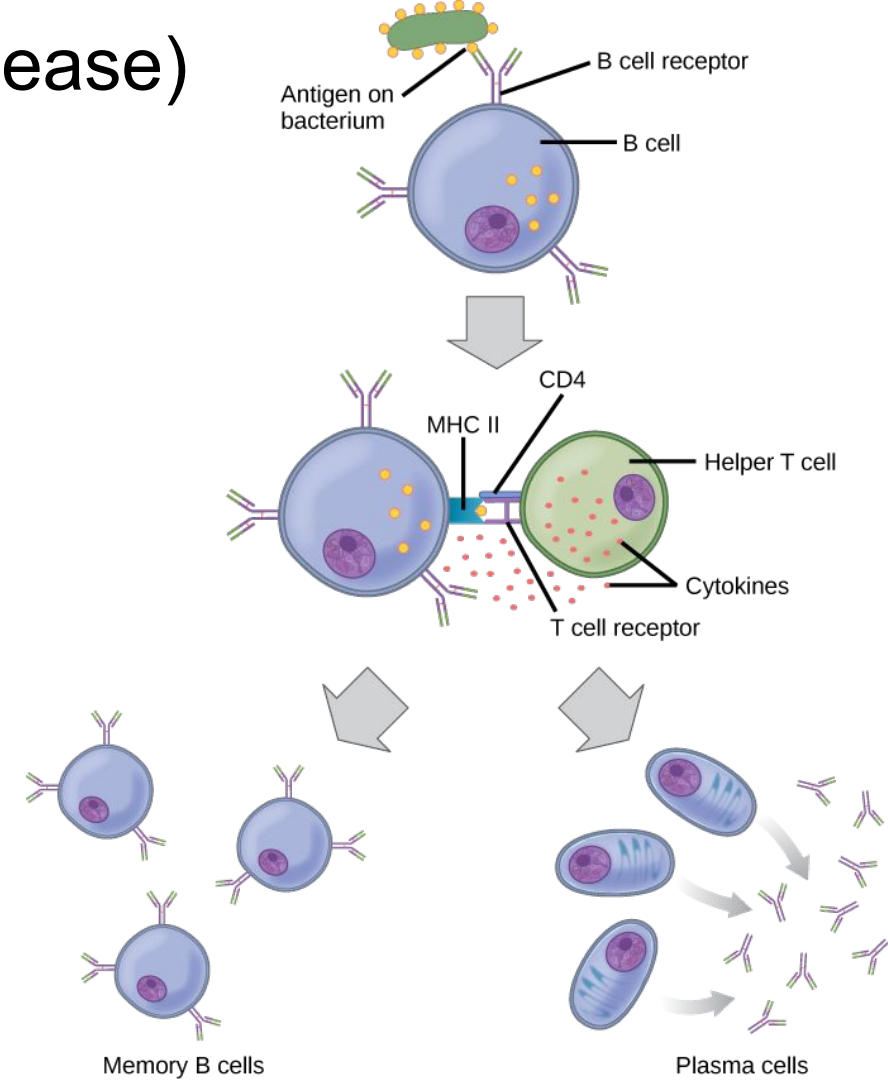
- Adenosine deaminase(ADA) deficiency — ADA is necessary to deaminate adenosine and deoxyadenosine for extraction as waste products; build up of adenosine and deoxyadenosine is toxic to lymphocytes.



Etiologies (causation of a disease)
You can get SCID through:

- MHC II deficiency — MHC class II is nesserray for $CD4^+$ helper T cells activation and cytokine release,

- if $CD4^+$ T cells cannot be activated then there will be defect function of $CD8^+$ T cells and B-cells.



Characteristics

- Susceptibility to :

1. Viral infection
2. fungal infection

because they don't have T cells.

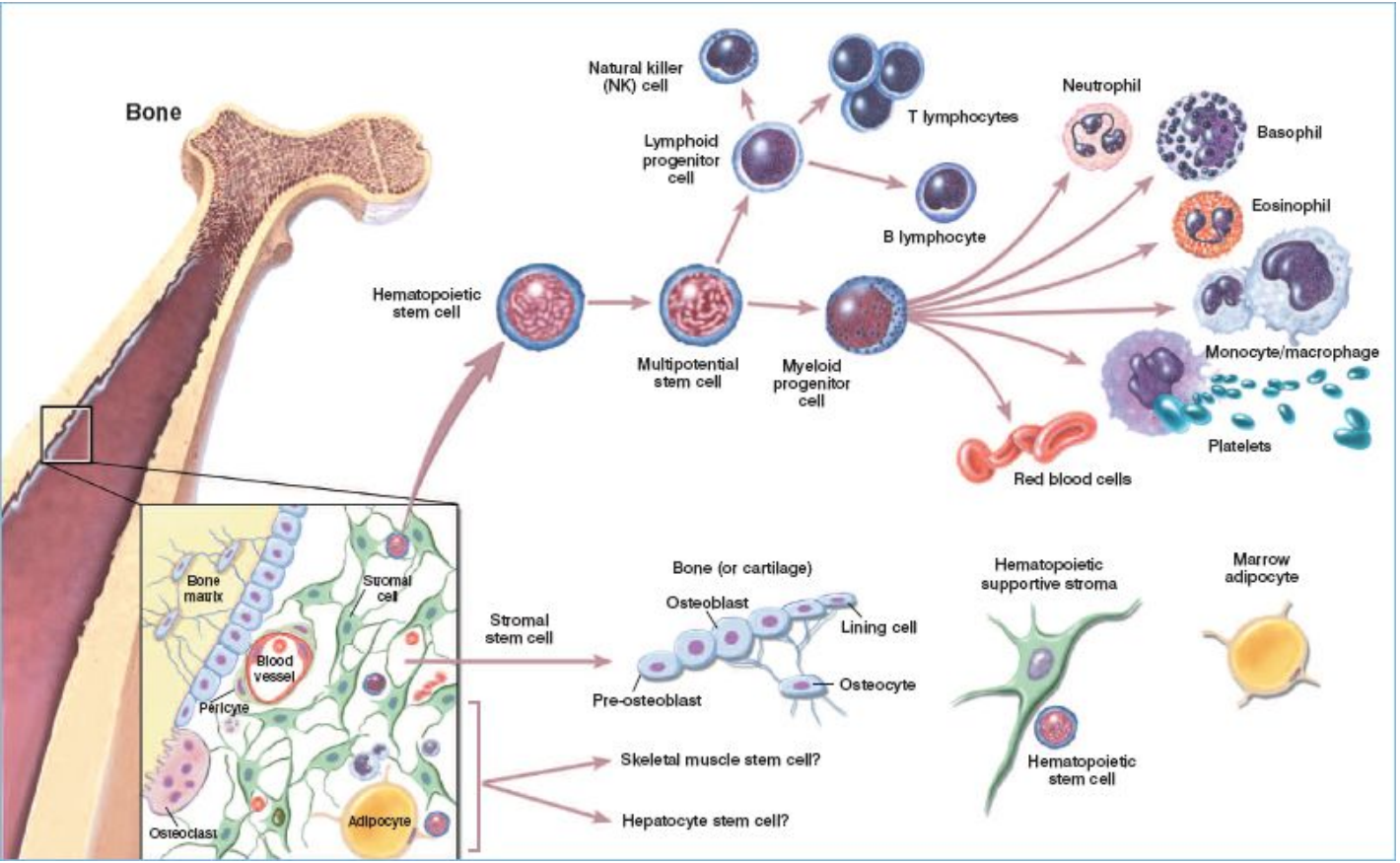
3. Bacterial infection
4. protozoal infection

because they don't have B cells.

- Increase risk for opportunistic infections and live vaccines.

Treatment

- Sterile isolation “ temporary measure”: they are called bubble baby.
- Stem cells transplant



The normal stem cells are injected in the bone marrow of SCID patient, and then the hematopoietic stem cells will generate both T and B cells; hence, the patient will have the ability the develop immune response to fight infections.

Genetic mutations associated with SCID

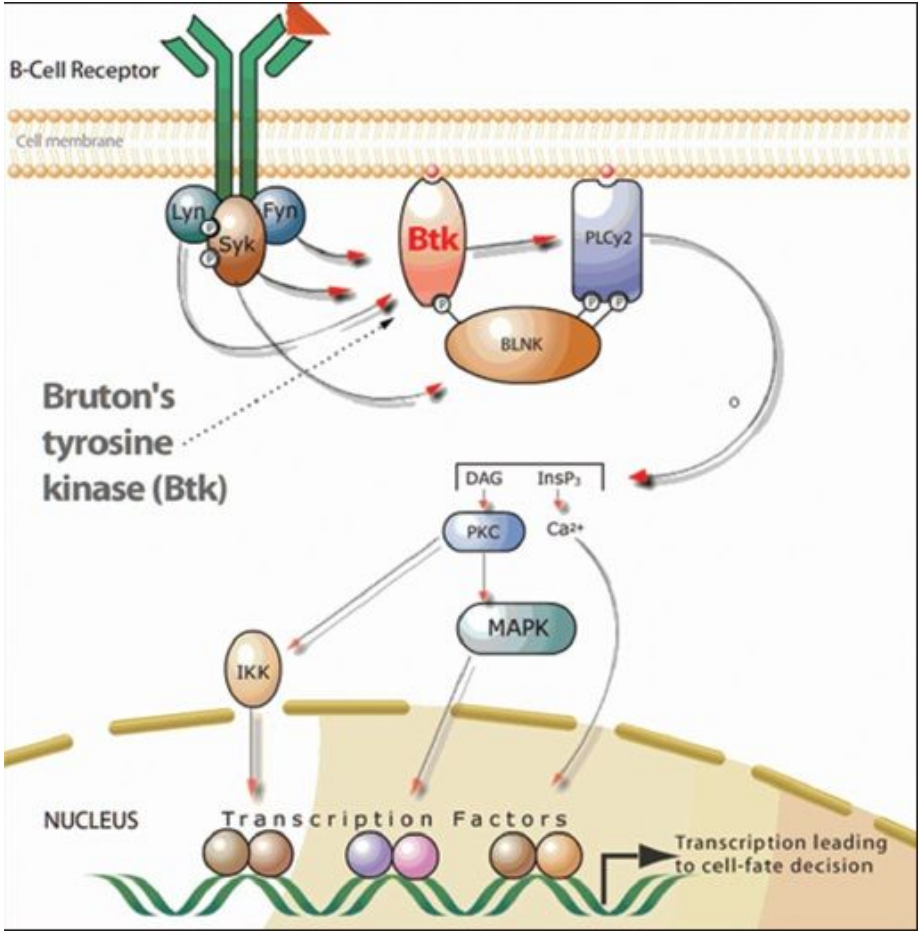
Gene	Function	Phenotype	Chromosomal location	Year Published
ADA	Purine salvage enzyme Recycles adenosine and deoxyadenosine after DNA breakdown	T, B-, NK+	20q12-13	1972
TCR abn	Signaling through TCR	T^{lo}, B+,NK+	11q23	1987
γ chain	Common g chain (IL-2,4,6,15,21)	T-,B+, NK-	Xq13	1993
ZAP 70	Tyrosine Kinase	CD8 def	2q12	1994
Janus kinase- 3	Tyrosine kinase Signaling through γC	T-, B+, NK-	19p13	1995
RAG1, RAG-2 •Omenn's syndrome	Recombinase activating genes initiation of VDJ recombination	T-B-NK+ T+, B-,NK+	11p13	1996
IL7-Ra	Cytokine Receptor	T-, B+, NK+	5p13	1998
Artemis	DNA repair enzyme	T-B-NK+	10p	1998

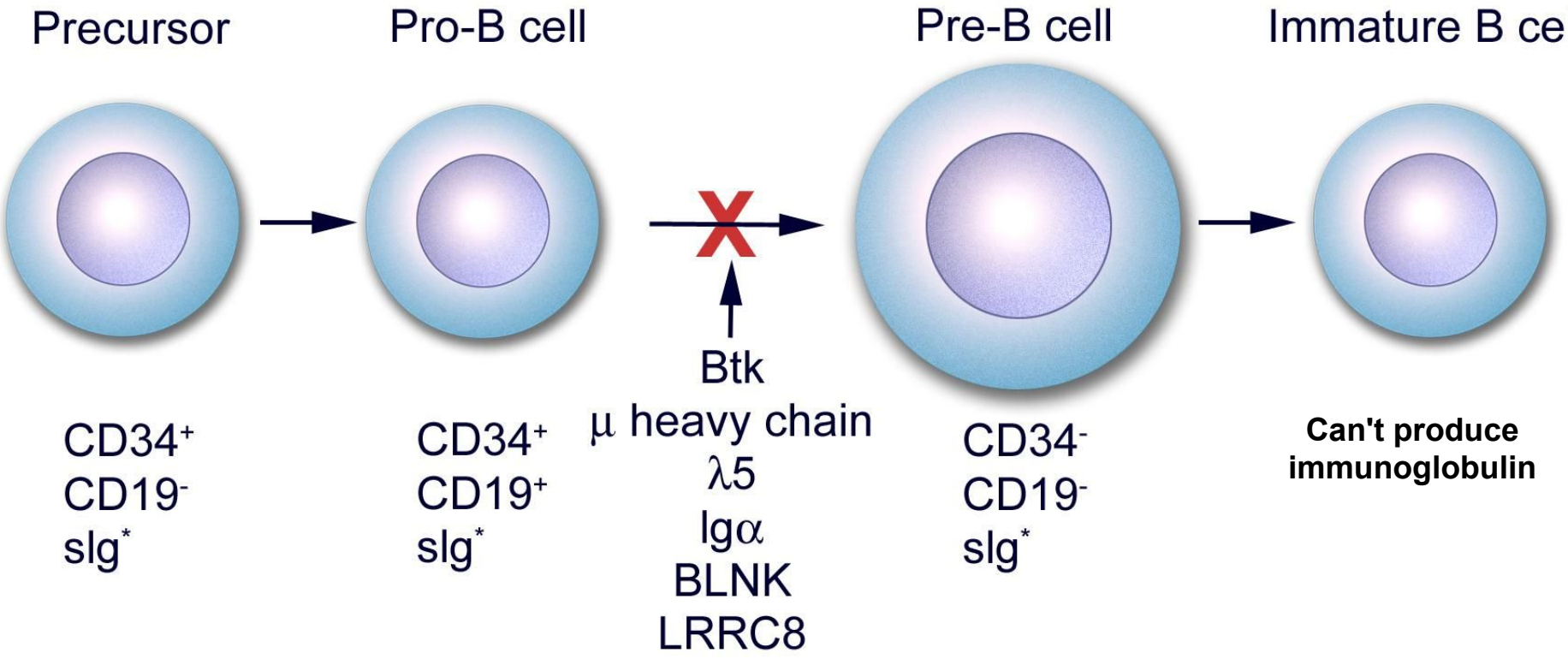
X-Linked Agammaglobulinemia (XLA)

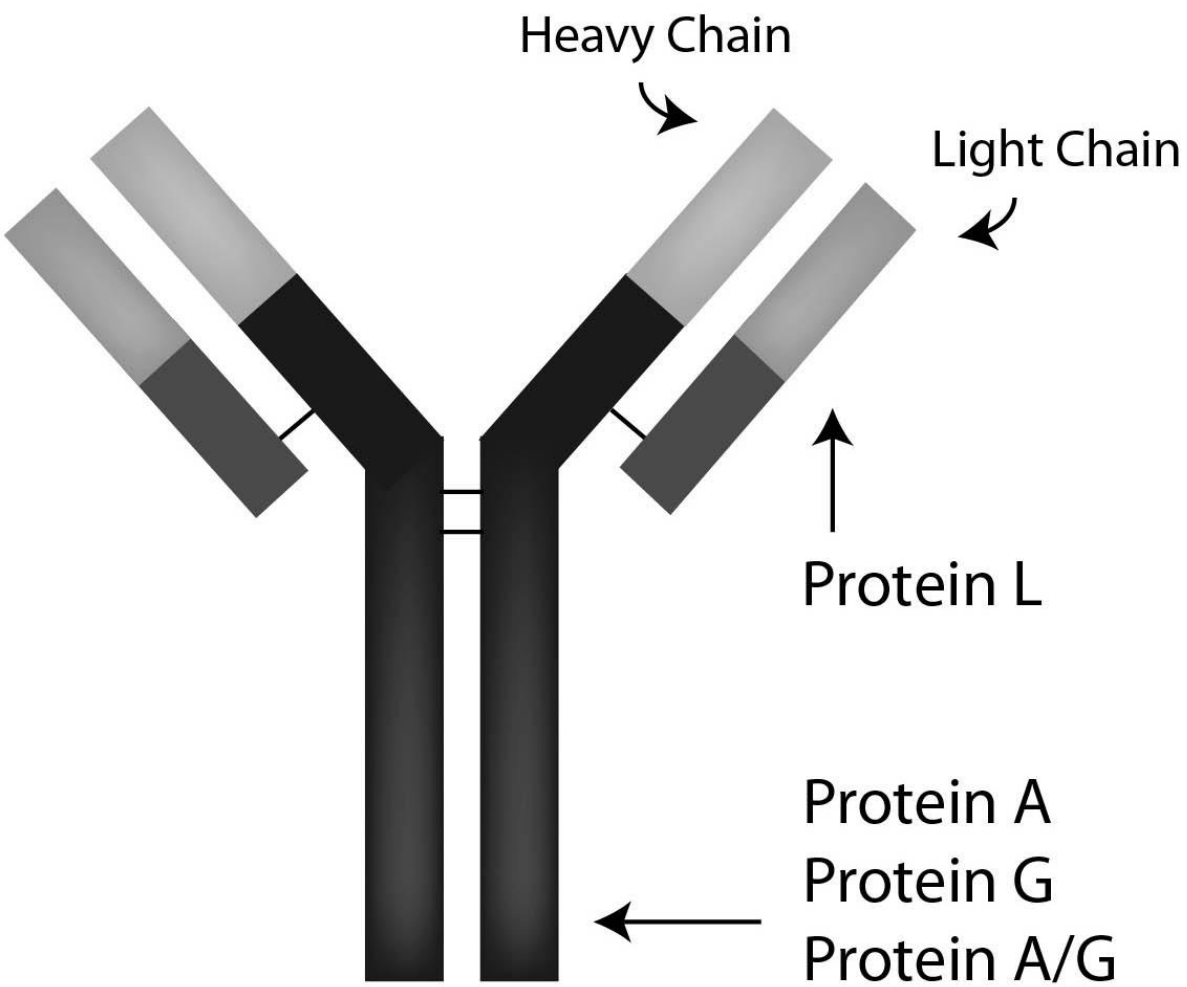
- It is one of the more common forms of primary immunodeficiency, occurring at a frequency of about 1 in 100,000 male infants.
- Means complete lack of immunoglobulin in blood
- Due to disorder in the maturation of B-cell
- Naïve B cell cannot mature to plasma cells.
- It's plasma cells that have the ability to secrete immunoglobulin into the blood, hence; if naïve B cells cannot mature to plasma cells then it cannot drop immunoglobulin into the blood.

Due to mutated Bruton tyrosine Kinase (BTK)

- BTK is a signaling molecule that is necessary for B cell to become plasma cell, it is X-linked.
- When it is mutated it causes the disease X-linked agammaglobulinemia.
- When BTK is nonfunctional, the pre–B-cell receptor cannot signal the cells to proceed along the maturation pathway.



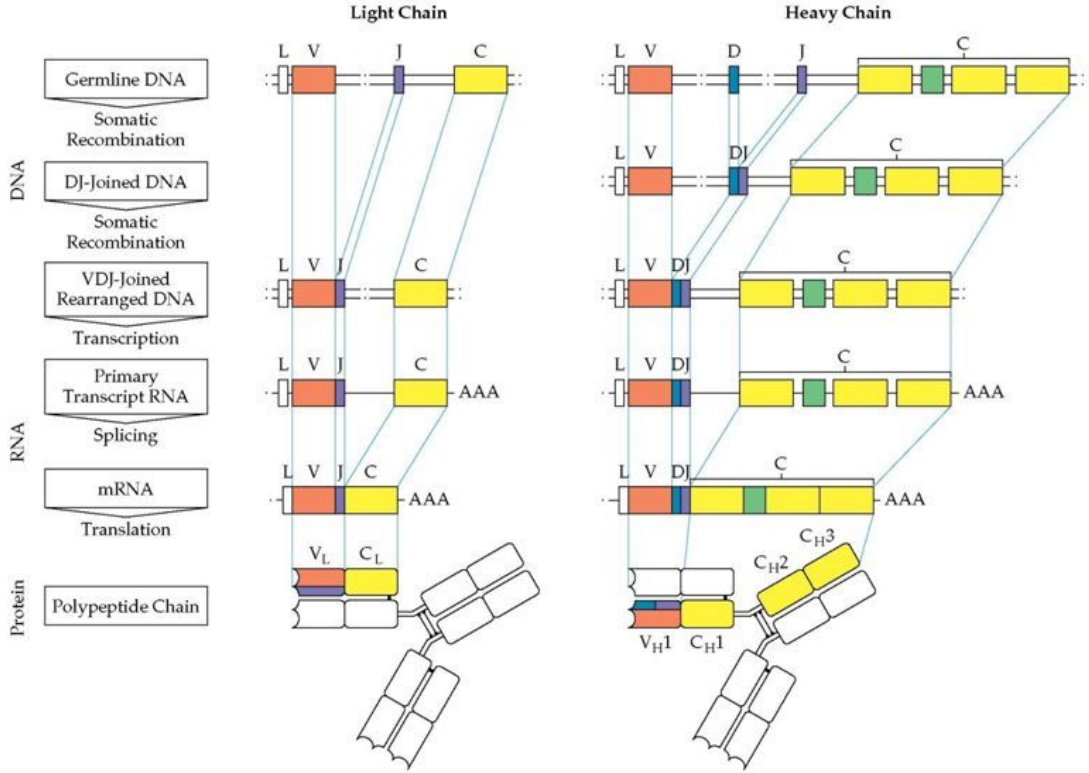

Precursor
Pro-B cell
Pre-B cell
Immature B cell
CD34+
CD19-
slg*
CD34+
CD19+
slg*
Btk
μ heavy chain
λ5
Igα
BLNK
LRRC8
CD34-
CD19-
slg*
Can't produce immunoglobulin



Complete Ig, it consists from 2 heavy chains and 2 light chains.

- Ig light chains are not produced, and the complete Ig molecule containing heavy and light chains cannot be assembled and transported to the cell membrane, although free heavy chains can be found in the cytoplasm.

Rearrangement of Ig gene segments:

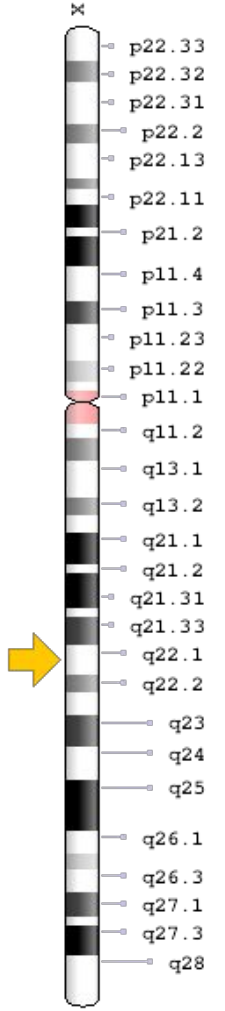


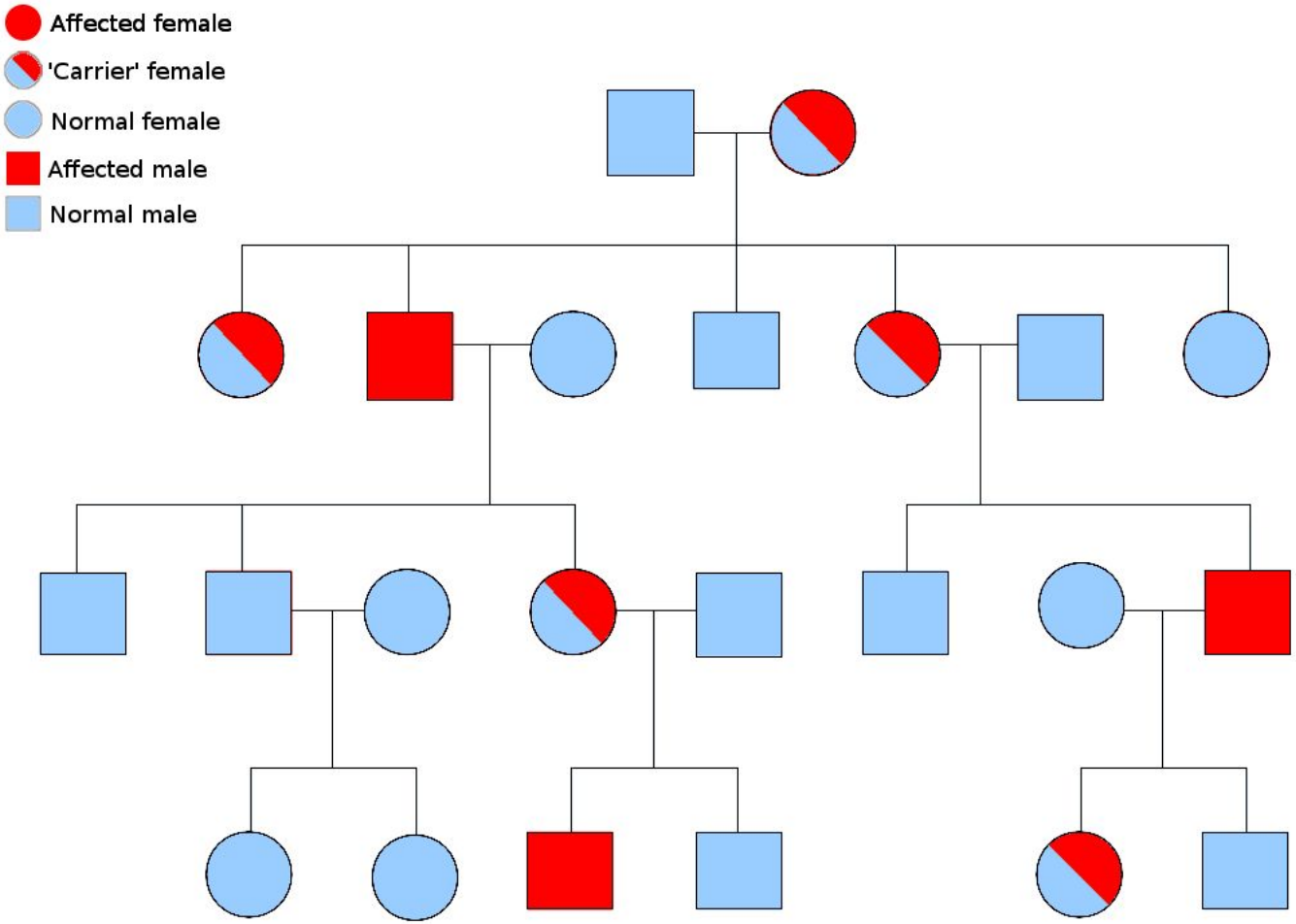
http://what-when-how.com/wp-content/uploads/2012/04/tmp4B108.jpg

- During normal B-cell maturation, immunoglobulin (Ig) heavy chain genes are rearranged first, followed by light chain genes.

- At each stage, signals are received from the expressed components of the antigen receptor that drive maturation to the next stage; these signals act as quality controls, to ensure that the correct receptor proteins are being produced.

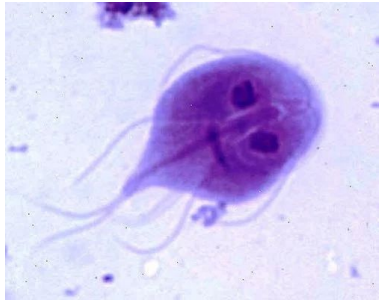
- In XLA, B-cell maturation stops after the initial heavy chain gene rearrangement because of mutations in a tyrosine kinase that is associated with the pre–B-cell receptor and is involved in pre-B-cell signal transduction. This kinase is called *Bruton tyrosine kinase (BTK)*.

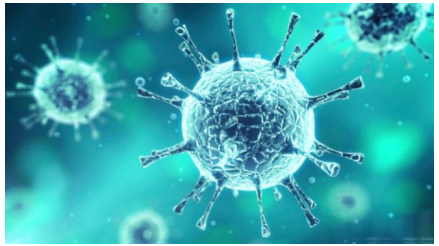



Affected female
'Carrier' female
Normal female
Affected male
Normal male

Presentation

- After 6 months of life; as maternal antibodies that were transported via the placenta are depleted.
- Recurrent **bacterial** “ because no IgG is present to protect against it”, **enterovirus** (Polio and coxsackievirus) and ***Giardia lamblia*** infections,
- Last two infect the mucous surfaces and IgA protect against it, with the absence of IgA the patient become susceptible to it.
- Live vaccines must be avoided.





- The disease is characterized by a profound reduction in the number of B cells in the blood and secondary lymphoid organs and an absence of germinal centers and plasma cells in these organs.

- T-cell numbers and responses may be normal.

- The treatment of X-linked agammaglobulinemia is replacement therapy with intravenous immunoglobulin (IVIG) from pooled human serum.

Germinal centers or germinal centres (GCs) are sites within secondary lymphoid organs – lymph nodes and the spleen where mature B cells proliferate, differentiate, and mutate their antibody genes

X-Linked Agammaglobulinemia — Bruton's Disease

- It is a failure of pre-B cells to differentiate into mature B cells.
- Clinical recognition - after six months of age. Recurrent bacterial infections such as pharyngitis, sinusitis, otitis media, bronchitis, and pneumonia call attention to the underlying immune defect. The causative organisms are *Haemophilus influenzae, Streptococcus pyogenes, Staphylococcus aureus,* or the pneumococci.
- Most viral, fungal, and protozoal infections are handled normally by cell-mediated mechanisms.

*

X-linked agammaglobulinemia (XLA)

- ✓ X-linked disorder of B cell development due to mutation of the *BTK* (Bruton's tyrosine kinase) gene which signals downstream of the pre-B cell receptor
- ✓ B cell development is arrested in the bone marrow at the pre-B cell stage resulting in complete absence of peripheral B cells
- ✓ IgG levels fall after maternal IgG naturally declines, pyogenic infections with bacteria occur starting 6-9 months
- ✓ prone to chronic enteroviral meningoencephalitis
- ✓ avoid live virus vaccines

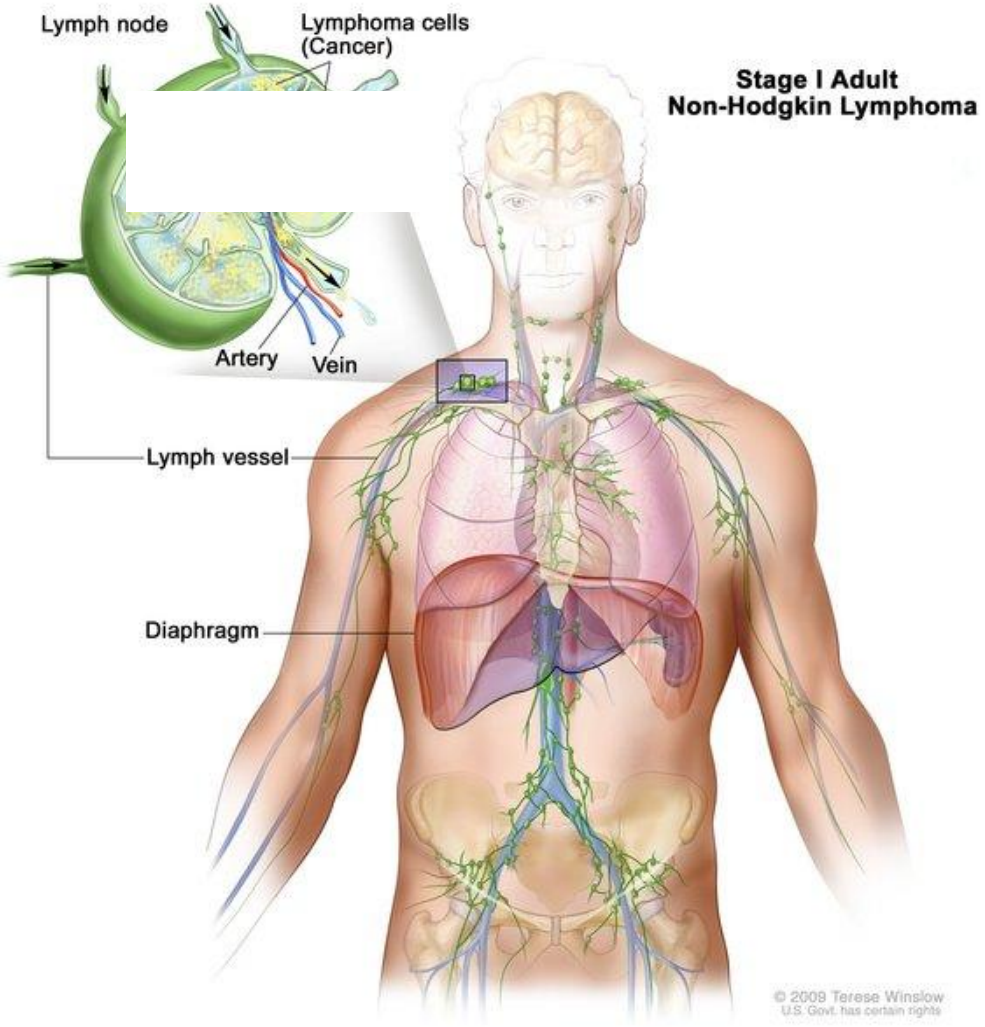
Common variable immunodeficiency (CVID)

- Low immunoglobulin due to **B-cell or helper T -cell** (produce IL-4 and IL-5 and induce Ig production) **defects**
- Increased risk of bacterial, enterovirus and *Giardia lamblia* infections
- About 20% of patients have recurrent herpesvirus infections, and serious enterovirus infections causing meningoencephalitis
- They are often asymptomatic, and usually the onset of symptoms is later, in childhood or adolescence
- In contrast to X-linked agammaglobulinemia, common variable immunodeficiency affects both sexes equally
- Increased risk for autoimmune disease and lymphoma.

Lymphoma is cancer that begins in infection-fighting cells of the immune system, called lymphocytes.

These cells are in the lymph nodes, spleen, thymus, bone marrow, and other parts of the body.

When you have lymphoma, lymphocytes change and grow out of control



(CVID)

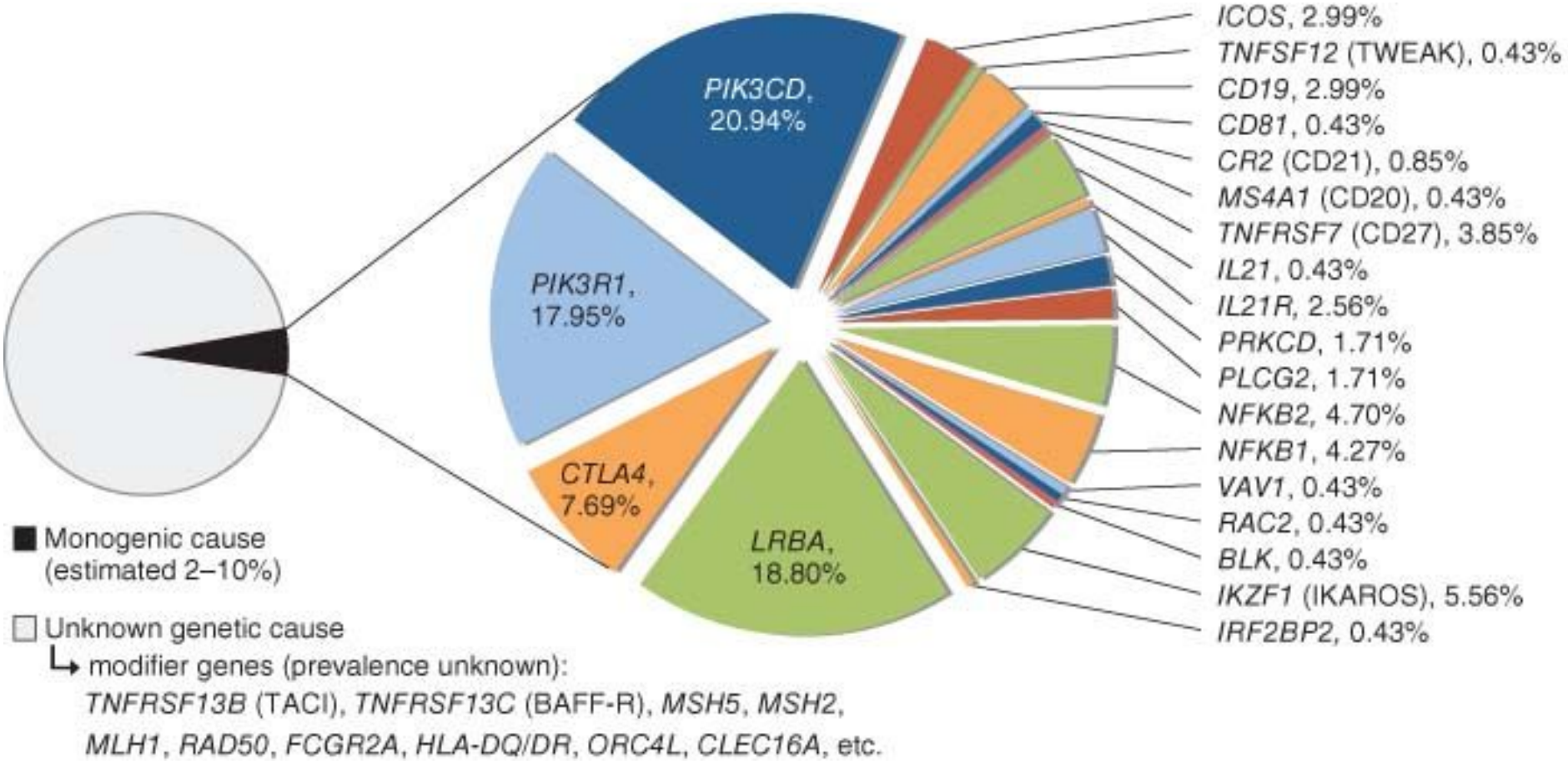
- Common variable immunodeficiency may be genetic or acquired, but mostly genetic.
- Different genetic causes have been discovered, including mutations in a receptor for BAFF, a cytokine that promotes the survival and differentiation of B cells.
- and in a molecule called ICOS, a homologue of CD28 that contributes to the function of T helper cells.
- However, in the majority of cases, the genetic basis is unknown.

Genetic Causes

- Due to the unclear genetic nature of CVID, a clear pattern of inheritance has not been defined.
- In some instances, more than one family members are deficient in one or more types of immunoglobulins
- **CVID is autosomal recessive.**

Gene Mutations in CVID

- inducible co-stimulatory (ICOS)
- protein on B-cells (CD19)
- Mutations in a cell receptor (TACI)



Estimated proportion of each disease gene within the CVID population based on published cases. Reproduced with permission from Bogaert et al.

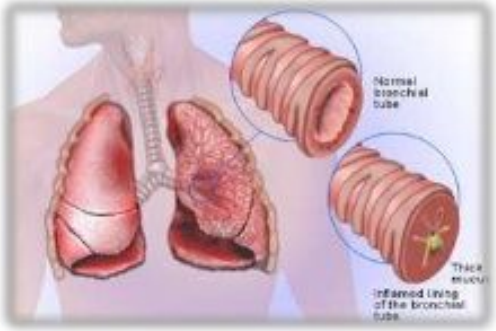
IgA deficiency

- Low serum and mucosal IgA; Most common immunoglobulin deficiency.
- IgA is the major immunoglobulin in mucosal secretions and is thus involved in defending the airways and the gastrointestinal tract.
- So, there are increased risk for mucosal infection, especially viral.
- recurrent infections in places such as the ears, sinuses or urinary and intestinal tracts.
- Some may not only suffer from recurrent infections but may take longer to heal from them or need additional rounds of antibiotics to fend off an infection.
- Most patients are asymptomatic.

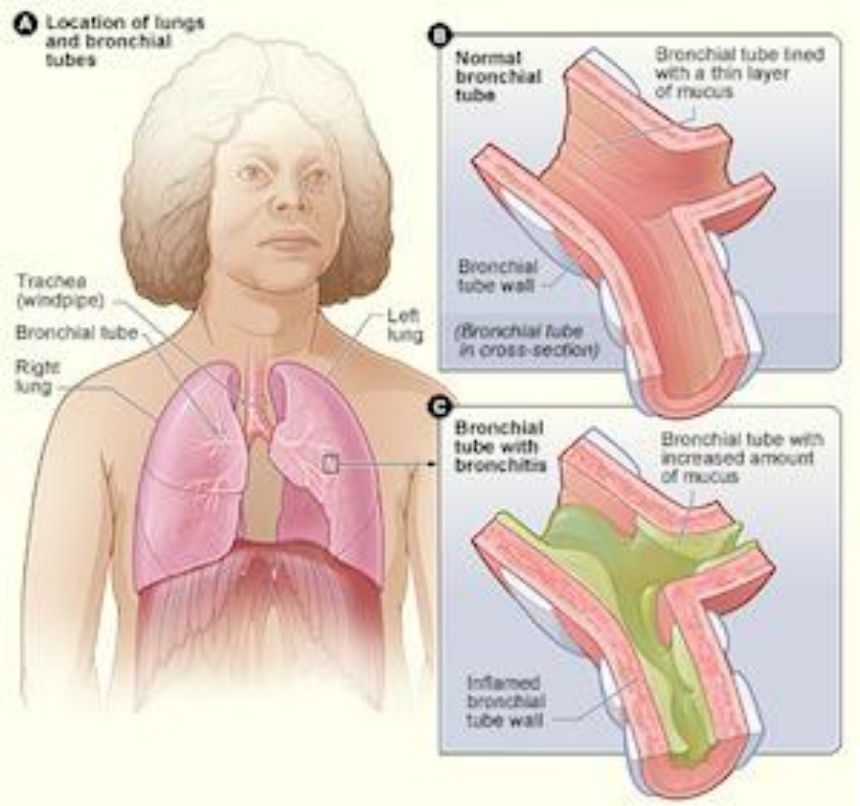
Symptoms (1)

85–90% of IgA-deficient individuals are asymptomatic.

◆ The most common symptom of Selective IgA Deficiency is susceptibility to infections including:



- Bronchitis.
- Chronic diarrhea.
- Conjunctivitis.
- Gastrointestinal inflammation.
- Mouth infection.

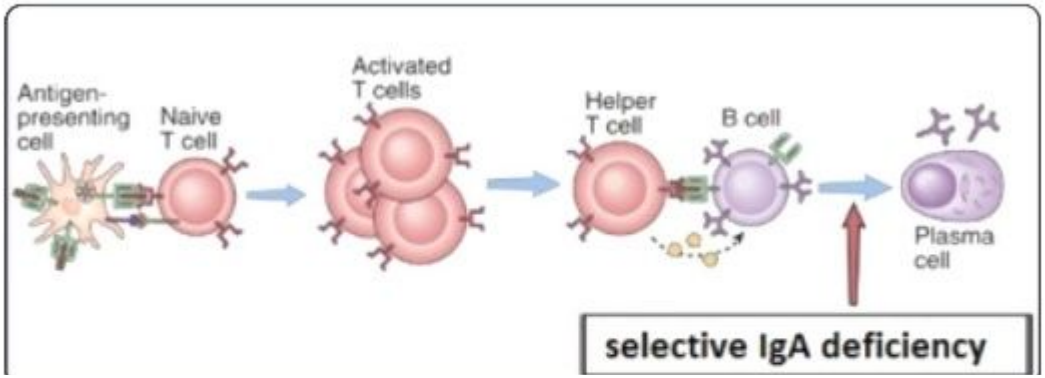


The top panel shows a healthy lung and the bottom shows a lung infected with bronchitis which is common in patients with IgA deficiency

- The pathogenesis of IgA deficiency seems to involve a block in the terminal differentiation of IgA-secreting B cells to plasma cells; IgM and IgG subclasses of antibodies are present in normal or even supranormal levels.

- Celiac disease is a GI disease that is associated with Iga deficiency.

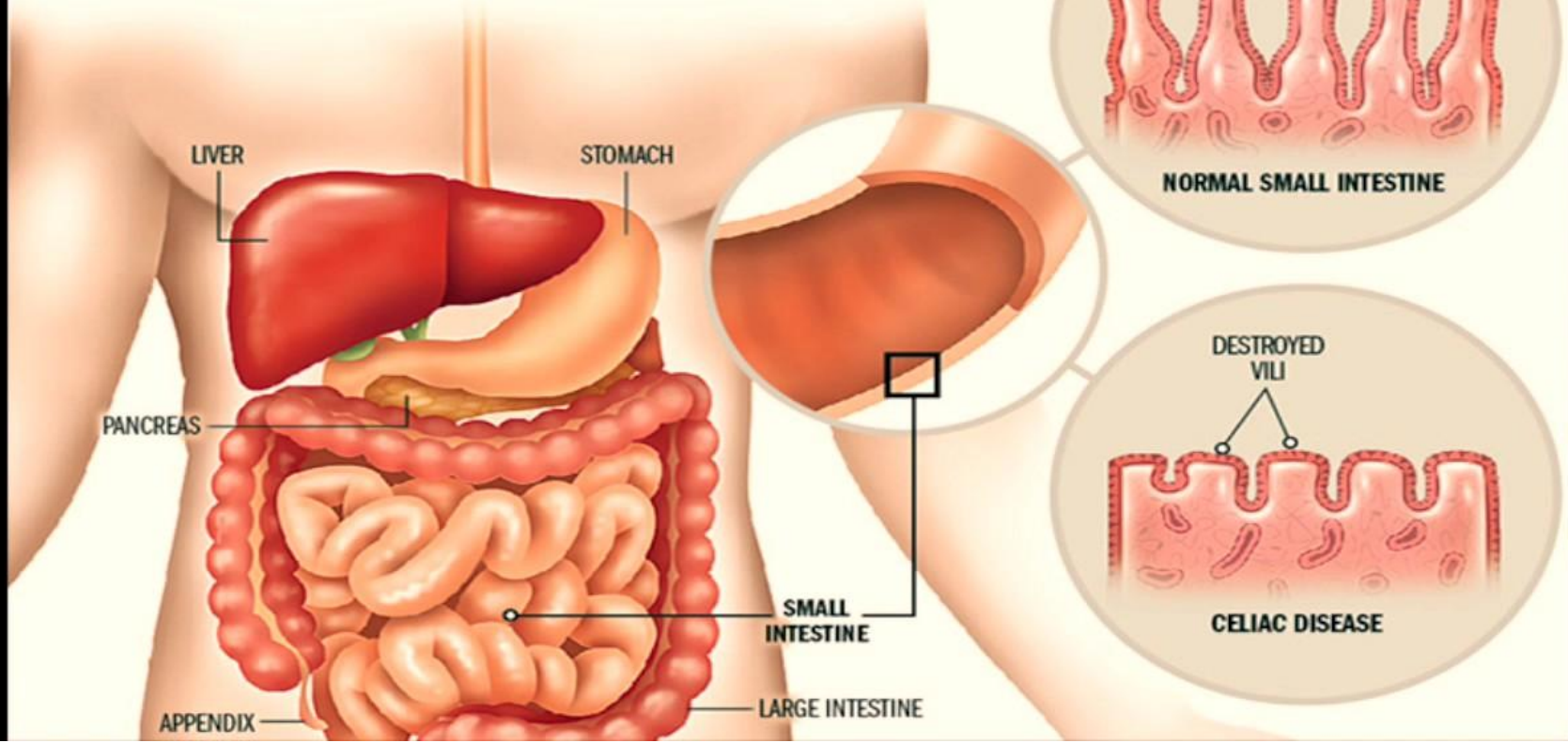
- People with IgA deficiency should be tested for celiac disease because they are 10 to 20 times likely to develop an autoimmune response to gluten than the general population.



"B lymphocytes are unable to produce Ig A"

Damage from celiac disease

In a healthy small intestine, tiny hairlike projections called villi absorb nutrients from food. When people with celiac disease eat foods containing wheat, barley, or rye, the body's immune system attacks the gluten proteins. This immune response also destroys the villi, leading to nutritional deficiencies.



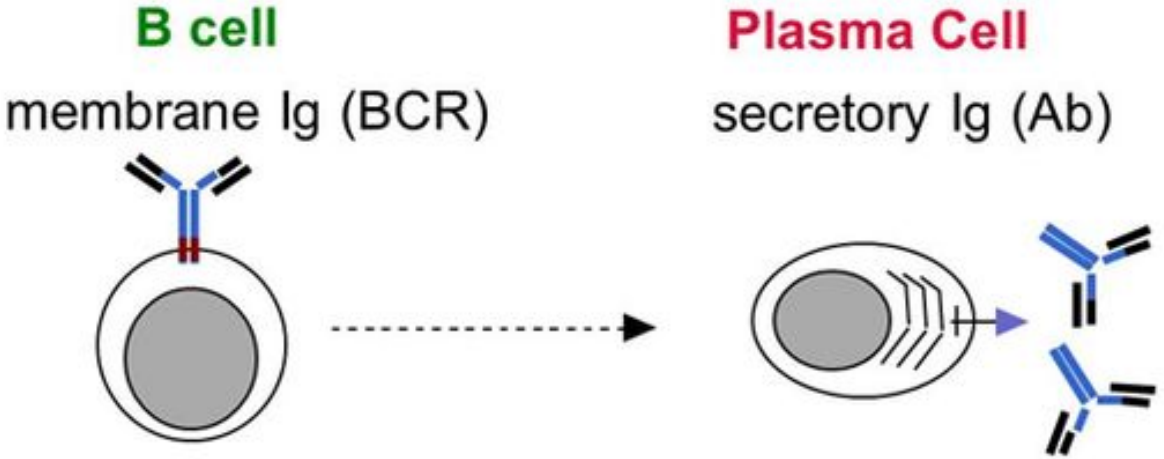
causes

- Unknown in many cases
- mutation of heavy chain constant regionin some.
- IgA deficiency is could be inherited (20% of cases) , which means it is passed down

Hyper- IgM Syndrome

- Characterized by elevated levels of IgM
- To understand how this happens we need to go back to how B cells are activated; there are two ways:

1. Antigen binds IgM that present on the surface of naïve B cells; that results in IgM secreting plasma cells.



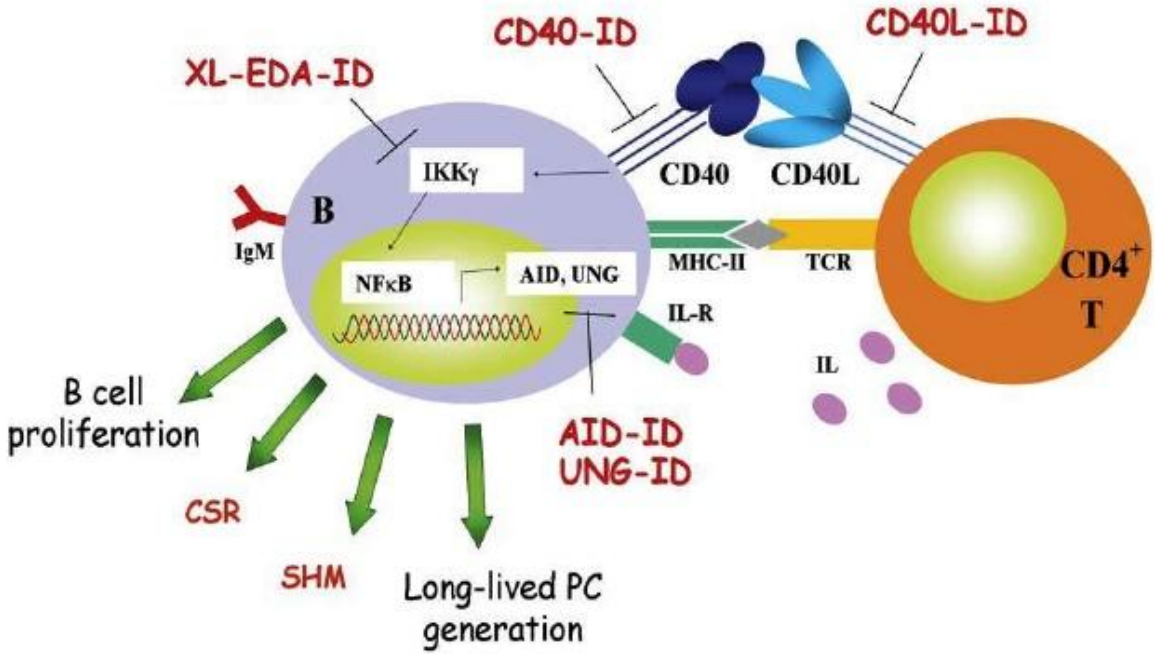
Hyper- IgM Syndrome

2. B cells can actually present MHCII on its surface;

$CD4^+$ T cells will bind that antigen and that will result in the first stimulus of B cells,

the second stimulus happens when CD40 ligand binds CD40 receptor on the surface of T cells,

this binding activates T cells allowing it to produce IL-4 and IL- 5; which allows B cell maturation and class switching, so these B cells will produce IgA, IgG and IgE.



Notarangelo et al. J ALLERGY CLIN IMMUNOL 2006; 117(4): 855-64

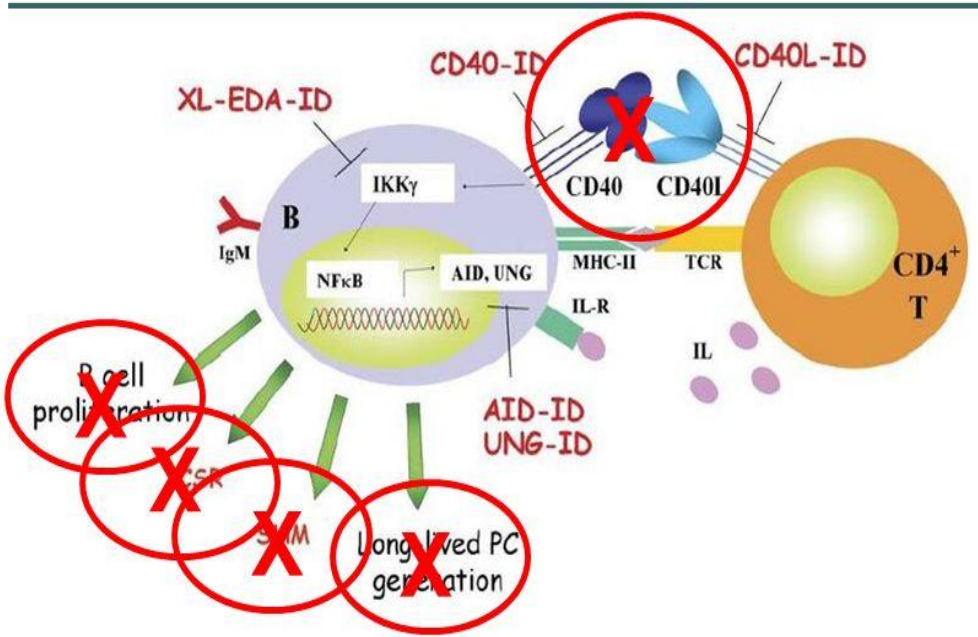
Hyper- IgM Syndrome

- Due to **mutated CD40L** (on helper t cells) or **CD40 receptor** (on B cells).

1. Second signal cannot be delivered to helper T cells during B cell activation.

2. Consequently, IL-4 and IL-5 necessary for Ig class switching are not produced.

3. Low IgA, IgG and IgE results in:
   a. recurrent pyogenic infections “pus forming” (due to poor opsonization, due to low IgG), especially at mucosal sites (due to low IgA).



- The the first mechanism is intact so IgM is produced with no problem; that's that cause of the high IgM levels.

- Occasionally, the IgM react with blood cells, giving rise to autoimmune hemolytic anemia, thrombocytopenia, and neutropenia.

- In older patients, there may be a proliferation of IgM-producing plasma cells that infiltrate the mucosa of the gastrointestinal tract.

Hyper IgM Syndrome

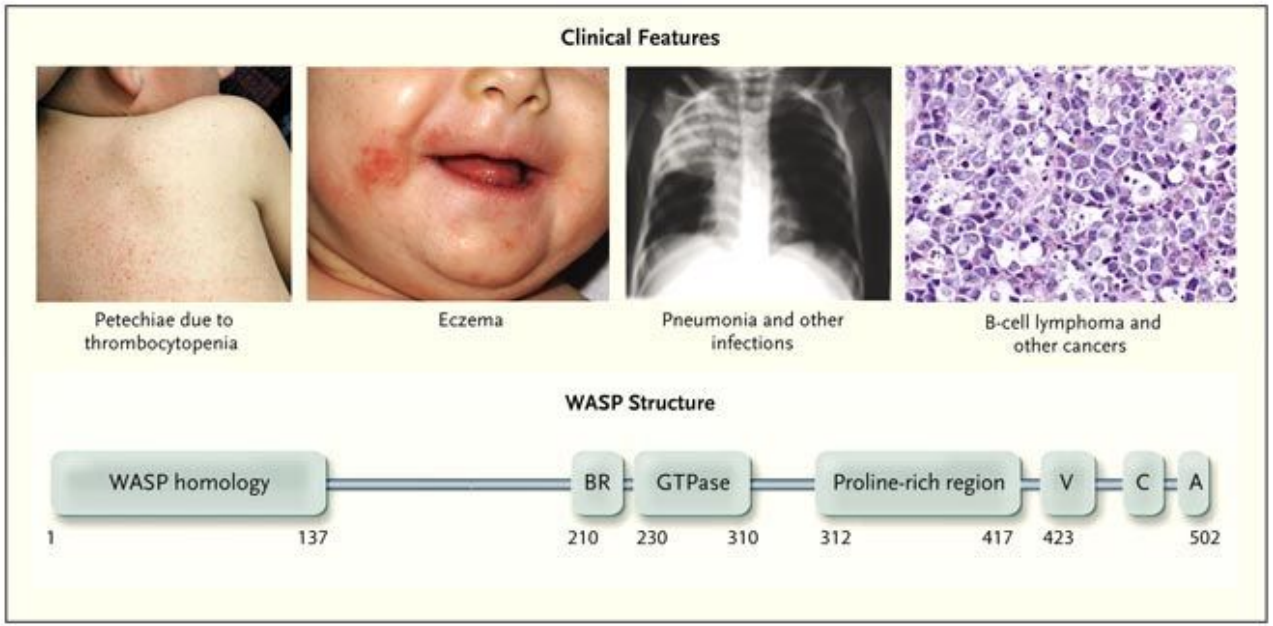
- **Hyper IgM syndrome** is a family of genetic disorders in which the level of Immunoglobulin M (IgM) antibodies is relatively high
- Patients with Hyper IgM (HIM) syndrome have an inability to switch production of antibodies of the IgM type to antibodies of the IgG, IgA, or IgE type.
- The hyper IgM syndrome results from a variety of genetic defects that affect this interaction between T-lymphocytes and B-lymphocytes.
- The most common form of hyper IgM syndrome results from a defect or deficiency of a protein that is found on the surface of activated T-lymphocytes. The affected protein is called "CD40 ligand"

Wiskott-Aldrich syndrome

- It characterized with triad:

1. Thrombocytopenia: so they have an increase risk of bleeding.
2. Eczema: Skin rash.
3. A variety of recurrent infections; as they have defective humoral and cellular immunity

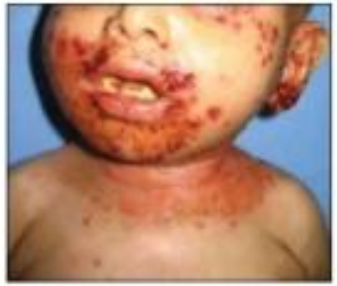
In these patients bleeding is a major cause of death.

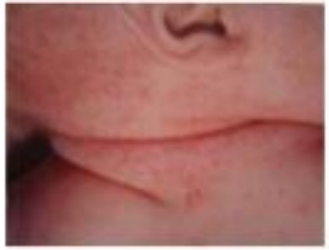


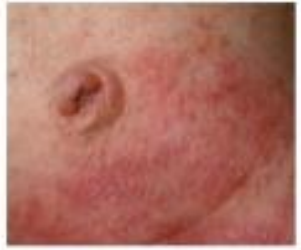
Wiskott–Aldrich Syndrome

Wiskott-Aldrich syndrome

- ❑Infant males ♂
- ❑severe diarrhea,
- ❑eczema, and
- ❑thrombocytopenia







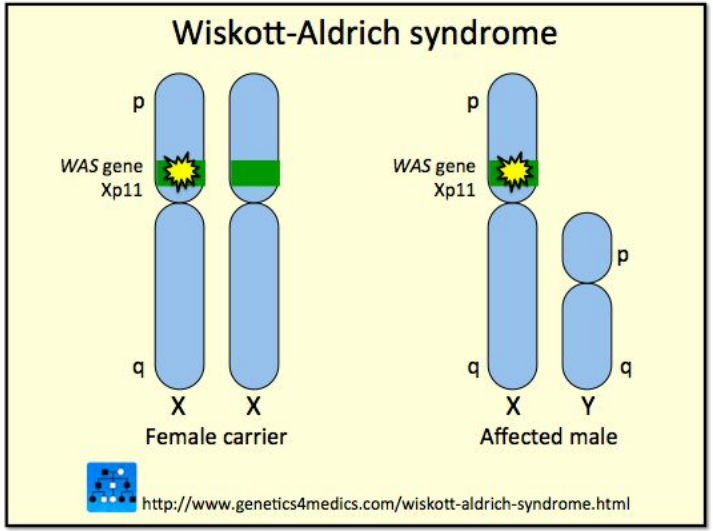
Because of severe thrombocytopenia

(small platelets and a reduced number of platelets)

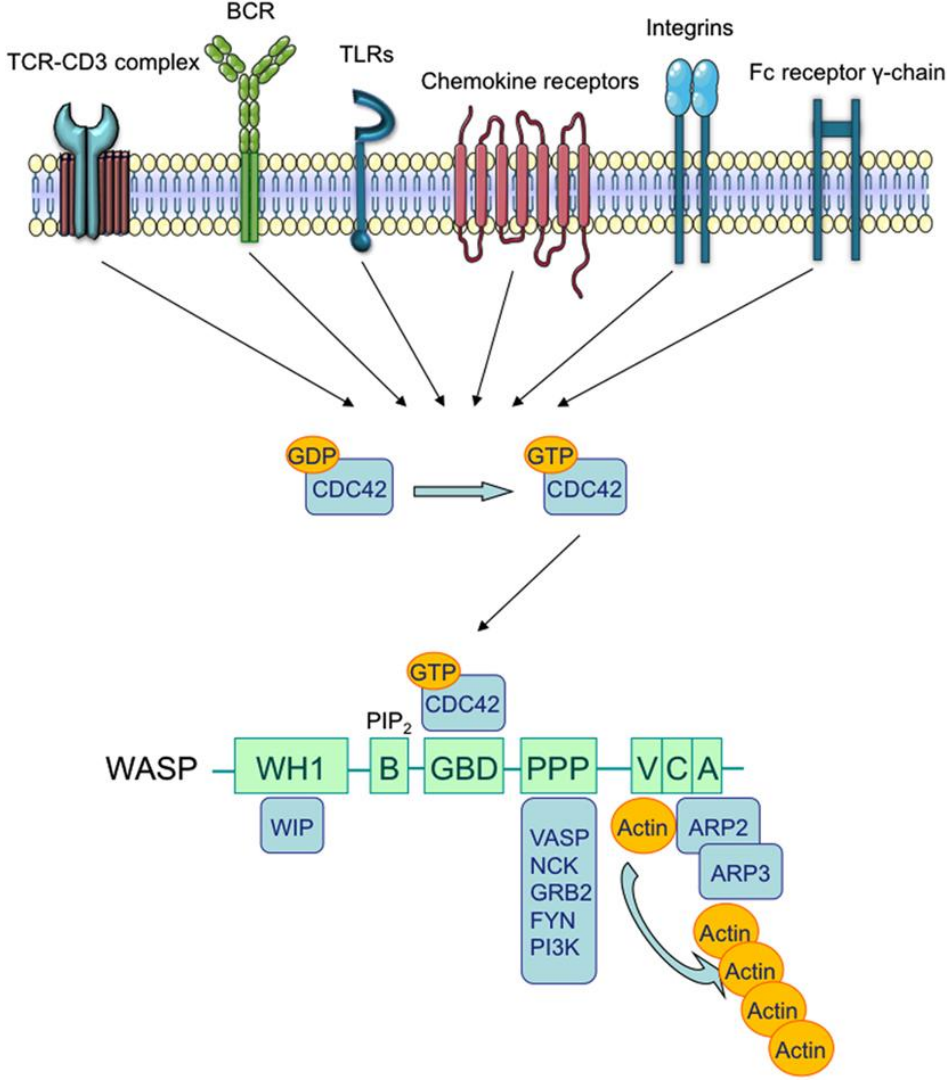
- bloody diarrhea
- hemorrhagic manifestations

Wiskott-Aldrich syndrome

- The syndrome is caused by mutations in an X-linked gene encoding Wiskott-Aldrich syndrome protein (WASP).
- WASP belongs to a family of signaling proteins that link membrane receptors, such as antigen receptors, to cytoskeletal elements.



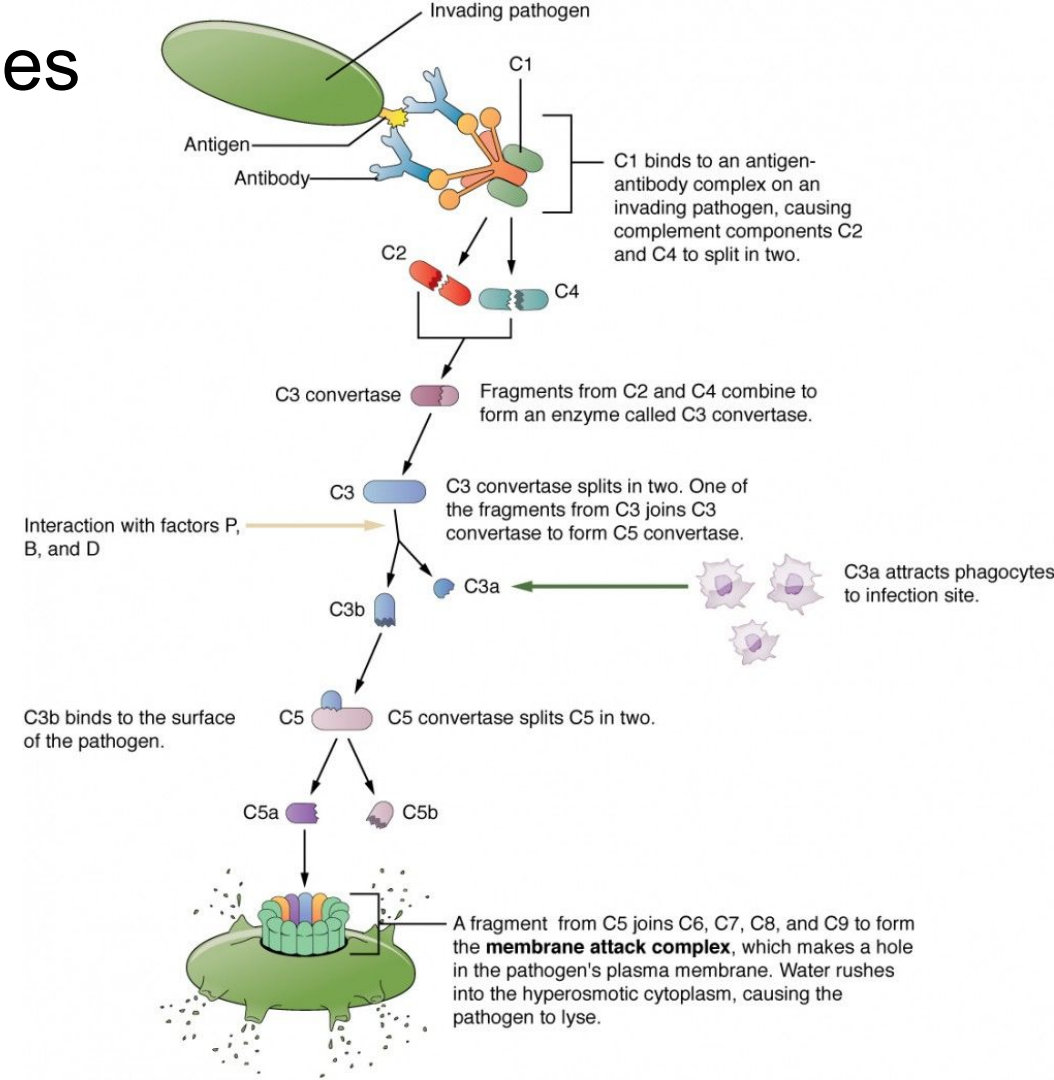
- The WASP protein is involved in cytoskeleton-dependent responses, including cell migration and signal transduction.



Complement deficiencies

1. If a patient is deficient in any of C5-C9 : results in increased susceptibility to recurrent neisserial (*N gonorrhoeae* and *N meningitidis*) infections,

   as *Neisseria* bacteria have thin cell walls and are especially susceptible to the lytic actions of complement.

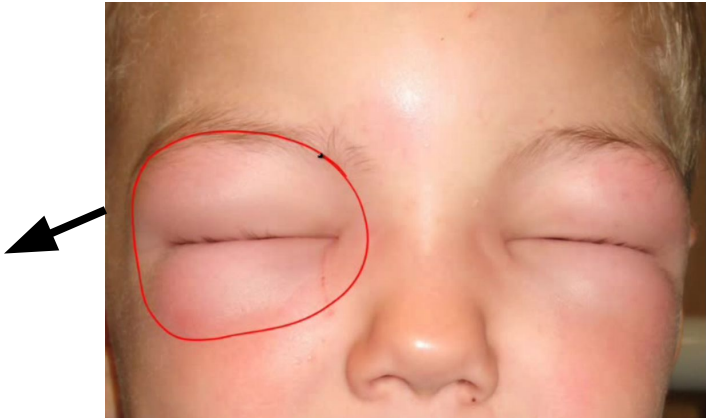


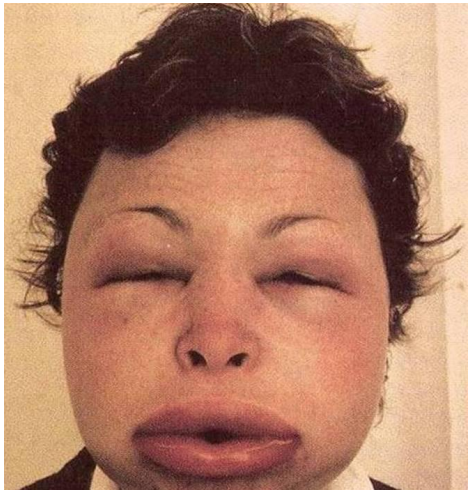
Complement deficiencies

2. C1 inhibitor deficiency: results in over activation of C1 and therefore overactivation of complement

This causes vasodilation, increased vascular permeability -> acute inflammation that causes edema

So this is called hereditary angioedema, which is characterized by edema of the skin and mucosal surfaces, especially periorbital.





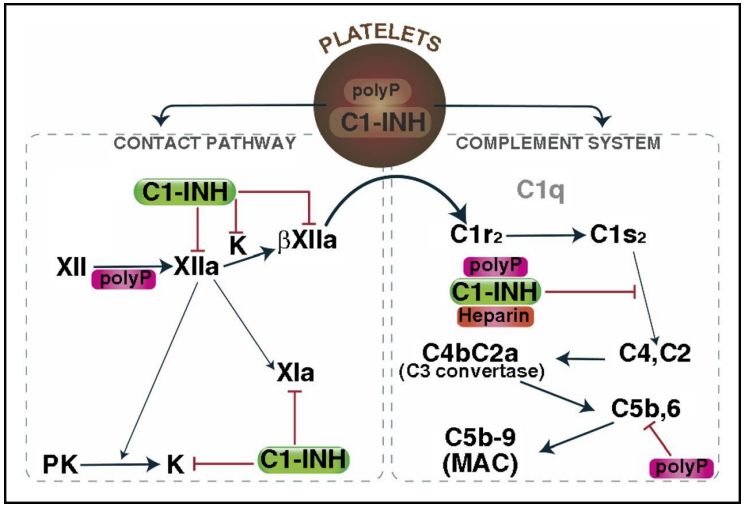
Complement deficiencies

- A deficiency of *C1 inhibitor (C1 INH)* gives rise to an autosomal dominant disorder called *hereditary angioedema*.

- C1 INH is an inhibitor of many proteases, including kallikrein and coagulation factor XII, both of which are involved in the production of vasoactive peptides such as bradykinin.

- Therefore, defective C1 INH activity leads to over-production of bradykinin, which is a potent vasodilator.

- Affected patients have episodes of edema affecting skin and mucosal surfaces.



Genetic Defects in the Immune System

Genetic Transmission	Clinical Disease	Genetic Abnormality	Immune Defects	Infections
X-linked				
	XLA	B cell progenitor kinase	B cell formation	Encapsulated respiratory bacteria
	Hyper-IgM	CD40 ligand (CD39) on T cells	T cell interaction with B cells to switch Ig isotypes	See XLA
	XSCID	Truncated γ chain gene common to IL-2, IL-4, IL-7, IL-9, and IL-15 receptors	T cell formation T/B cell function	Many opportunistic agents
	XCID	Missense mutation in γ_c chain gene	Less severe than XSCID	Fewer types of infections than XSCID
	WAS	Mutations in a gene coding for a proline-protein Xp11.22-23	T & B cell immunity ↑ IgA & IgE, ↓ IgM	↑ infections middle ears, sinuses, lungs
	CGD	gp90 of cytochrome b_{558}	Intracellular killing by PMNs	Catalase⁺ bacteria/fungi
Autosomal recessive				
	SCID	Adenosine deaminase; purine nucleoside phosphorylase	T cell formation B cell function	See XSCID
	AT	Protein-like PI-3 kinase	T cell formation B cell function, ↓ IgA	See XLA
	CGD	$p22^{phox}$ $p47^{phox}$ $p67^{phox}$	Intracellular killing by PMNs	
	LAD	C11b/ CD18	Leukocyte adherence	Similar to CGD

XLA is agammaglobulinemia; **hyper-IgM**, the hyper-IgM antibody deficiency disease; **XSCID**, X-linked severe combined immunodeficiency; **XCID**, X-linked combined immunodeficiency; **WAS**, Wiskott-Aldrich syndrome; **AT**, ataxia telangiectasia; **CGD**, chronic granulomatous disease; **LAD**, the leukocyte adherence defect.

Immunodeficiency Diseases

Primary: **Usually congenital, resulting from genetic defects in some components of the immune system.**

Secondary (Acquired): **as a result of other diseases or conditions such as:**

- **»HIV infection**
- **»malnutrition**
- **»immunosuppression**

Two major types of immunodeficiency diseases

- Secondary immunodeficiencies
  - immunodeficiency resulting from infections and other diseases
  - immunodeficiency resulting from iatrogenic causes
  - immunodeficiency due to aging or malnutrition
- Primary immunodeficiency
  - Inherited immunodeficiencies

Secondary Immunodeficiency Disorders

- :***Immune deficiencies secondary to other diseases or therapies are much more common than the primary (inherited) disorders.***
- **Secondary immune deficiencies may be encountered in patients with:**
  - **Infection (HIV)**
  - **Malnutrition,**
  - **Aging,**
  - **Immunosuppression, as in cancer, and renal disease**
  - **Autoimmunity,**
  - **Chemotherapy.**
  - **However, the most common cases of immune deficiency are therapy-induced suppression of the bone marrow and of lymphocyte function.**