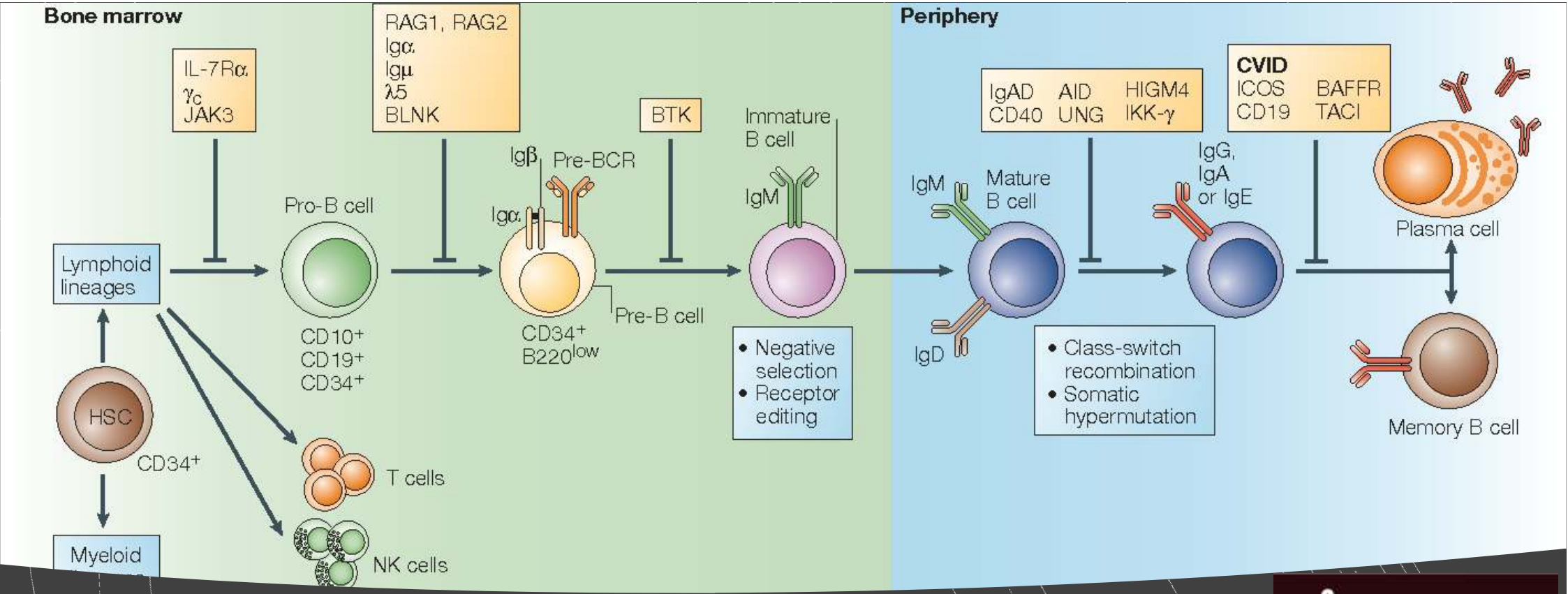


Συγγενείς διαταραχές Β-λεμφοκυττάρων

Βασιλική Λαμπροπούλου

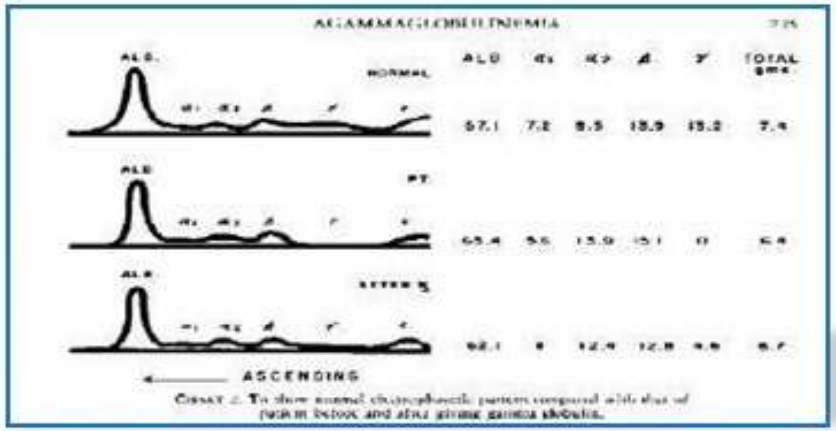
Αιματολόγος, Επιμελήτρια Α΄ΕΣΥ

Αιματολογικό Τμήμα Παθολογικής Κλινικής ΠΓΝΠατρών

Primary Immunodeficiency

- The **primary Immunodeficiencies** result from one or more abnormalities of the immune system and that manifest clinically as an increased **susceptibility to infection**.
- This group of human diseases was first described by a clinician who carefully studied a child with recurrent respiratory infections and who later documented the first immune deficiency disorder in the human.
- Knowledge of B-cell biology has arisen from studies of the primary immune defects that prevent normal B-cell development

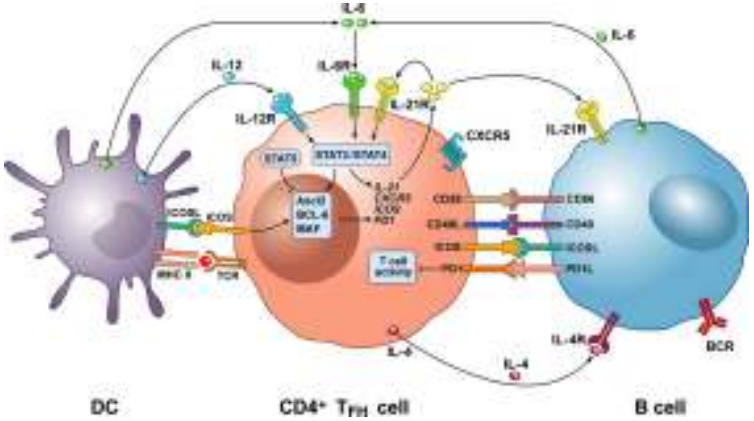
- First recognized human immune deficiency
- Discovered in 1952 by **Colonel Ogden Bruton**
- Case report : 8-year-old boy, recurrent infections over a 4-year period
  - Majority of infections: pneumococcus
  - Bruton attempted to vaccinate → no γ globulin was production
  - Treated with monthly intramuscular injections of human γ globulin with significant clinical improvement
  - No family history
- Subsequent cases revealed a similar clinical phenotype with an X-linked pedigree

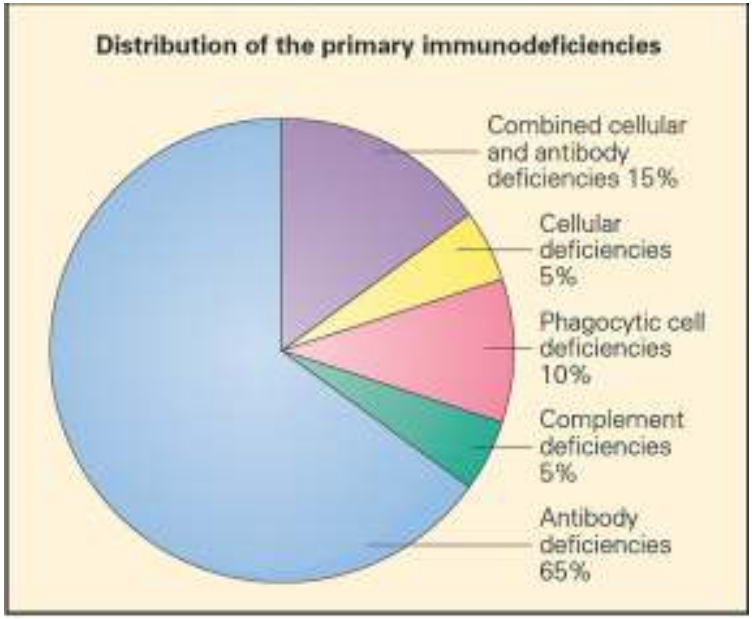


From: Bruton, OC: Agammaglobulinemia, Pediatrics 1952 1952;9;722-728

Primary B-cell immunodeficiencies

- Primary B-cell immunodeficiencies result from **impaired antibody production** due to either molecular defects **intrinsic to B-cells** or a **failure of interaction between B-cells and T-cells**.
- While more than **300 primary immune defects** are now known, clinically, the **most common defects** found in patient populations are those that **impair B-cell development or function.**





Rank	PID defects	Global number
1	Predominantly antibody deficiencies, including selective IgA deficiency, unspecified hypogammaglobulinemia, and hyper-IgM syndrome	13,333
2	Common variable immunodeficiency (CVID), AR	11996
3	Chrom 22q11.2 deletion syndrome (de novo HS or AD)	5215
4	IgG subclass deficiency, isolated, AR	4612
5	Specific antibody deficiency (normal Ig and B cells), AR	4072
6	Hypogammaglobulinemia of infancy, transient (normal B cells), AR	4028
7	MEFV deficiency (familial Mediterranean fever (FMF), AD/AR)	2835
8	ATM deficiency (ataxia-telangiectasia (AT)), AR	2514
9	C1QA deficiency (C1 inhibitor), AD	2420
10	BTK deficiency, XL	2486
11	TACI deficiency	2239
12	Immunodeficiencies affecting cellular and humoral immunity, including SCID	2178
13	Autoinflammatory disorders, including PFAPA	1983
14	Complement deficiencies	1629
15	Congenital defects of phagocyte number, function, or both	1563
16	IgA with IgG subclass deficiency, AR	1562
17	CGD, XL (gp91phox deficiency)	1385
18	WAS deficiency (Wiskott-Aldrich syndrome), XL	1258
	Total	67308

Primary B-cell immunodeficiencies

- B-cell immunodeficiencies are often distinguished from other immune defects, by **age** of onset, **clinical parameters**, **severity and mode of inheritance.**
- The types of infections that hallmark an underlying B-cell defect include recurrent infections that are **typically encapsulated bacteria**, distinct from patients with **T-cell or combined immunodeficiencies,** who are more likely to have **opportunistic or severe viral** infections.

Chart 1 - Clinical characteristics of primary immunodeficiencies.

Characteristics	Predominant defect in the T cell	Predominant defect in the B cell	Phagocytic defect	Complement defect
Age at onset	Precocious	After maternal antibodies are catabolized (5-12 months) or at the end of childhood	Precocious	Any age
Most common pathogens	Mycobacteria, pseudomonas, CMV, EBV, varicella, enteroviruses, *Candida* sp., *Pneumocystis jiroveci*	*Streptococcus pneumoniae*, Hib, *Staphylococcus aureus*, *Campylobacter* sp. enteroviruses giardia, cryptosporidium	*S. aureus*, *Pseudomonas* sp., *Serratia* sp., *Klebsiella* sp., *Candida* sp., *Nocardia* sp., *Aspergillus* sp.	*Neisseria meningitidis*, *Escherichia coli*
Most common alterations	Inadequate growth, chronic diarrhea, persistent candidiasis	Sinopulmonary infections, gastrointestinal symptoms, malabsorption, arthritis, meningoencephalitis	Cellulitis, abscesses, adenitis, periodontitis, osteomyelitis	Meningitis, arthritis, septicemia, sinopulmonary infections
Special characteristics	Graft-versus-host disease caused by maternal cells or transfusion of non-irradiated blood, inflammation after BCG vaccination, hypocalcemic tetany	Autoimmune disease, lymphoma, thymoma, paralysis caused by the oral vaccine against poliomyelitis	Delay in the drop off of the umbilical stump, delayed healing	Vasculitis, systemic lupus, dermatomyositis, glomerulonephritis, angioedema

CMV: cytomegalovirus; EPV: Epstein-Barr virus; and Hib: *Haemophilus influenzae* type B. Adapted from Woroniecka & Ballow.[23]

Primary B-cell immunodeficiencies result in:
a variable loss of B-cells, reduction or absence of serum immunoglobulins and/or loss of antibody function.

1) **Severe reduction** in **all** serum **immunoglobulin** isotypes with profoundly **decreased or absent B cells**, recognized as **agammaglobulinemia**

2**) Severe reduction** in serum **IgG and IgA** with **normal/elevated IgM** with normal numbers of B cells **(Hyper IgM syndrome)**

3) **Severe reductio**n in at least **2 serum immunoglobulin isotypes** (typically **IgG** and **IgA**) with normal or low number of B cells (**CVID** phenotype)

4) **Isotype or light chain deficiencies** with generally normal numbers of B cells.

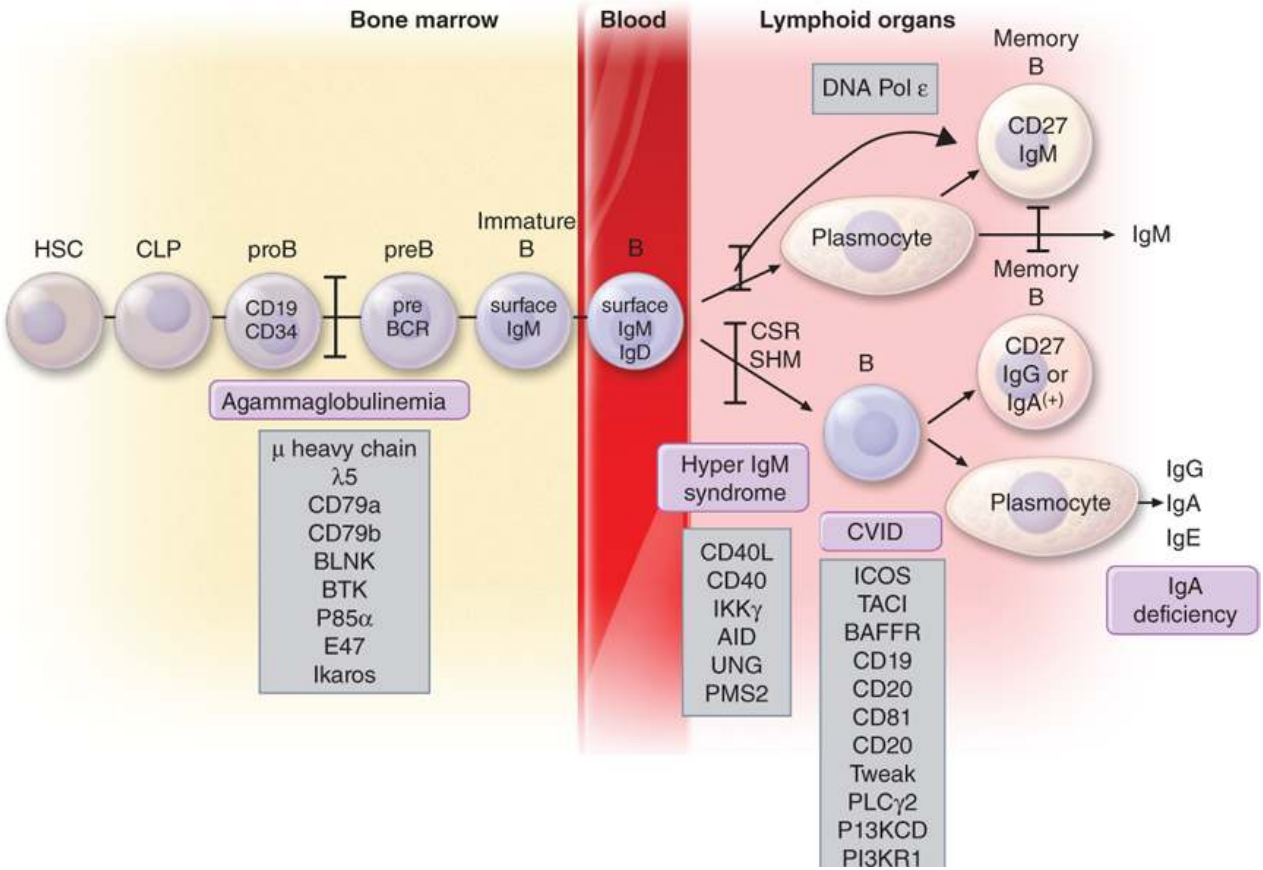
Primary B-cell immunodeficiencies

The major B cell defects can be divided into three major categories of antibody deficiencies:

(1) defects in early B cell development,

(2) hyper-IgM syndromes (also called class-switch recombination defects), and

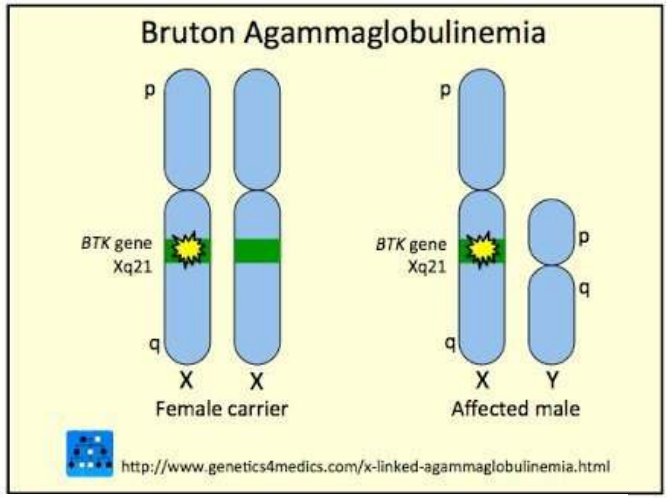
(3) common variable immunodeficiency (CVID)

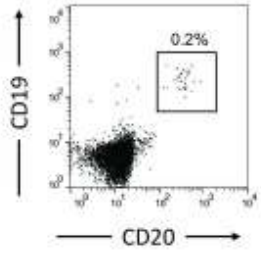


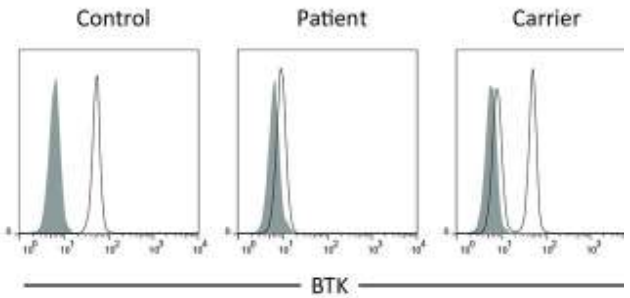
Defects in early B cell development

Agammaglobulinemia: X-linked agammaglobulinemia (XLA)

- Agammaglobulinemia is characterized by **absence of circulating B-cells with severe reduction in all serum immunoglobulin levels.**
- This is a rare defect (1:100,000 to 1:200,000 depending on ethnicity and the specific genetic defect).
- Both **X-linked and autosomal recessive** forms of the disease have been described.
- The classic disorder of B-cell development is X-linked agammaglobulinemia (XLA), first described in 1952 by Ogden Bruton.
- An X-linked inheritance pattern was observed.



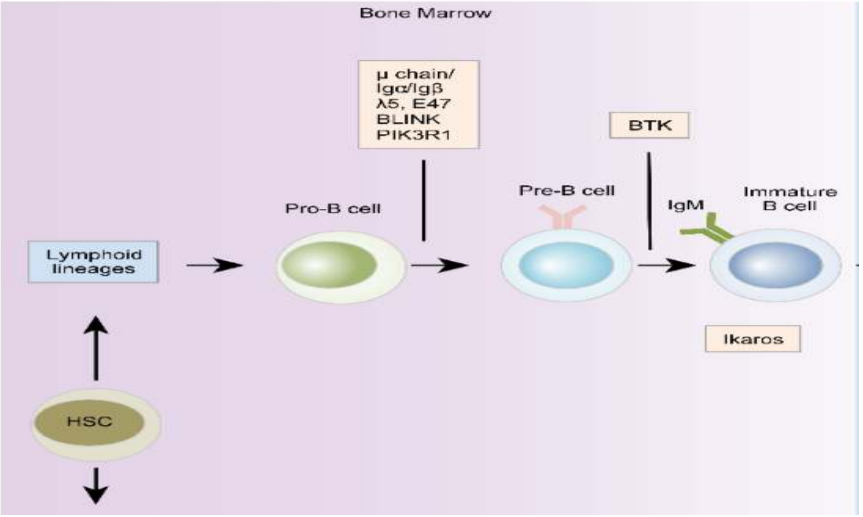


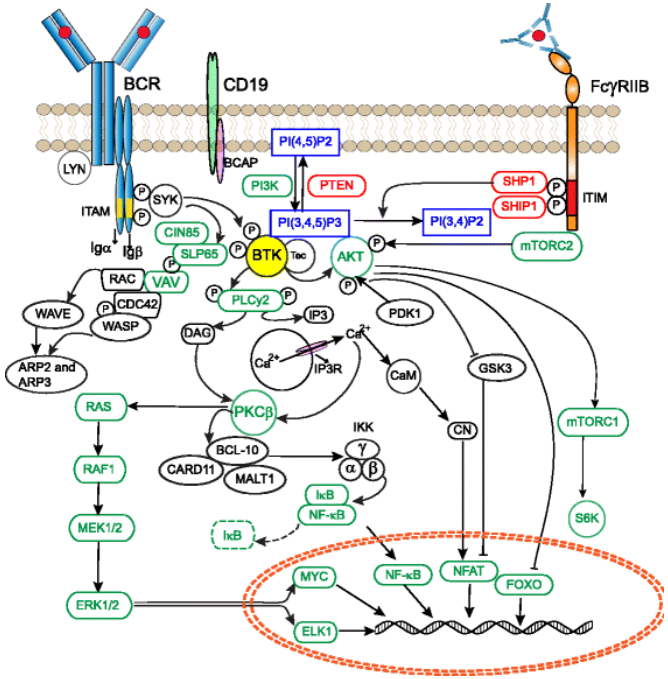


Defects in early B cell development

X-linked agammaglobulinemia (XLA)

- Pro-B-cell and pre-B-cells are present in the bone marrow **but** are not able to efficiently progress to maturation.
- **BTK** is a member of a family of cytoplasmic tyrosine kinases and **is expressed at all stages of B-cell differentiation except for plasma cells**.
- Mutations in BTK account for approximately **85%** of patients presenting with congenital agammaglobulinemia.

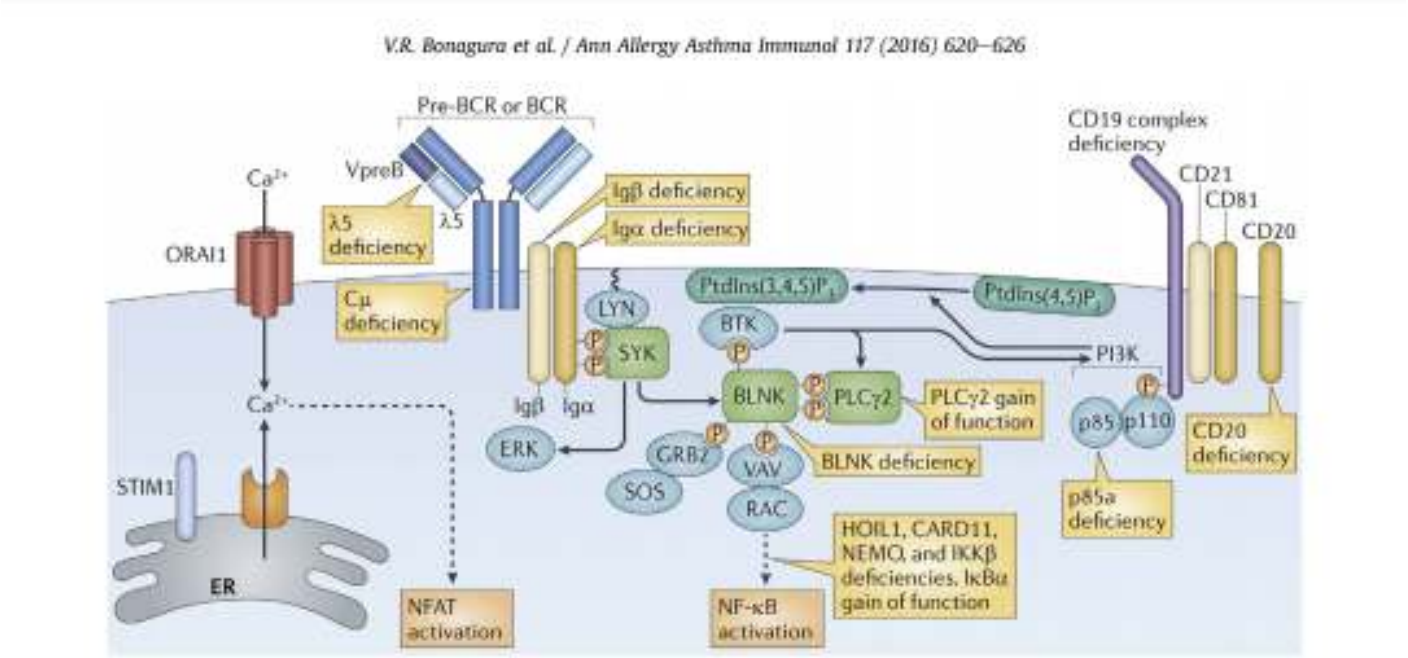




Defects in early B cell development

Autosomal agammaglobulinemias

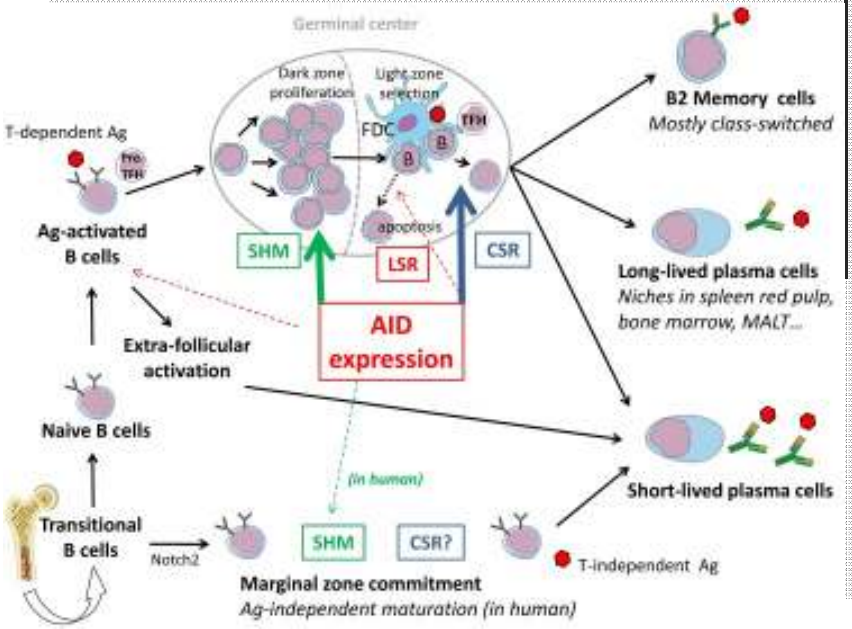
- In 1970s, a few females were identified with phenotypical features identical to XLA with an **autosomal recessive** inheritance pattern.
- Defects of the BCR structure itself, including the **μ heavy chain, surrogate light chains (VpreB and λ5), the Igα (CD79A) and Igβ genes (CD79B)** lead to autosomal forms of agammaglobulinemia.



Disease [a]	Genetic defect	Inheritance [b]	Immunoglobulin level and antibody response
Severe Reduction in All Serum Immunoglobulin Isotypes with Profoundly Decreased or Absent B Cells (Agammaglobulinemia			
BTK deficiency, X-linked agammaglobulinemia (XLA)	*BTK*	XL	All isotypes decreased in most, some have detectable immunoglobulins
μ heavy chain deficiency	*IGHM*	AR	All isotypes decreased
λ 5 deficiency	*IGLL1*	AR	All isotypes decreased
Igα deficiency	*CD79a*	AR	All isotypes decreased
Igβ deficiency	*CD79b*	AR	All isotypes decreased
BLNK deficiency	*BLNK*	AR	All isotypes decreased
PIK3R1 deficiency	*PIK3R1*	AR/AD	All isotypes decreased
E47 transcription factor deficiency	*TCF3*	AD	All isotypes decreased

Smith T, Cunningham-Rundles C, Hum Immunol. 2019 Jun;80(6):351-362.

Hyper IgM Syndrome: Severe Reduction in Serum IgG and IgA with Normal/Elevated IgM and Normal B-cell numbers



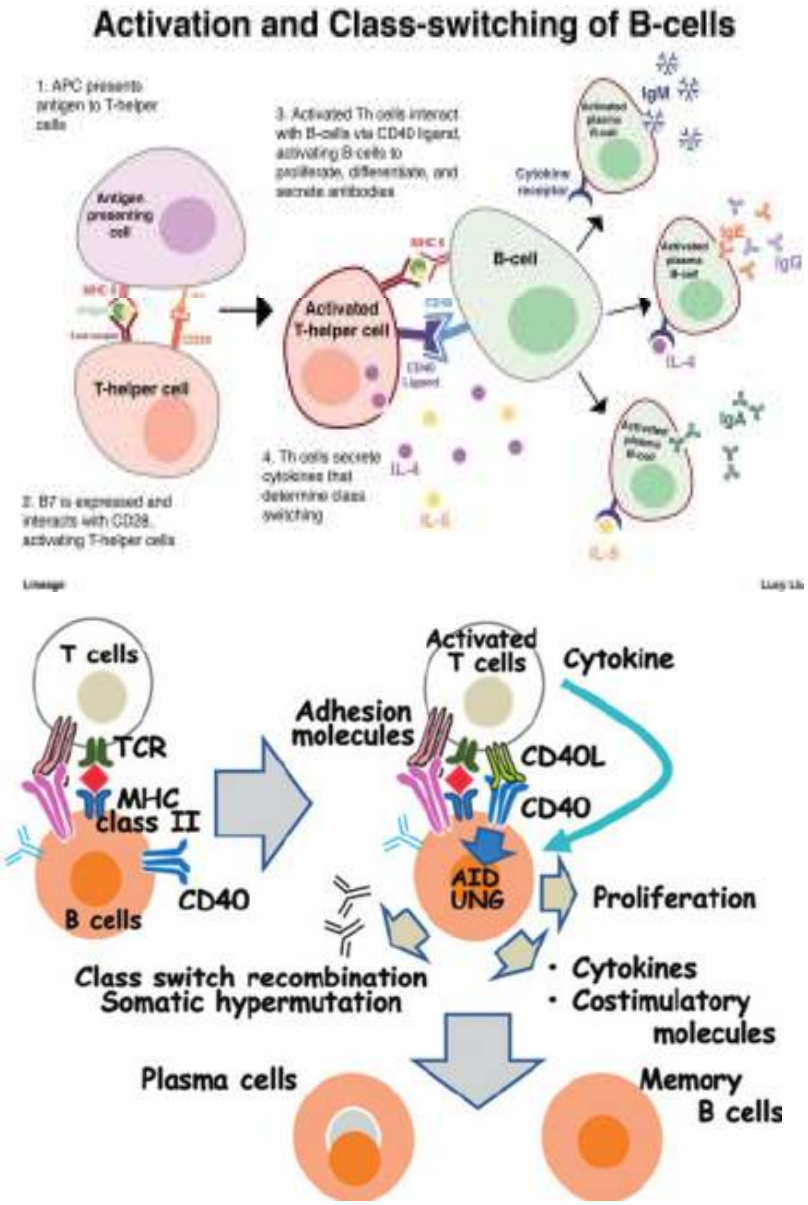
- **Class-switch recombination (CSR)** occurs downstream **of T-cell dependent B-cell activation in germinal centers.**
- T follicular helper cell→activate follicular B-cells → CSR and somatic hypermutation (SHM).
- CSR and SHM **result in high-affinity antibody production** and the differentiation of B cells into long-lived **memory B-cells and plasma cells.**
- Immunoglobulin class switch recombination deficiencies, previously termed **"hyper-IgM syndromes (HIGM)**" are **rare primary** immunodeficiencies characterized by impaired production of switched immunoglobulin isotypes and normal or elevated IgM levels.

Class-switch recombination defects

CD40L - CD40

- **CD40L on activated T-cells** cognate interactions with CD40 on B-cells
- CD40L deficiency-**X-linked trait**, is the most common form of HIGM, estimated frequency is **2:1,000,000** males.
- CD40L deficiency often presents in **infancy** with increased susceptibility to **recurrent** sinopulmonary infections **encapsulated bacteria Streptococcus pneumoniae and Haemophilus influenza**.

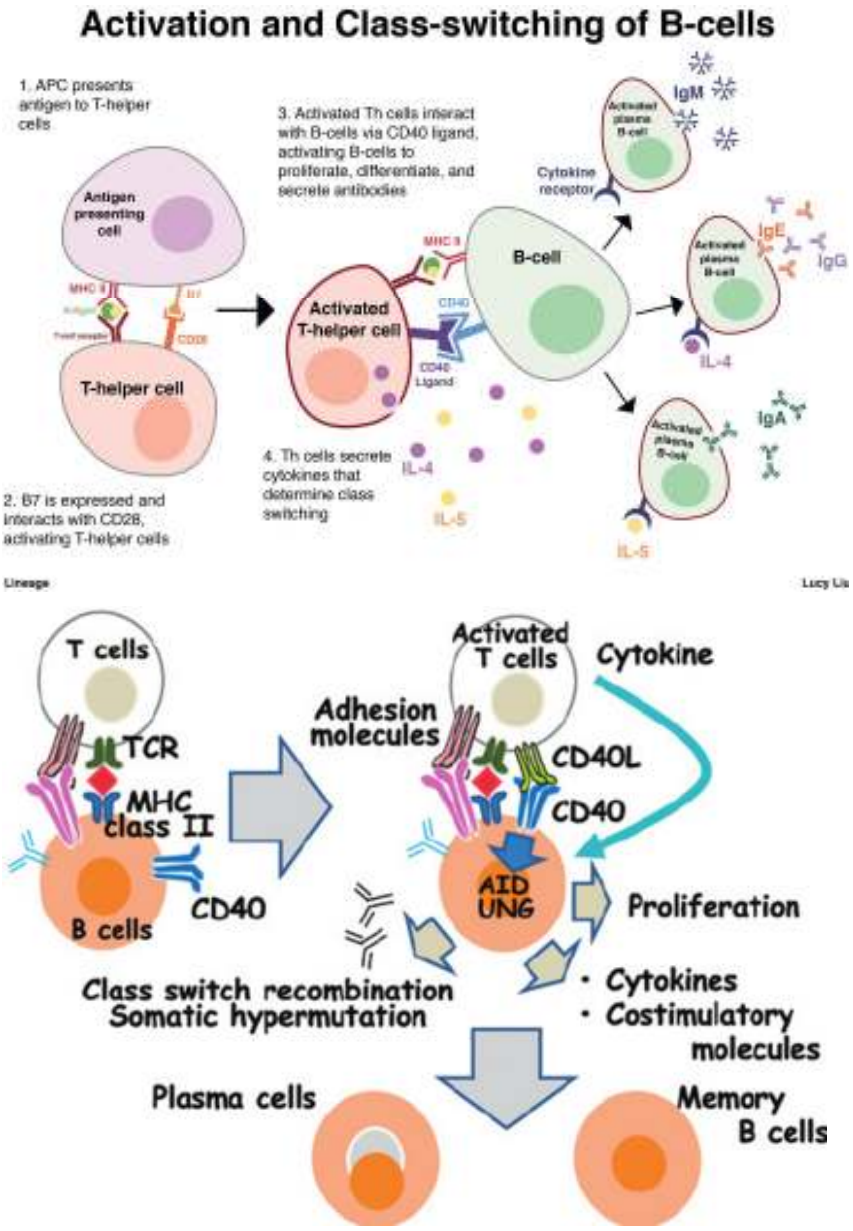
- Patients are at a higher risk of developing early in life **opportunistic infections**: **Pneumocystis, Cryptosporidium, and Histoplasma**
  CNS infections with **Cryptococcus and Toxoplasma, JC virus-related enteroviral meningoencephalitis** and **progressive multifocal leukoencephalopathy (PML)**
  biliary tract diseases: sclerosing cholangitis and cholangiocarcinoma



Class-switch recombination defects

CD40L - CD40

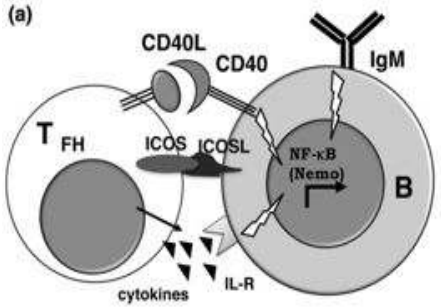
- CD40L deficiency causes **recurrent oral ulcers and proctitis**, often associated with **chronic or cyclic neutropenia** in half of patients.
- **Long term survival may be poor, due to early in life Pneumocystis carinii pneumonia, liver disease and/or malignancy.**
- **Recessive mutations in the B-cell surface receptor CD40→**similar clinical features as CD40L deficiency

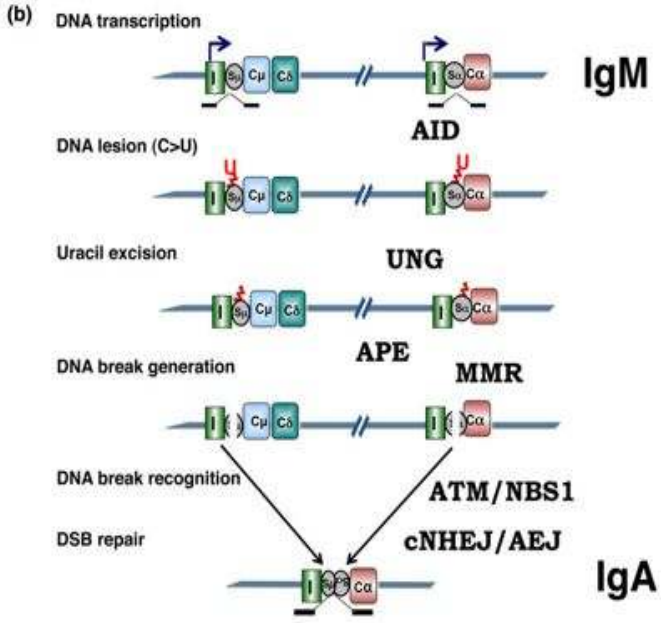


Class-switch recombination defects

Activation Induced Cytidine Deaminase (AID)

- **AID deaminates deoxycytidine to deoxyuracil** →trigger for the base-excision repair pathway→ DNA breaks→ **CSR and SHM**.
- AID is only expressed in **activated B-cells** (**autosomal recessive** and less frequently as **autosomal dominant).**
- Patients can have symptoms as early as 2-years-old, however, diagnosis can be delayed by decades.
- Patients have bacterial infections from **encapsulated bacteria** and gastrointestinal infections mainly due to **viruses** and to **Giardia lamblia**.
- Patients with AID deficiency **have enlargement of lymphoid organs** such as the spleen, tonsils, and lymph nodes.
- **Autoimmune complications** have been reported in patients and include cytopenias, hepatitis, inflammatory bowel disease, and arthritis.

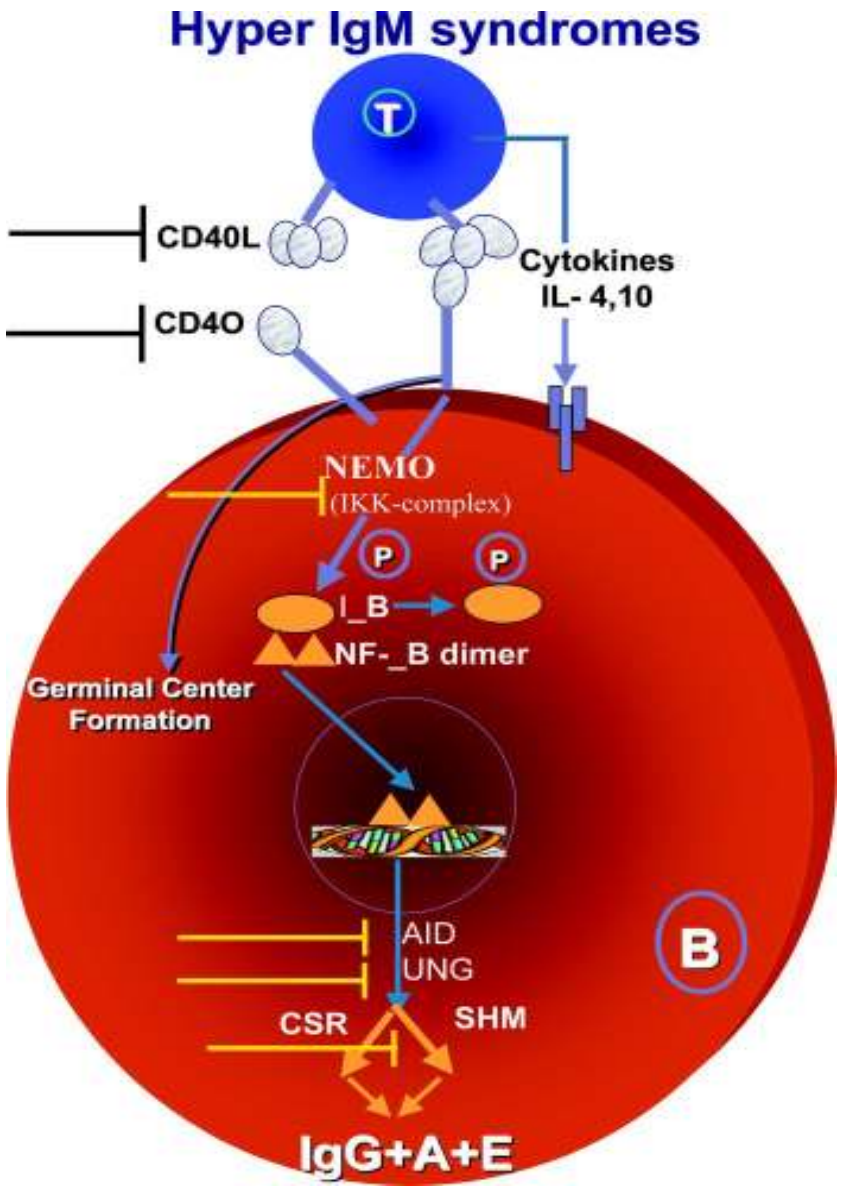




Class-switch recombination defects

Uracil-DNA glycosylase (UNG)

- UNG is the enzyme that **removes uracil** on single-stranded DNA → CSR and SHM
- UNG deficiency is inherited as **autosomal recessive** and only few cases have been described.
- UNG deficiency is indistinguishable from AID deficiency

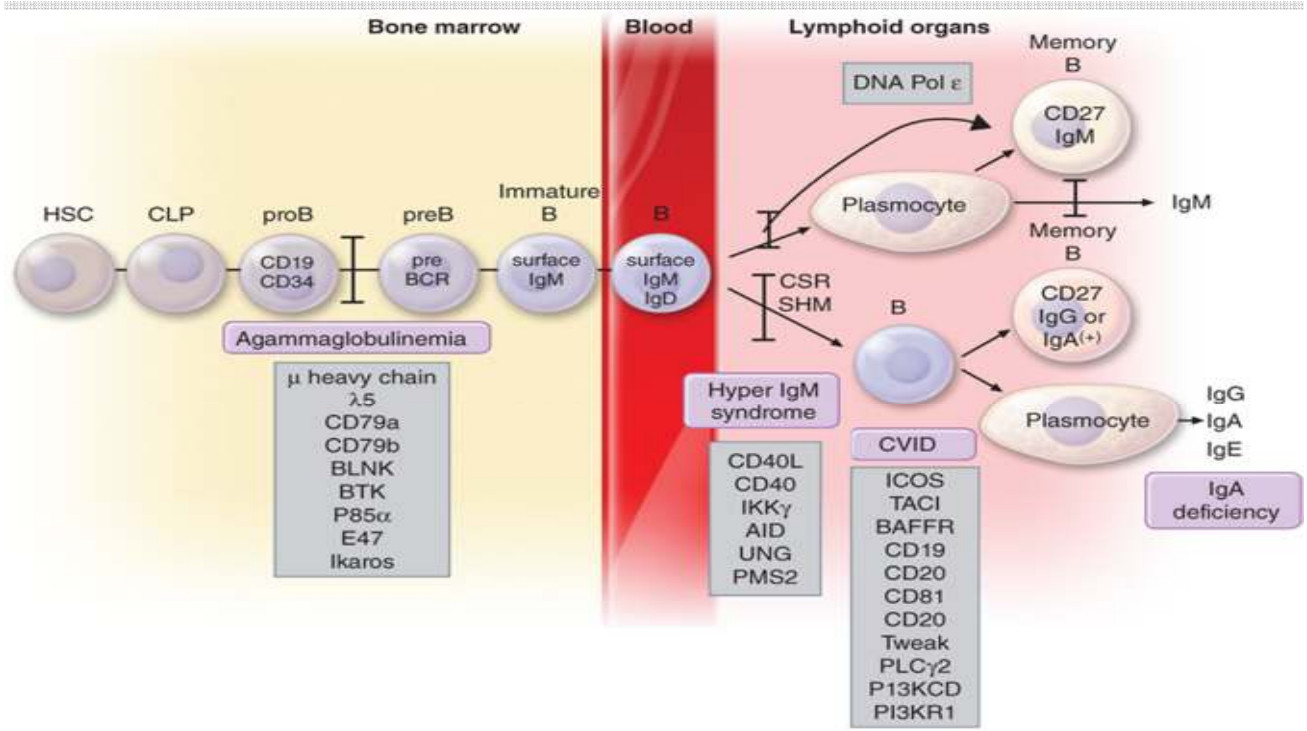


Severe Reduction in Serum IgG and IgA with Normal/Elevated IgM and Normal Numbers of B cells (Hyper IgM syndrome)

CD40L deficiency	*CD40LG*	XL	IgG and IgA decreased, IgM increased	
CD40 deficiency	*CD40*	AR	IgG and IgA decreased, IgM increased	
AID deficiency	*AICDA*	AR	IgG and IgA decreased, IgM increased	Bacte
UNG deficiency	*UNG*	AR	IgG and IgA decreased, IgM increased	

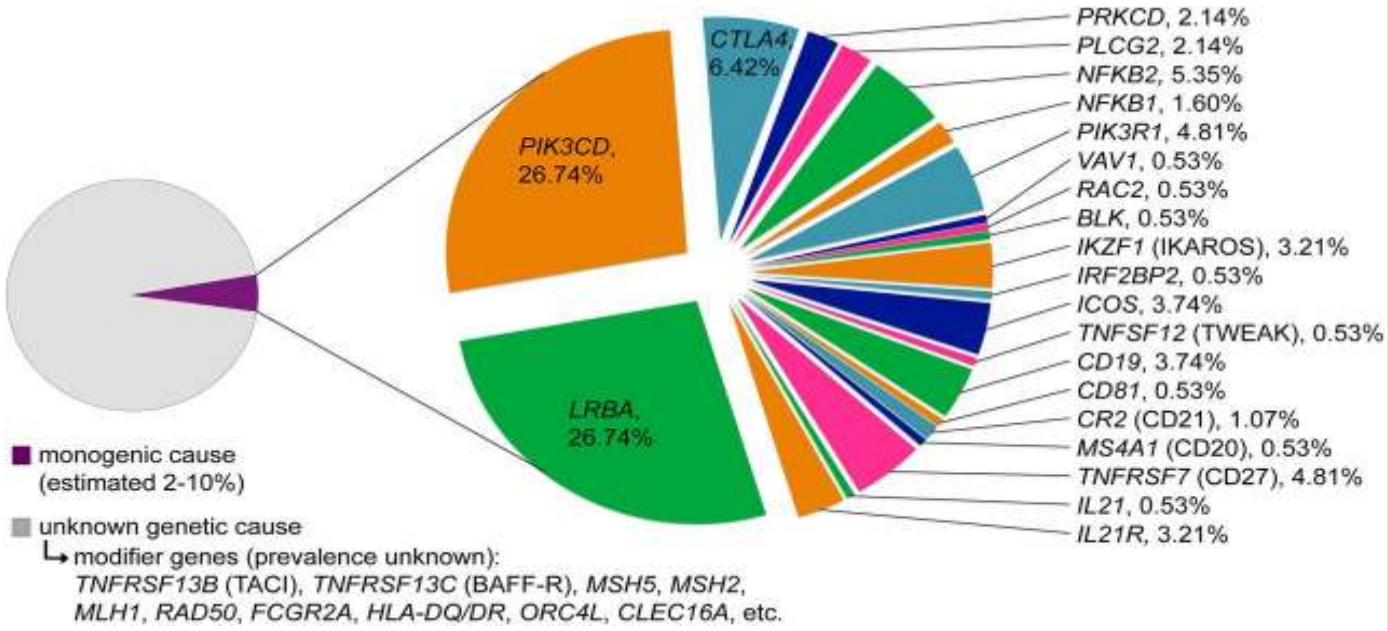
Smith T, Cunningham-Rundles C, Hum Immunol. 2019 Jun;80(6):351-362.

Common Variable Immune Deficiency (CVID)



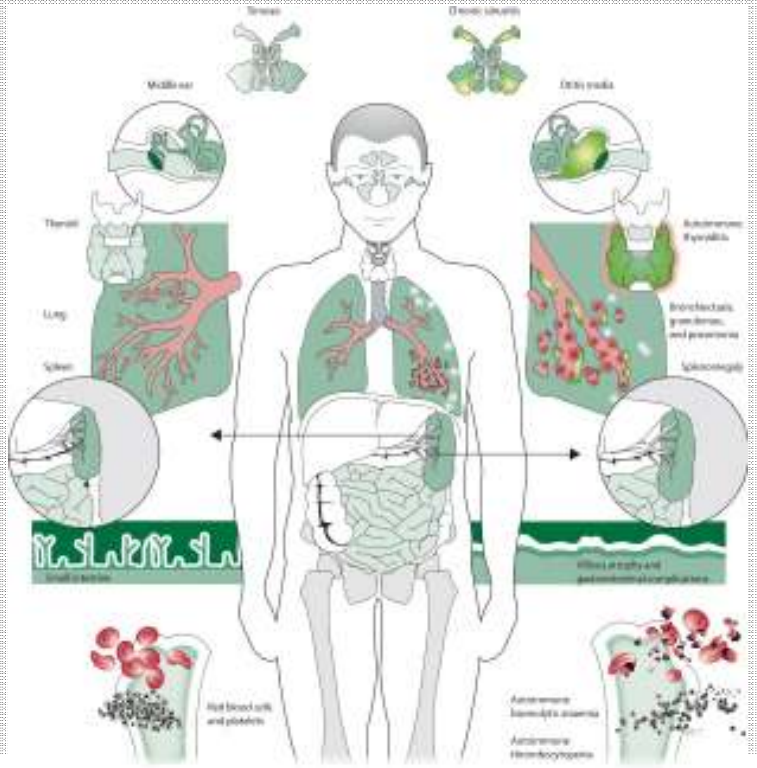
- B-cells move from the bone marrow to the spleen and peripheral lymphoid tissues, where **additional maturational events** occur which lead to plasma cell development.
- Failing any of these steps results in varying degrees of hypogammaglobulinemia known as common variable immune deficiency (CVID).
- CVID is estimated to affect between **1: 25,000 and 1: 50,000** of the population, with the majority of patients diagnosed between the ages **of 20 and 45 with males and females being affected equally.**

Common Variable Immune Deficiency (CVID)



This heterogeneous group of PIDs was first recognized in 1954 and is characterized by **decreased serum immunoglobulin IgG with a decrease in serum IgA and/or IgM, along with defective specific antibody production.**

Common Variable Immune Deficiency (CVID)

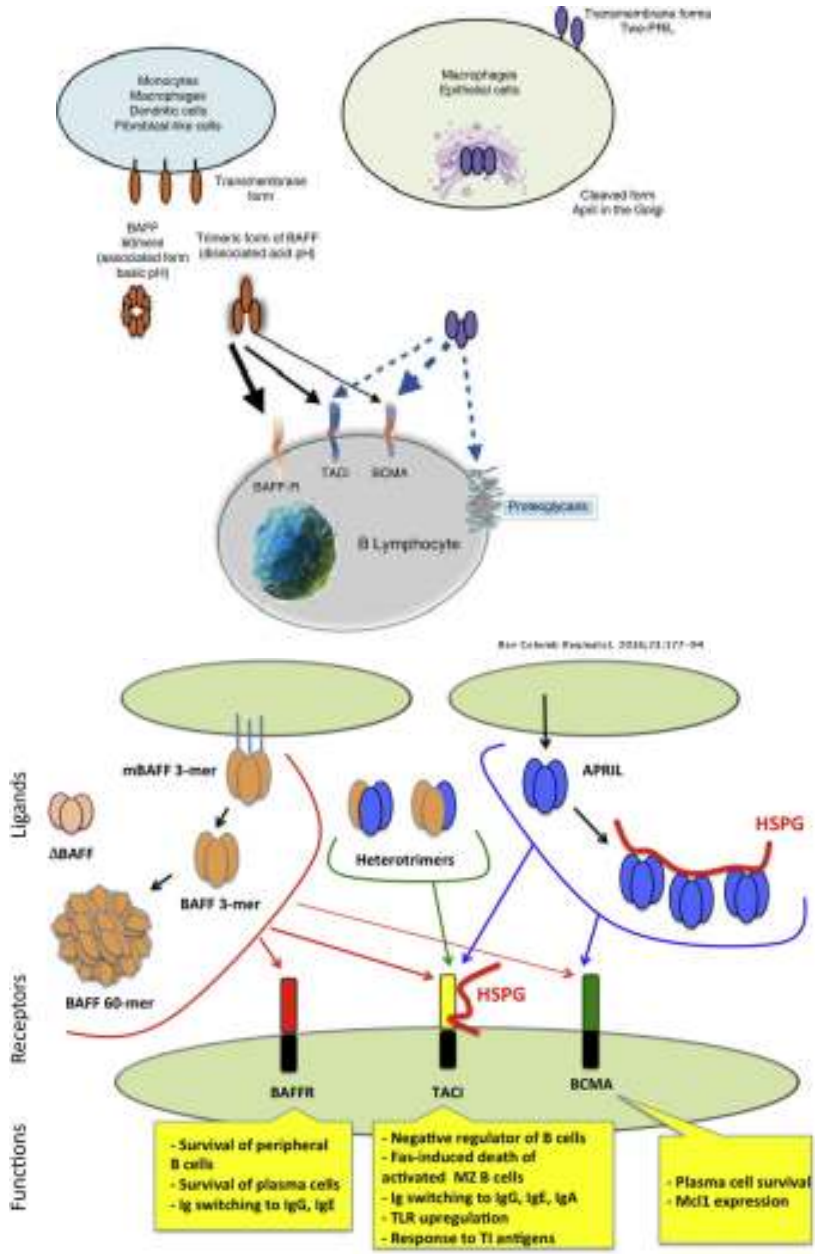


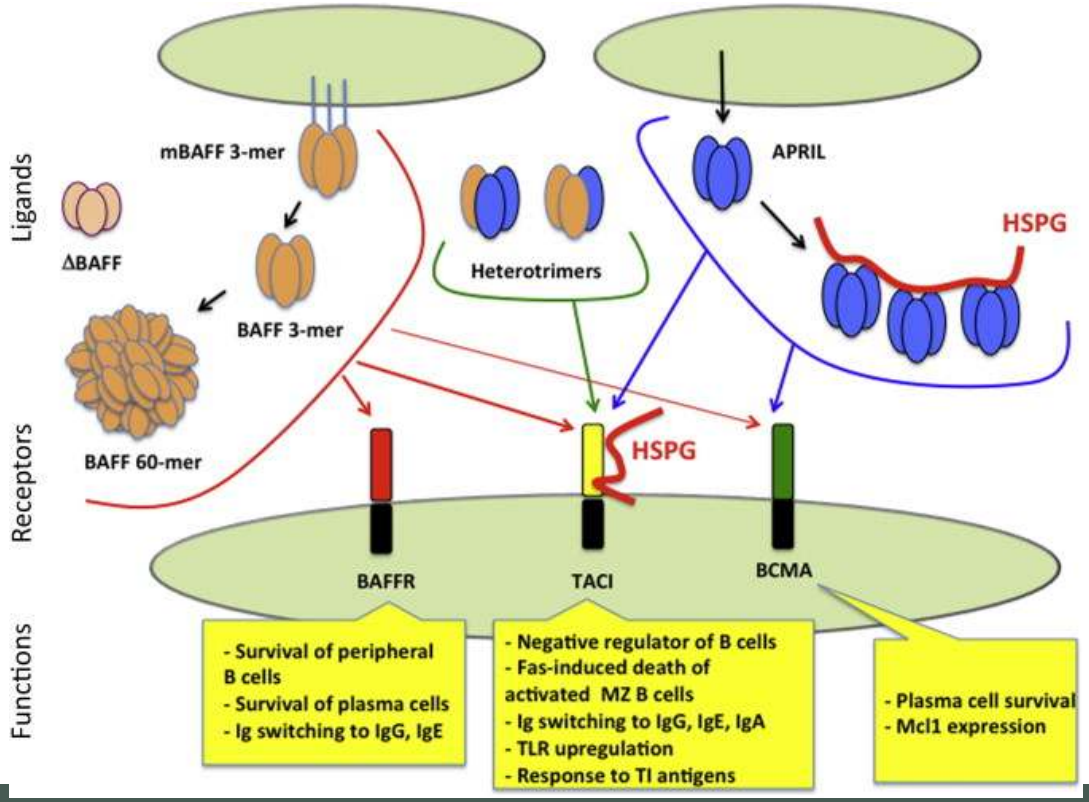
- The clinical spectrum of CVID is broad and consists of **recurrent infections while in approximately 25–50% of patients**, **autoimmune and/or inflammatory features** are present, including **enteropathy**, noninfectious immune-mediated **lung disease** and/or **granulomatous disease**, which lead to significant morbidity and mortality.
- Patients with CVID have **normal sized or enlarged tonsils** but approximately 25% of patients have **splenomegaly** and/or generalized **lymphadenopathy.**
- Individuals with CVID are **susceptible to malignancy**, **particularly non Hodgkins lymphoma**, and have an estimated **1.8- to 5-fold increased risk** of developing **cancers of all types.**

Genetic Defects leading to the CVID phenotype

TACI deficiency

- **Transmembrane activator and CAML interactor (TACI)** is expressed on mature B-cells and **binds both APRIL and BAFF** only when presented in an oligomeric or membrane-bound form.
- TACI mutations found in **8–10% of CVID patients**
- Patients are found to have **hypogammaglobulinemia and autoimmune manifestations** and **lymphoid hyperplasia** potentially due to **lack of normal mechanisms of establishing tolerance**.

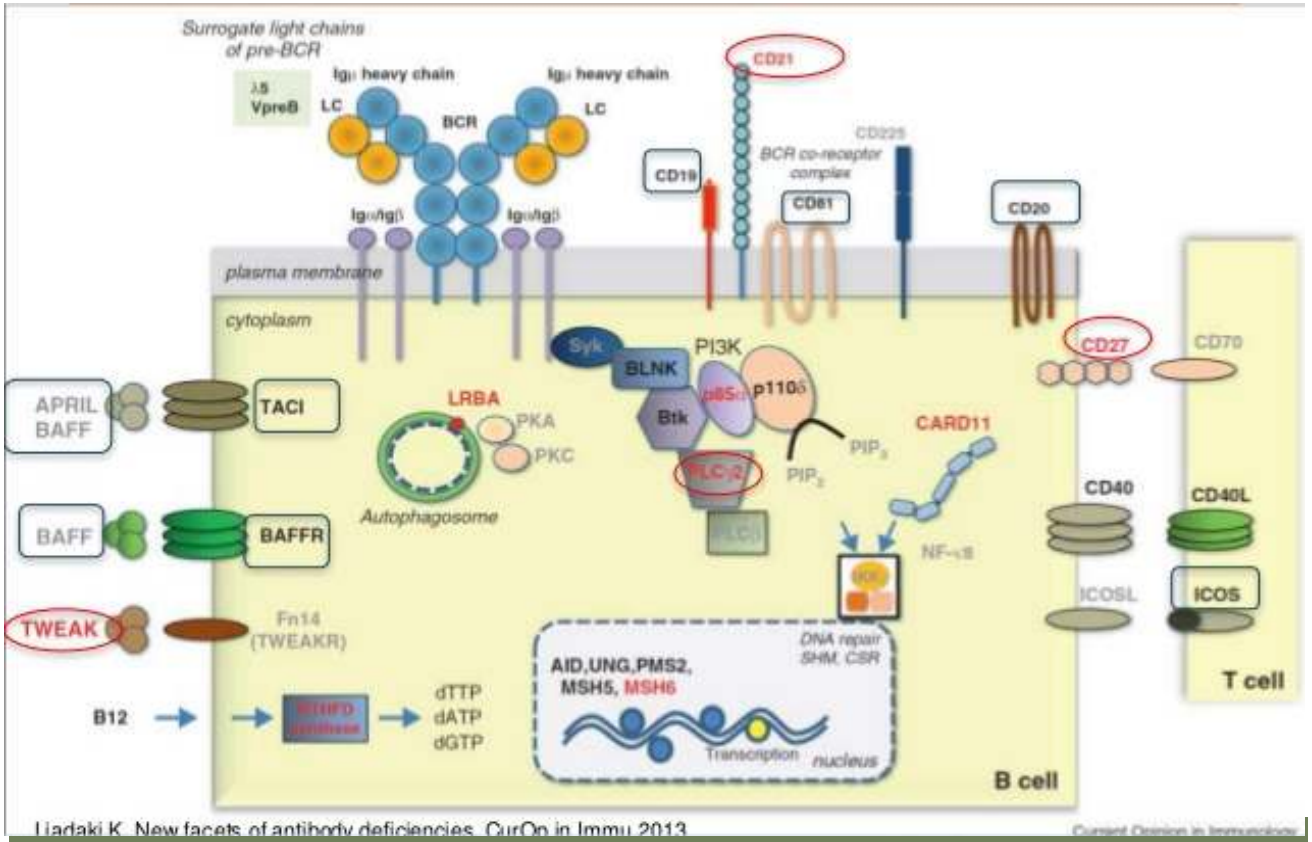




Genetic Defects leading to the CVID phenotype

BAFF receptor deficiency

- Maturation of splenic B-cells is regulated by interactions with **B-cell activating factor of the tumor necrosis family (BAFF),** acting on its receptor (BAFF-R).
- Expression of Bcl-2 family members and downregulation of pro-apoptotic factors.
- BAFF-R together with the **BCR, TACI and B-Cell Maturation Antigen (BCMA)** forms a complex receptor network which required for BAFF-mediated proliferation and survival.
- Autosomal **recessive** mutations in BAFF-R were identified in two siblings, leading to **adult onset hypogammaglobinemia** .

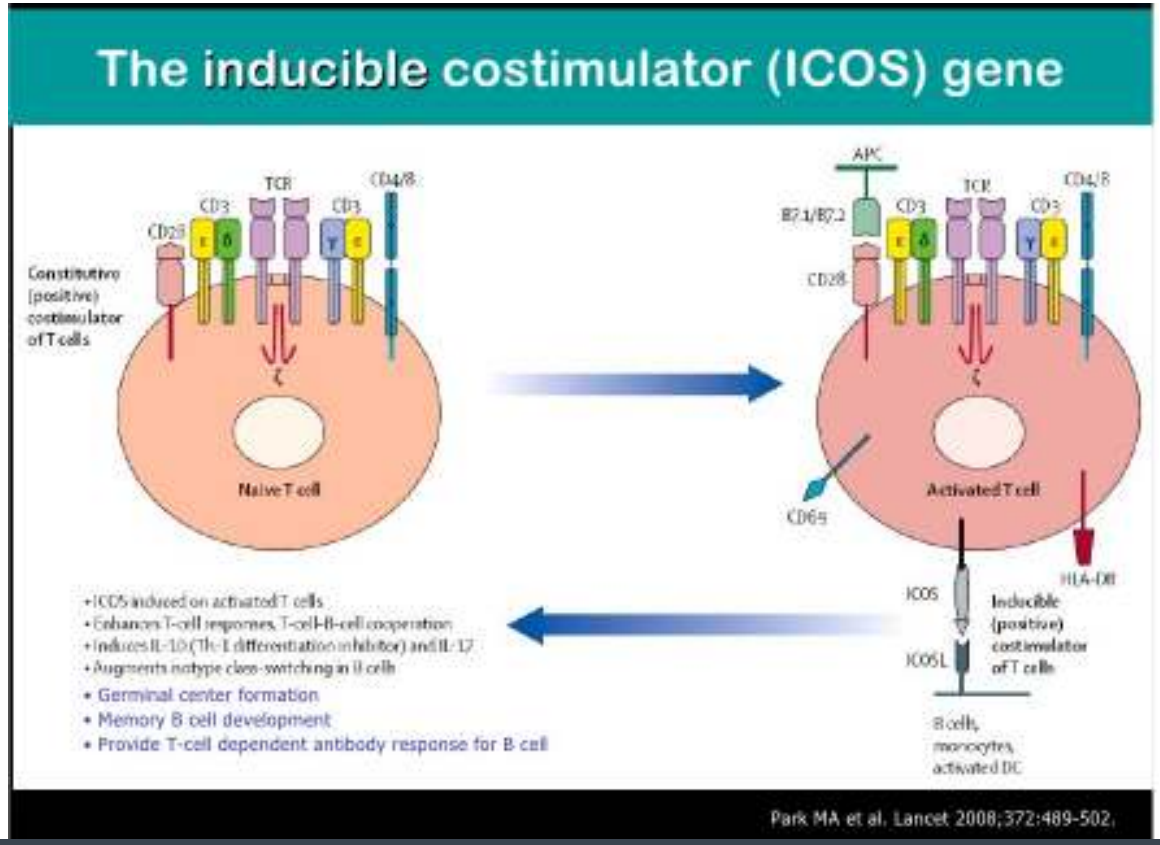


Ujadaki K. New facets of antibody deficiencies. CurOp in Immu 2013

Genetic Defects leading to the CVID phenotype

TWEAK Deficiency

- **TNF-like weak inducer of apoptosis (TWEAK)** has also been described as having a role in BAFF signaling and B-cell survival.
- An autosomal **dominant** mutation in TWEAK associated with recurrent infections.



Genetic Defects leading to the CVID phenotype

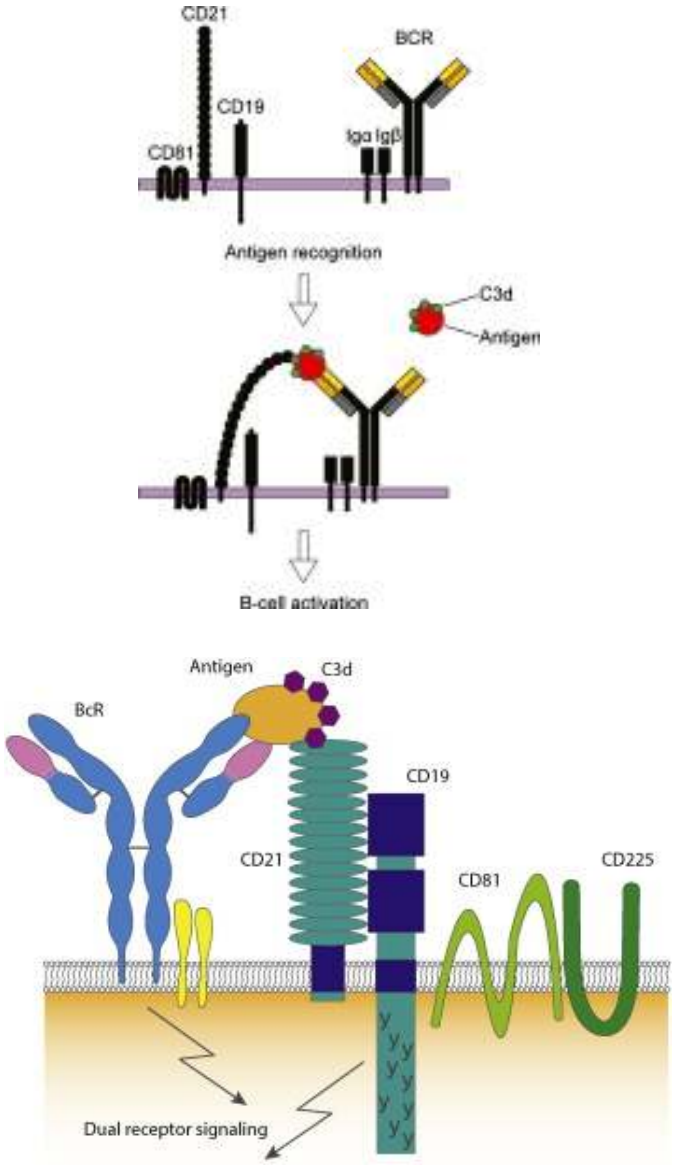
ICOS Deficiency

Autosomal **recessive** mutations in the gene encoding the **inducible T-cell costimulator (ICOS)**, a T-cell surface receptor, was one of the first genetic causes of CVID to be identified.

Genetic Defects leading to the CVID phenotype

B-Cell Costimulatory Molecule Deficiencies CD19, CD20, CD21, CD27, CD81

- **CD19** forms a complex with **CD21 and CD81** in the membrane of mature B-cells
- Quite rare **autosomal recessive** mutations
- Patients present **with recurrent infections**, however, in **CD19 and CD81 defects, glomerulonephritis** has been reported.
- **CD20 deficiency** has been reported in a case of **recurrent infections with hypogammaglobulinemia**
- **Autosomal recessive** mutations in **CD27**, a marker of **human memory B-cells**, have also been described in patients with the CVID phenotype.



B-cell defects linked to immune dysregulation

Mutations in genes that **control immune regulation** are likely to present with the clinical **phenotype of antibody deficiency**, with hypogammaglobulinemia being an early and cardinal feature.

These syndromes also commonly include **autoimmunity, enteropathy, splenomegaly and generalized lymphoid hyperplasia**.

- **LRBA and CTLA4 deficiency**
- **Activated phosphoinositide 3-kinase delta syndrome (APDS)**
- **Nuclear Factor Kappa-B (NF-κB)**

Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with Normal or Low Number of B Cells (CVID phenotype)

CVID of unknown gene defect	Unknown	AD or AR	Low IgG and IgA with low/normal IgM; poor antibody response
TACI deficiency	*TNFRSF13B (TACI)*	AD or AR	Low IgG and IgA and/or IgM
BAFF receptor deficiency	*TNFRSF13C (BAFF-R)*	AR	Low IgG and IgM
TWEAK deficiency	*TWEAK (TNFSF12)*	AD	Low IgM and A, lack of anti-pneumococcal antibody
CD19 deficiency	*CD19*	AR	Low IgG and IgA and/or IgM
CD81 deficiency	*CD81*	AR	Low IgG, low or normal IgA and IgM
CD20 deficiency	*CD20*	AR	
CD21 deficiency	*CD21*	AR	Low IgG, impaired anti-pneumococcal response

Smith T, Cunningham-Rundles C, Hum Immunol. 2019 Jun;80(6):351-362.

Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with Normal or Low Number of B Cells (CVID phenotype)

LRBA deficiency	*LRBA*	AR	All isotypes decreased
CTLA4 deficiency	*CTLA4*	AD	All isotypes decreased
PIK3CD mutation (GOF)	*PIK3CD GOF*	AD	All isotypes decreased
NFκB1 deficiency	*NFKB1*	AD	
NFκB2 deficiency	*NFKB2*	AD	Normal or low IgG, IgA, IgM, low or normal B cells, low memory B cells Low serum IgG, A and M; low B cell numbers

Smith T, Cunningham-Rundles C, Hum Immunol. 2019 Jun;80(6):351-362.

Isotype, Light Chain, or Functional Deficiencies with Generally Normal Numbers of B-cells

Selective IgA deficiency (SIGAD)

- **Selective IgA deficiency is the most common primary antibody** deficiency,(**1:143 to 1:18,500**). It affects males and females equally and is defined as a serum **IgA level of less than 7 mg/dl** and normal levels of serum IgG and IgM in a patient **older than 4 years old.**
- Secondary causes due to medications such as **anticonvulsants** (phenytoin, carbamazepine, valproic acid), **disease-modifying anti-rheumatic drugs** (sulfasalazine, hydroxychloroquine), **nonsteroidal anti-inflammatory drugs** and others.
- An **underlying gene defect has not been identified in SIGAD**.
- **Two-third of patients with SIGAD remain asymptomatic**, whereas symptomatic patients suffer from **allergies, recurrent sinopulmonary and mucosal infections, both infectious and non-infectious gastrointestinal diseases and gastrointestinal and lymphoid malignancies.**
- Patients with **SIGAD have progressed to CVID**.

IgG subclass deficiency with and without IgA deficiency

- Human IgG is subdivided into four subclasses: **IgG1, IgG2, IgG3 and IgG4.**
- The most common IgG subclass deficiency is **IgG4 deficiency** (40%), followed by IgG2 (28%), IgG3 (17%) and IgG1 deficiency (14%).
- IgG subclass deficiencies can be associated other conditions such as **atopic disorders, chronic airway diseases or autoimmunity.**
- **2-20% of healthy individuals have lower than** normal level of one or more IgG subclasses.
- IgG subclass deficiency **(especially IgG2)** may be associated with **IgA deficiency**.

Selective IgM Deficiency - Kappa (κ) chain deficiency

- **Selective IgM deficiency (SIgMD)** is a **very rare immune** disorder in which no serum IgM is detected and other isotypes are preserved. The causes are **unknown.**
- **Kappa (κ) light chain deficiency (IGKC)** is a quite rare **autosomal recessive disease** but the reason is **unknown.**

Specific antibody deficiency with normal Ig levels and normal B-cells

- **Specific antibody deficiency (SAD)** is characterized in **patients over 2 years** old who present with recurrent infections and are found to have **impaired antibody response** to **polysaccharide antigens.**
- **5-20% in children and adults**
- Patients with SAD → recurrent **bacterial sinopulmonary**, and a subset of patients have a history of **allergy**, particularly **allergic rhinitis**.
- **Spontaneous recovery** and **progression towards IgG subclass deficiency or CVID.**

Transient hypogammaglobulinemia of infancy

- Transient hypogammaglobulinemia of infancy (THI) have **low IgG levels** with possible involvement **of IgA** and **less frequently IgM** that spontaneously return to normal, usually **within 2-3 years of age.**
- The timing of normalization often varies. Most remain **asymptomatic but** it can be associated with a **higher rate of recurrent infections**, especially of the **upper respiratory** tract.
- The pathophysiology of THI is **unknown.**
- The disease is **self-limited** and patients should be monitored over time until levels have normalized.

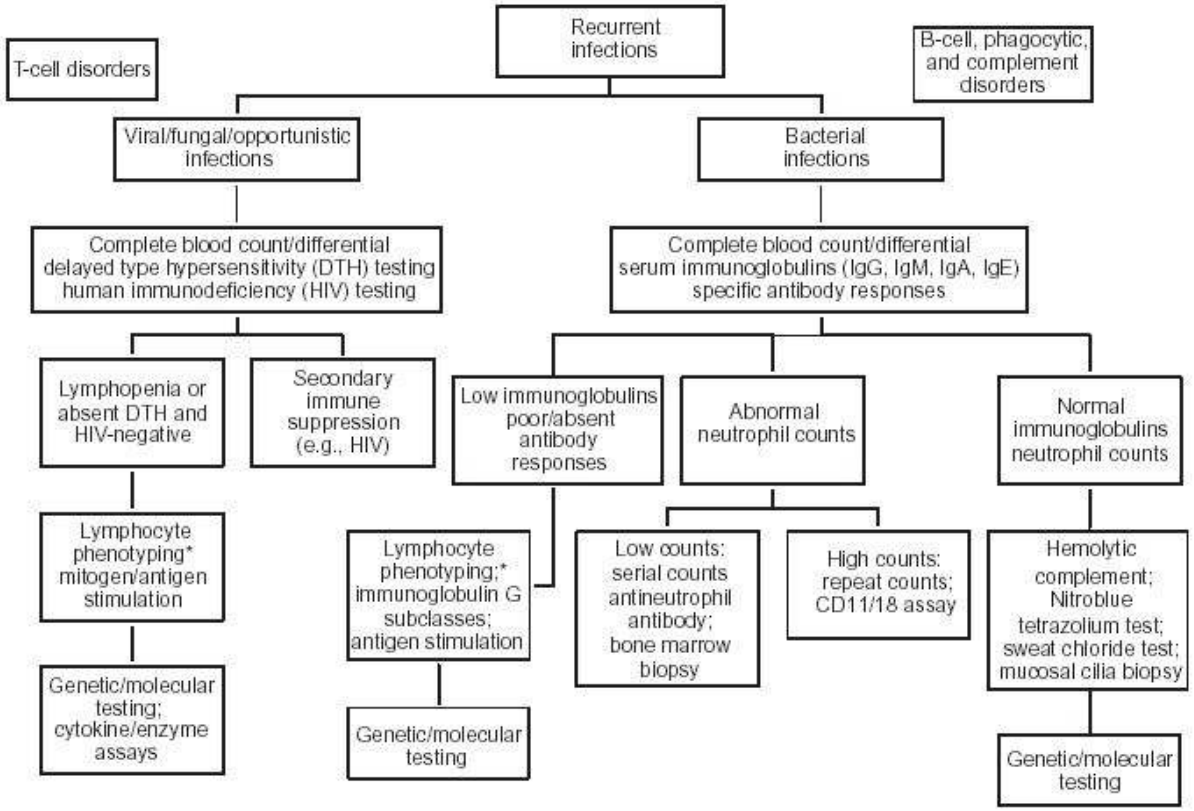
Isotype, Light Chain, or Functional Deficiencies with Generally Normal Numbers of B Cells

Ig heavy chain mutations and deletions	Mutation or chromosomal deletion at *14q32*	AR	One or more IgG and/or IgA subclasses as well as IgE may be absent
Kappa chain deficiency	*IGKC*	AR	All immunoglobulins have lambda light chain
Isolated IgG subclass deficiency	Unknown	?	Reduction in one or more IgG subclass
IgG subclass deficiency with IgA deficiency	Unknown	?	Reduced IgA with decrease in one or more IgG subclass
Selective IgA deficiency	Unknown	?	isotypes normal, normal subclasses and specific antibodies
Specific antibody deficiency with normal Ig levels and normal B cells	Unknown	?	Normal
Transient hypogammaglobulinemia of infancy	Unknown	?	IgG and IgA decreased
Selective IgM deficiency	Unknown	?	Absent serum IgM

Diagnosis

- Diagnosing a primary B-cell defect relies first on **clinical history and then on confirmatory laboratory evaluations**. This includes a detailed **family and infection history**, **age of onset, frequency and duration of treatments and if known.**
- **Laboratory evaluations** include **complete blood counts**, **full lymphocyte panels for T-cell, B-cell, and NK-cell** subsets, **quantitative serum immunoglobulin levels (IgM, IgG, IgA and IgE where indicated**) and evaluation of specific **antibody responses** to both protein and polysaccharide antigens.
- **Immunophenotyping of B- and T-cells** is also a useful adjunct for subcategorization, prognostication and management.
- **Gene sequencing** is commercially available for many of the known gene defects and include primary antibody deficiency panels. Molecular diagnosis can be important for **treatment optimization and for accurate genetic counseling**.

FIGURE 2. A diagnostic testing algorithm for primary immunodeficiency diseases



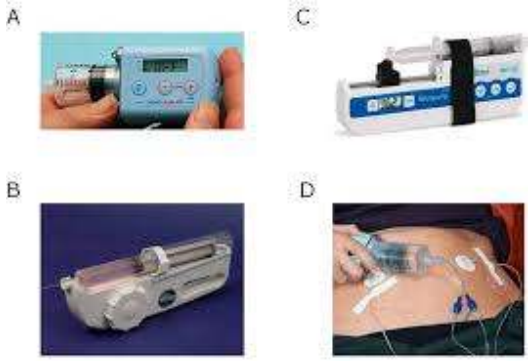
*Lymphocyte phenotyping includes enumeration of B, T, and NK cells.

Table 3. Clinical Signs That Suggest a Primary Immunodeficiency Disease

Positive family history
Infections in multiple anatomic locations
Increasing frequency and severity of infections with age
Recurrent serious infections with common pathogens
Serious infections with unusual pathogens

	Warning signs in children	Warning signs in adults
1	Equal or more than four new ear infections within one year	Equal or more than two new ear infections within one year
2	Equal or more than two serious sinus infections within one year	Equal or more than two new sinus infections within one year without allergy
3	Equal or more than two months on antibiotics with little effect	One pneumonia per year for more than one year
4	Equal or more than two pneumonias within one year	Chronic diarrhea with weight loss
5	Failure of an infant to gain weight or grow normally	Recurrent viral infections (colds, herpes, warts, condyloma)
6	Recurrent, deep skin or organ abscesses	Recurrent need for IV antibiotics to clear infections
7	Persistent thrush in mouth or fungal infection on skin	Recurrent, deep abscesses of the skin or internal organs
8	Need for intravenous antibiotics to clear infections	Persistent thrush or fungal infection on skin or elsewhere
9	Equal or more than two deep-seated infections including septicemia	Infection with normally harmless tuberculosis-like bacteria
10	A family history of PID	A family history of PID

Adapted from Jeffrey Modell Foundation http://www.info4pi.org/library/educational-materials/10-warning-signs. Accessed on 09/Oct/2019.



Treatment

- The management of primary B-cell immunodeficiencies focuses largely on **the prevention and treatment of infections** and secondarily on **controlling any complications** that may develop.
- Adequate **antibody replacement therapy** with intravenous or subcutaneous immune globulin formulations.
- **Microbial therapy** is used as needed for acute treatment, and in some cases, **chronic antibiotic prophylaxis.**
- For non-infectious complications→ treating such complications early is critical. **Immunosuppressive, anti-inflammatory, cytotoxic, and antineoplastic therapies** →autoimmune or malignant complications of primary B-cell defects.
- **Newer therapies targeting defective pathways** are becoming more widely accepted in practice. Current treatment strategies for select B-cell defects with immune dysregulation are prime examples.

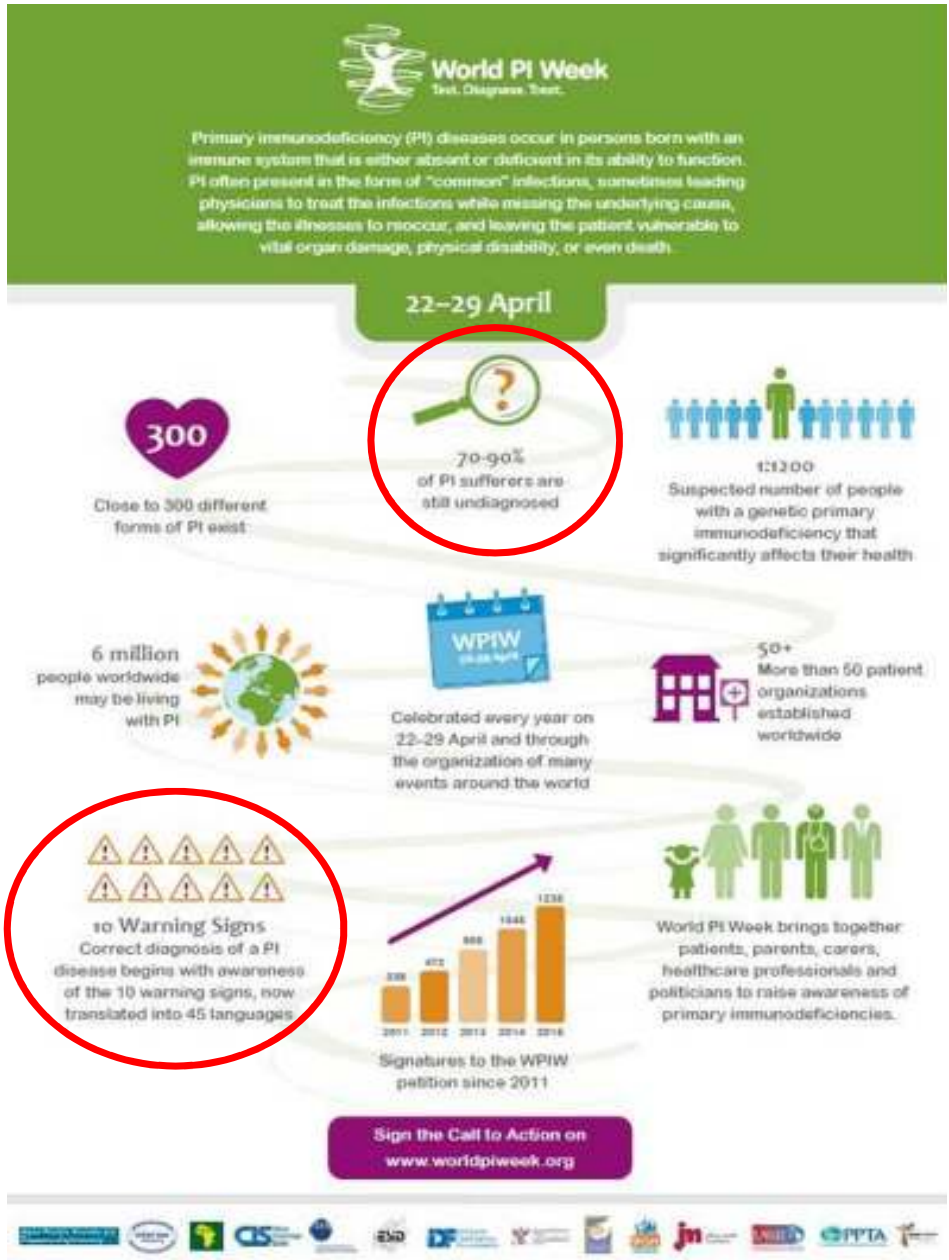
Treatment

- Patients with APDS have benefited from treatment with **rapamycin**, used for targeted therapy to inhibit the biologically relevant downstream PI3K effector.
- Emerging evidence for the use a selective **PI3Kdelta inhibitor** (Leniolisib/CDZ173) in APDS-causative p110delta variants is on the horizon.
- Another example includes **CTLA4-fusion protein replacement** (Abatacept and Belatacept) used in reversing life-threatening infiltrative and autoimmune disease in CTLA4 and LRBA deficient patients.
- Continued clinical studies are necessary to determine the effectiveness and safety of these targeted therapies.
- **Hematopoietic stem cell therapy (HSCT)** appears to be a treatment option for patients with **severe APDS**, **severe immune dysregulation in CTLA4** mutation carriers and **LRBA deficient** patients. With growing indications for HSCT in primary immunodeficiency, a careful discussion of the **risk/benefit ratio** should take place.
- **The mainstay of treatment for primary B-cell defects remains immunoglobulin replacement**.

Defects	Supportive treatment	Definitive treatment
CIDs/SCID	Ig replacement (IV or SC) Enzyme replacement Antibiotic prophylaxis Antifungal prophylaxis Aggressive prevention and management of infections Immunosuppressants for autoinflammation	Thymus transplantation [66] Stem cell transplant Gene therapy
Antibody deficiencies	Ig replacement therapy (IV or SC) Antibiotic prophylaxis Antifungal prophylaxis Biological agents or immunosuppressants for autoinflammation	Stem cell transplant Gene therapy
Innate immunodeficiencies	Antibiotic prophylaxis Antifungal prophylaxis Cytokine replacement Granulocyte colony stimulating factor Immunizations Ig replacement if indicated	Stem cell transplant Gene therapy
Autoimmune/autoinflammatory disorders	Corticosteroids Other immunosuppressants Biological agents	Stem cell transplant Gene therapy
Immune dysregulation disorders	Antibiotic prophylaxis Antifungal prophylaxis Immunizations Immunosuppressants Biological agents	Stem cell transplant Gene therapy

CONCLUSION

- The most basic principles of B-cell biology has been based on studies of primary immunodeficiencies.
- **X-linked agammaglobulinemia** permitted the elucidation of cytoplasmic tyrosine kinase **BTK, crucial for maturation of mature B-cells.**
- Defects of any of the components of the **BCR** result in autosomal agammaglobulinemia, demonstrating that **continuous BCR signals** are essential for the **maintenance of mature B-cell populations**.
- Genetic and immunological exploration of the most common immunodeficiencies CVID, IgA deficiency, Ig subclass and selective antibody deficiency, has only just begun. The advent of next-generation sequencing has greatly facilitated the search for novel genetic diseases.
- These advances suggested important avenues for therapy.



Objectives

- **Immunodeficiencies:** Definition, cause and types
- **Primary Immunodeficiencies:** Definition, types, diagnosis and therapy
- **Examples:** SCID, XLA, DiGeorge's syndrome, Ataxia-teleangectesia, Wiskott-Aldrich syndrome, CGD