Primary antibody deficiencies

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Learning Objectives

- Define and classify primary antibody deficiencies
- Review the role of clinical laboratory in the diagnosis of primary antibody deficiencies
- Review the genetics of
  (1) Agammaglobulinemia
  (2) Hyper-IgM syndrome
  (3) Common Variable Immunodeficiency
- Demonstrate the utility of molecular diagnosis in primary antibody deficiencies

Definitions

- Primary immunodeficiency (PID): genetic
- Secondary immunodeficiency: infection, malignancy, iatrogenic

Identification of patients with PID

→ Infections

- recurrent
- life-threatening
- unusual

→Autoimmune diseases

→Malignancies

PID

- Prevalence: 86.2/100,000
- Incidence: 10.3/100,000

(Joshi et al. 2009; Boyle and Buckley 2007)

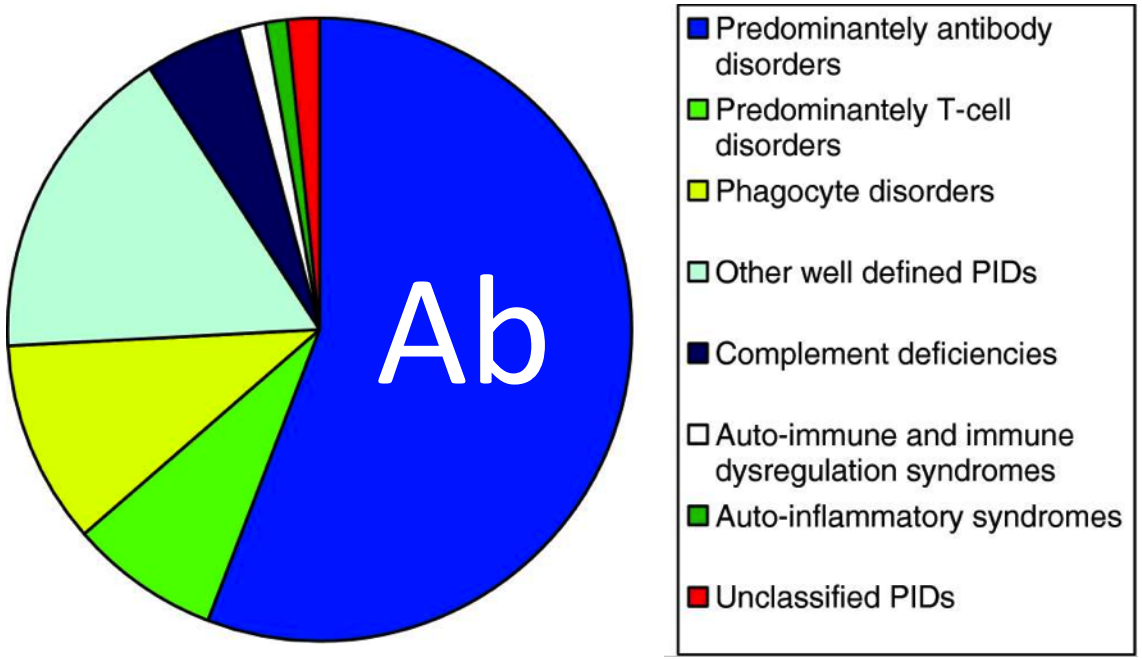
Leukemias

- Prevalence: 81.6/100,000
- Incidence: 12.5/100,000

(http://seer.cancer.gov/statfacts/html/leuks.html)

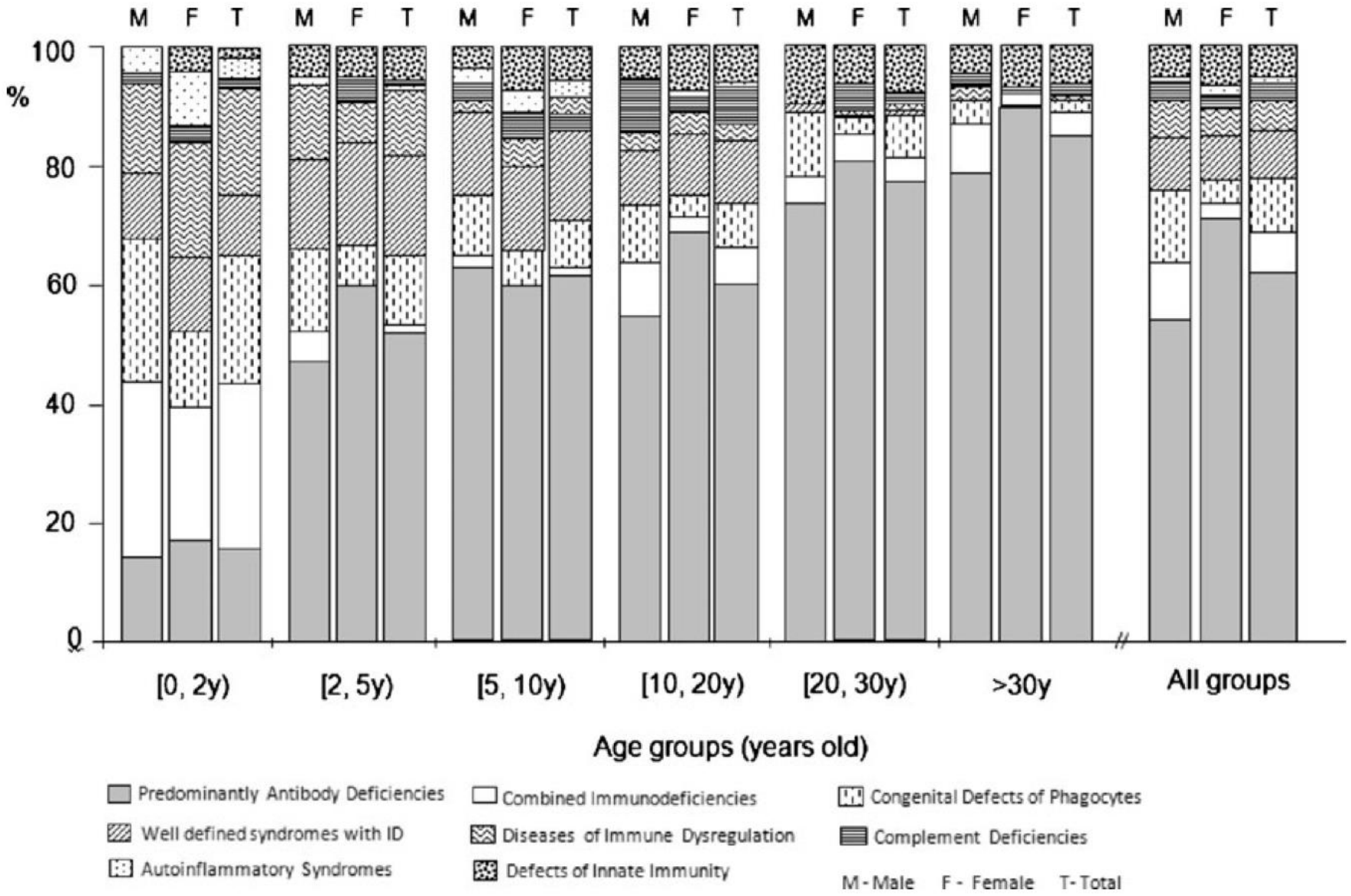
Primary antibody deficiencies are the most common PIDs

European ESID patient registry 2010



http://www.esid.org/statistics

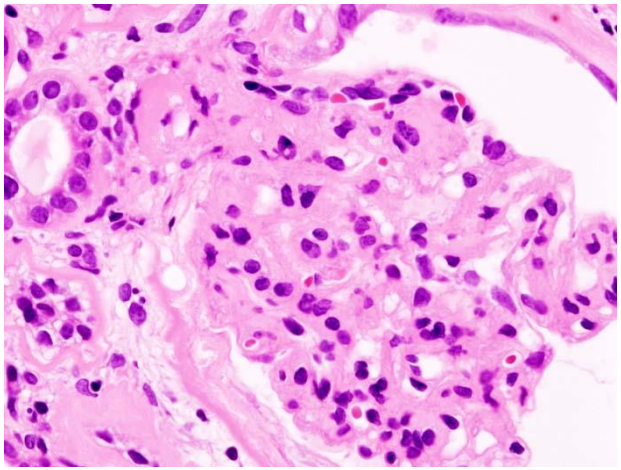
Antibody deficiencies



Carneiro-Sampaio M et al. J Clin Immunol 2013

Secondary antibody deficiencies

- **Secondary** antibody deficiencies:
  - nephrotic syndrome → proteinurea >3.5 grams per day/1.73m^2
  - protein-loosing enteropathy
  - drugs
  - hematological malignancies
  - infection



- **Primary** (genetic) antibody deficiencies
  - isolated
  - combined/syndromic

Diabetic glomerulosclerosis /Wikipedia

Secondary antibody deficiencies

- **Secondary** antibody deficiencies:
  - nephrotic syndrome
  - protein-loosing enteropathy → Fecal Alpha-1-Antitrypsin
  - drugs (Quantitative Radial Immunodiffusion)
  - hematological malignancies
  - infection

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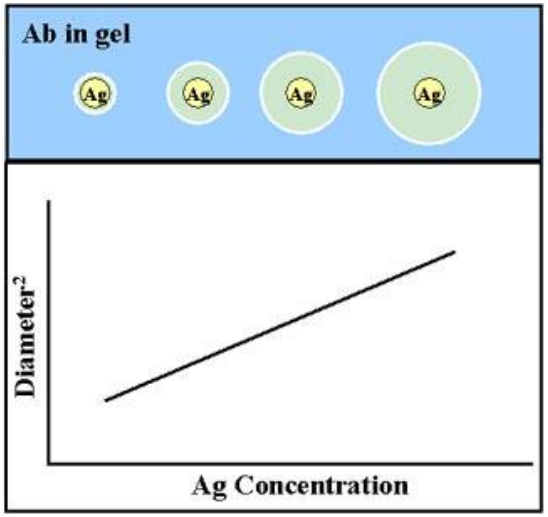

http://pathmicro.med.sc.edu/mayer/ab-ag-rx.htm

Secondary antibody deficiencies

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  - nephrotic syndrome
  - protein-loosing enteropathy
  - drugs → transplantation, autoimmune disease, etc.
  - hematological malignancies
  - infection

- **Primary** (genetic) antibody deficiencies
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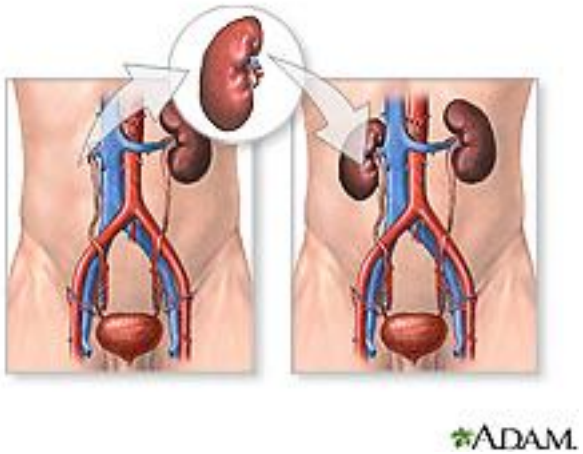

http://www.nlm.nih.gov/medlineplus/kidneytransplantation.html

Secondary antibody deficiencies

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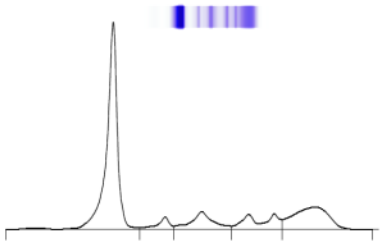
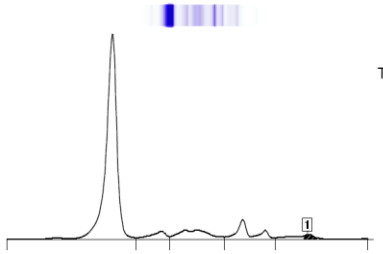
  - protein-loosing enteropathy
  - drugs
  - hematological malignancies →
  - infection



Total Protein: 6.5 g/dL T.P. Ref. Range: 6.0 - 8.3 g/dL

Fractions	Rel %	g/dL		Ref. %	Ref. g/dL
Albumin	56.6	3.68	-	55.1 - 65.7	3.75 - 5.01
Alpha 1	3.7	0.24		3.1 - 5.6	0.19 - 0.46
Alpha 2	9.7	0.63		8.0 - 12.7	0.48 - 1.05
Beta	10.0	0.65		8.5 - 12.8	0.48 - 1.10
Gamma	20.0	1.30		10.3 - 18.2	0.62 - 1.51



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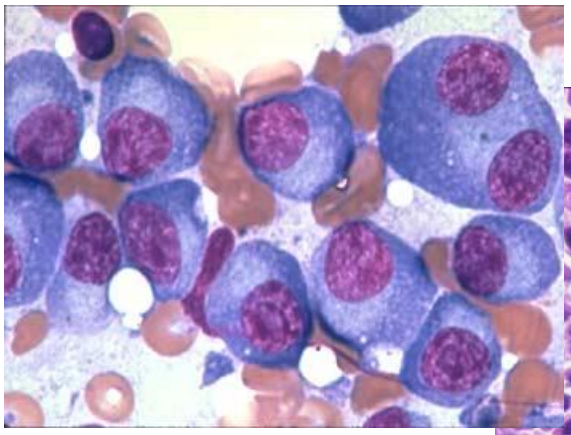
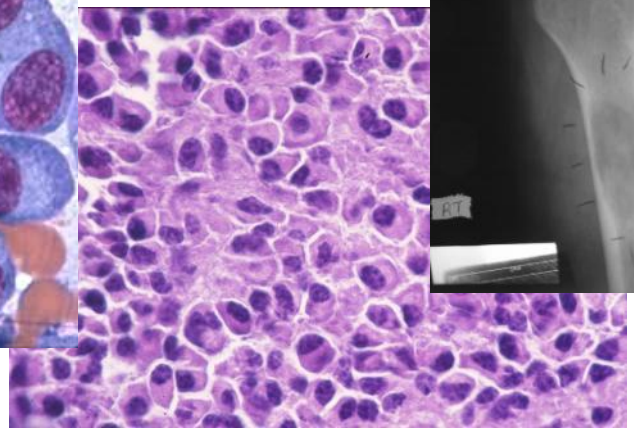
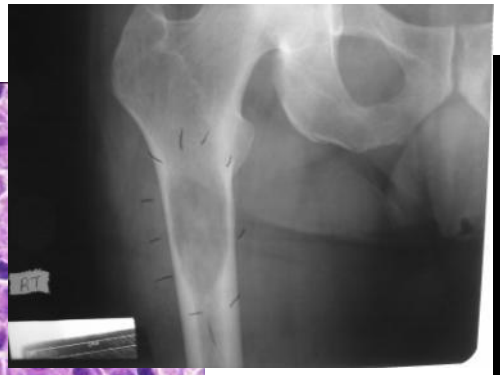
Fractions	Rel %	g/dL		Ref. %	Ref. g/dL
Albumin	73.2	4.39		55.1 - 65.7	3.75 - 5.01
Alpha 1	4.2	0.25		3.1 - 5.6	0.19 - 0.46
Alpha 2	9.6	0.58		8.0 - 12.7	0.48 - 1.05
Beta	9.0	0.54		8.5 - 12.8	0.48 - 1.10
Gamma	4.0	0.24	-	10.3 - 18.2	0.62 - 1.51
1	1.5	0.09			

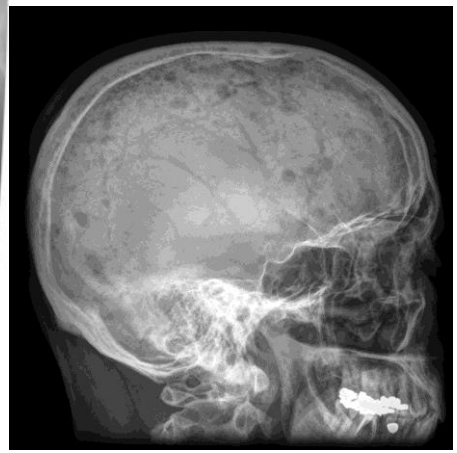


www.tumorlibrary.com





http://iahealth.net/multiple-myeloma/



www.Radiopaedia.org

→ Serum calcium

Secondary antibody deficiencies

- **Secondary** antibody deficiencies:
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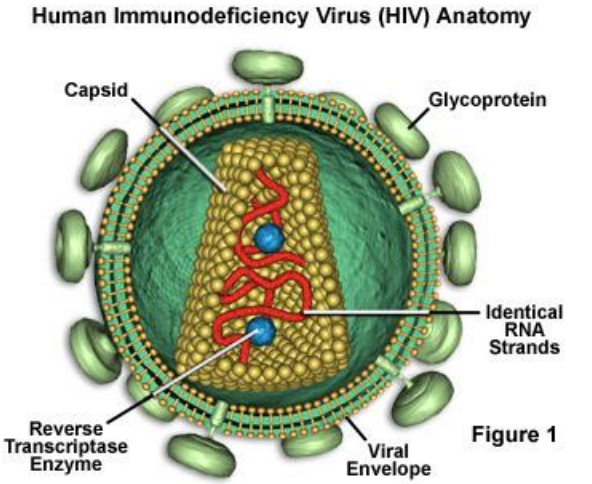
  - protein-loosing enteropathy
  - drugs
  - hematological malignancies
  - infection → HIV (Human Immunodeficiency Virus)



http://micro.magnet.fsu.edu/cells/viruses/hivvirus.html

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  - isolated
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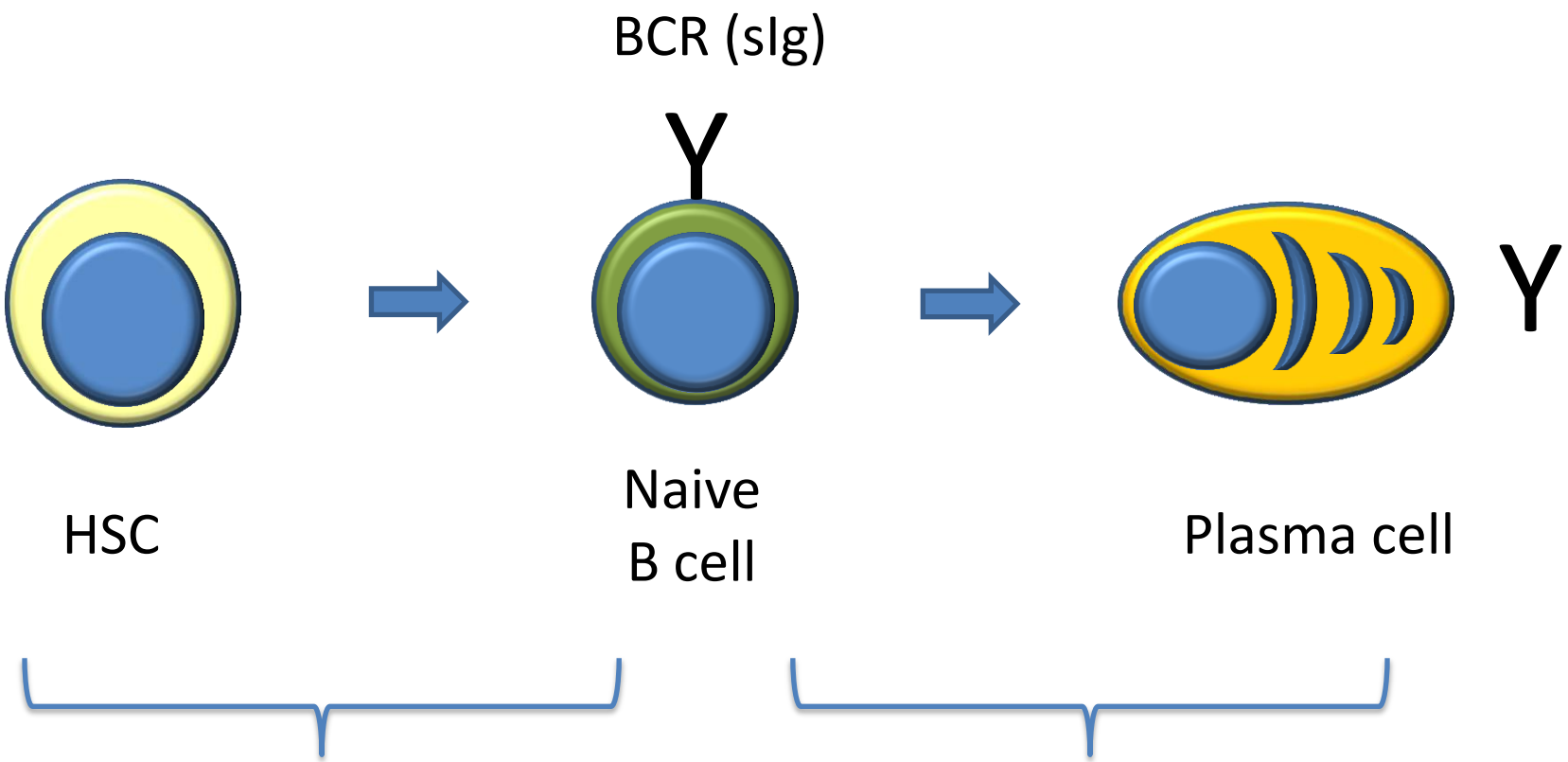
Primary antibody deficiencies: Spectrum of disorders

- X-linked/AR agammaglobulinemia (1:200,000)
- Class switch deficiency / Hyper-IgM syndrome (1:100,000)
- Common Variable Immunodeficiency (>1:25,000)
- IgA deficiency (1:700)
  - IgA deficiency and CVID in the same families
  - progression of IgA deficient pts. into CVID
  - IgA and IgG2 deficiency
- IgG subclass deficiencies (IgG1, IgG2, IgG3, IgG4)
- Selective Anti-polysaccharide def., Others (“Mild SCID”)

B cell development



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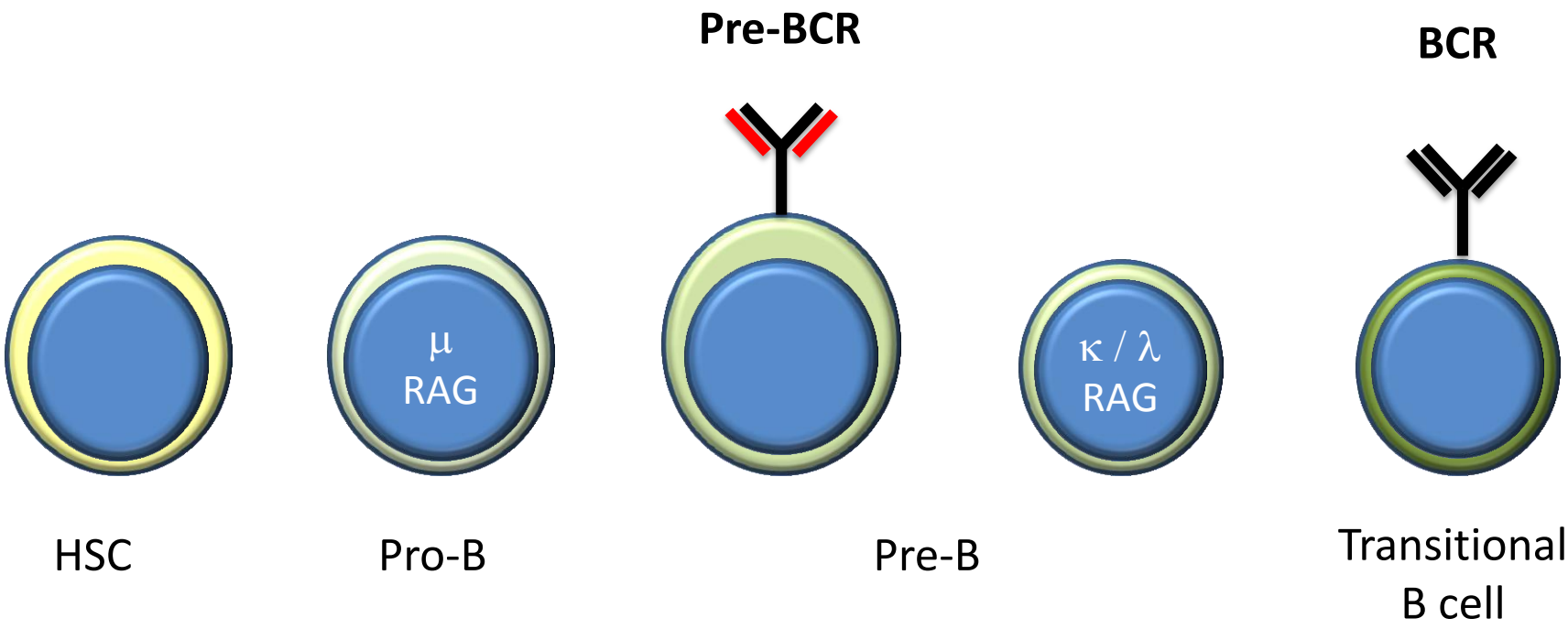

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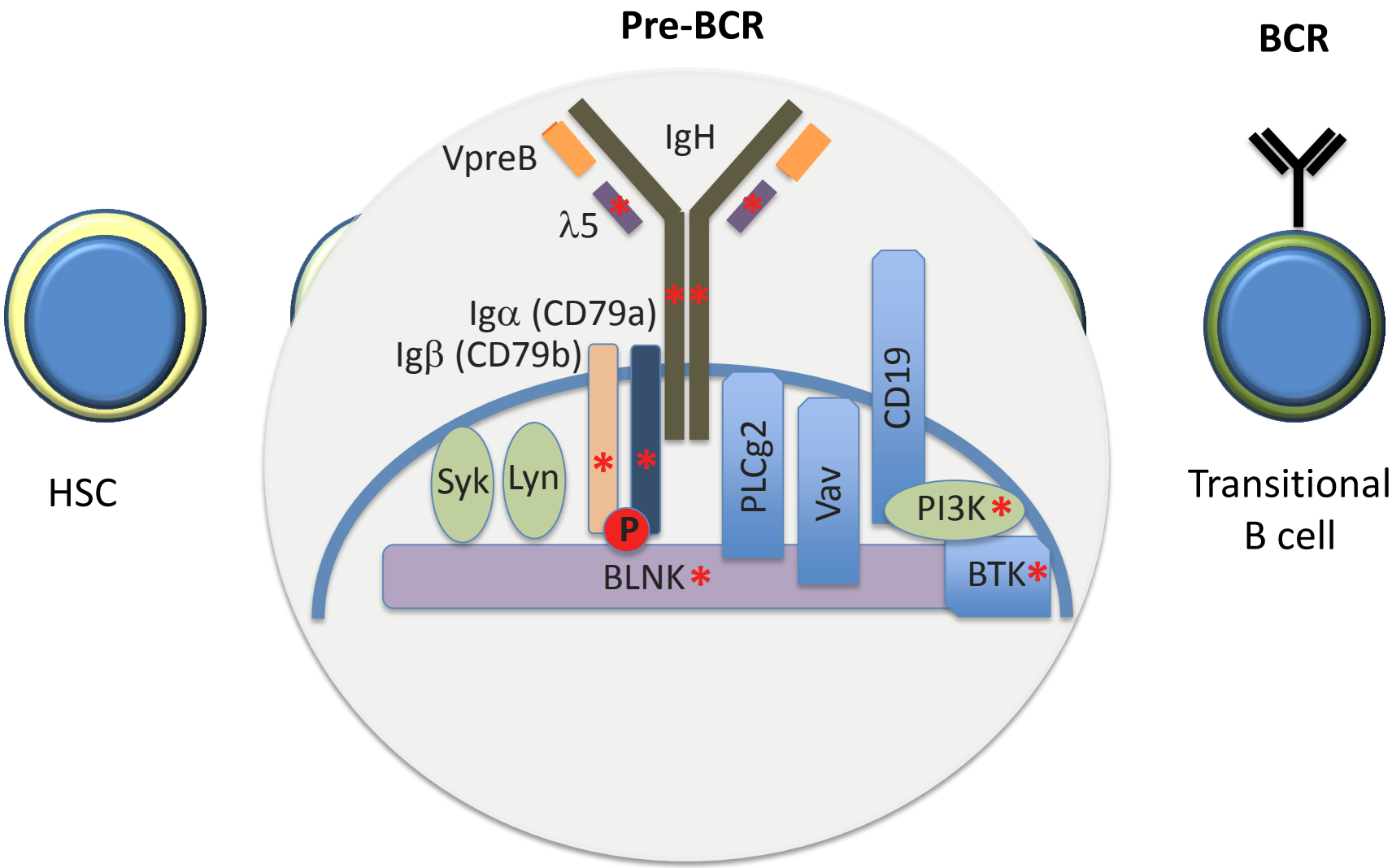
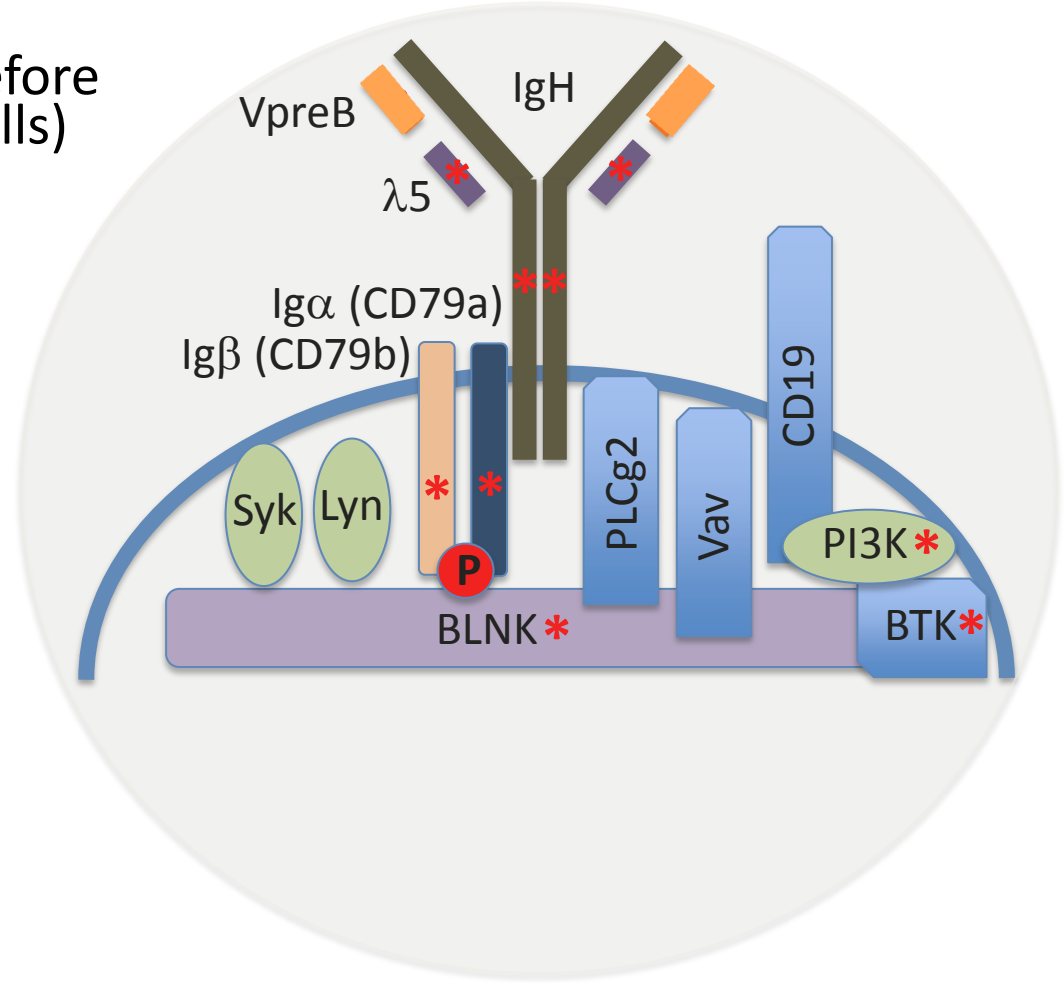


Agammaglobulinemia

- Onset of recurrent bacterial infections in the first 5 years of life
- Profound hypogammaglobulinemia
- Reduced or absent B cells in the peripheral circulation
- Block in B cell differentiation before mature B cells (sIg-positive B cells)

- 85% X-linked:
  - BTK

- 10% AR:
  - μ heavy chain (*IGHM*)
  - Igα (*CD79A*)
  - Igβ (*CD79B*)
  - λ5 (*IGLL1*)
  - BLNK
  - PIK3R1 (p85a subunit of PIK)



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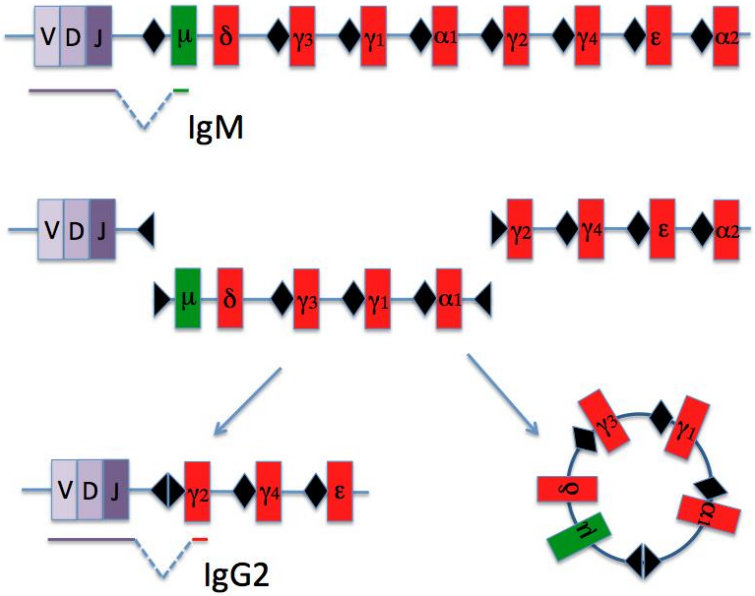
Hyper-IgM syndrome

- 1:100,000
- Second - antigen-dependent - stage of B cell development
- Heterogeneous group of genetic disorders resulting in defects of immunoglobulin class switch recombination (CSR), with or without defects of somatic hypermutation (SHM)
- Low IgG, IgA, and IgE levels with either normal or increased IgM

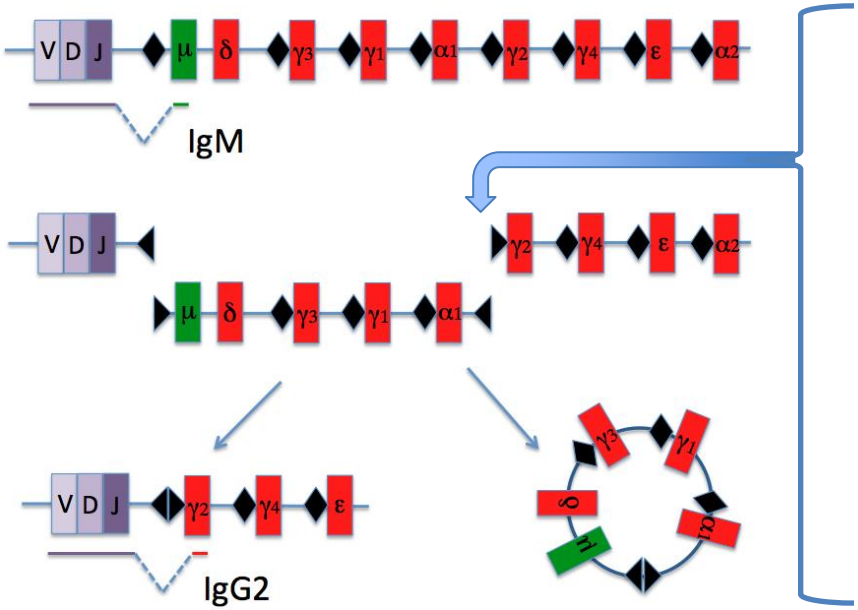


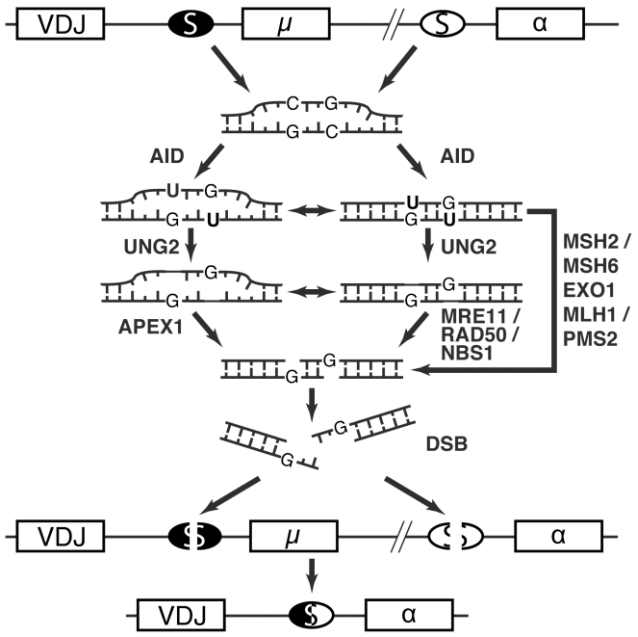
Hyper-IgM syndrome

- Class-switch depends on a number of signals including antigen engagement of the B cell receptor and co-stimulatory signals through the effects of cytokines and direct interaction with T cells

→ CD40L (T cells) - CD40 (B cell) interaction

→ Creation of dsDNA breaks, excision of the intervening sequences and dsDNA repair



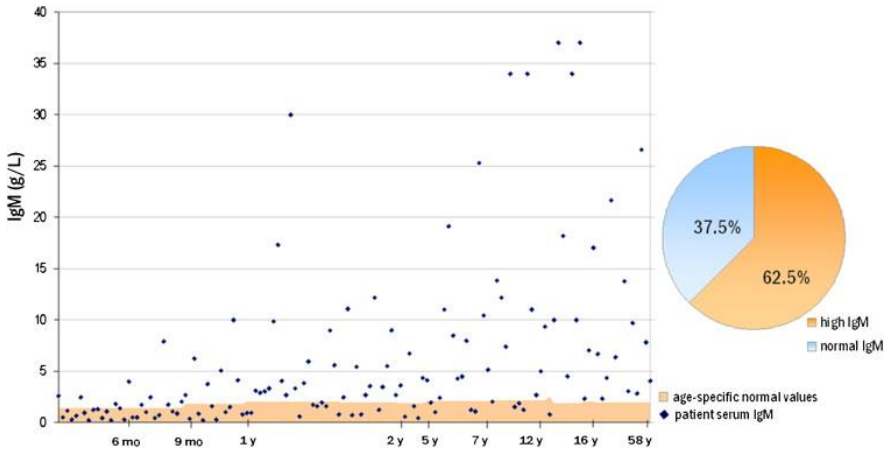


Offer et al. PLOS One 2010

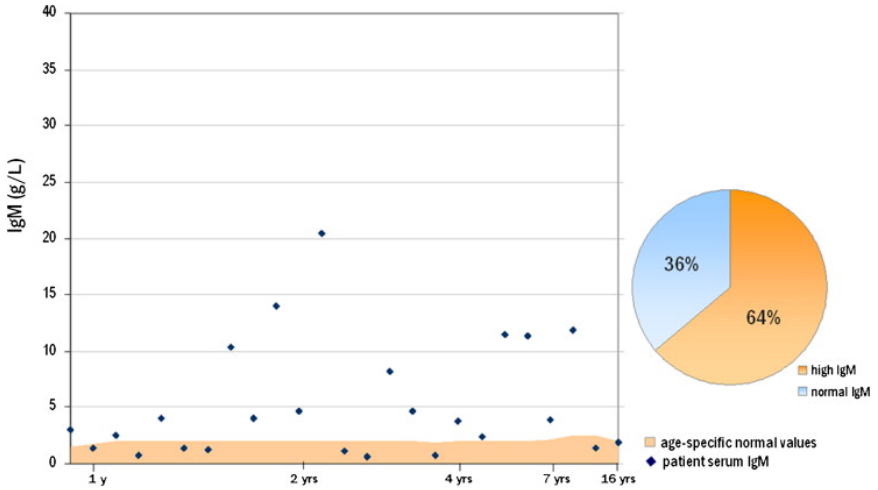
Hyper-IgM syndrome (Ig class-switch deficiency)

- Low IgG, IgA, and IgE levels with either normal or increased IgM
- Misnomer: 62.5% of HIGM patients has elevated IgM levels at the time of initial evaluation (and only 32% of toddlers) (Hennig C. et al. JACI 2011), ~5% have low IgM (Heinold A et al. 2010)

HIGM



Ataxia Teleangiectasia



Prevalence of AT is ~ 3x of HIGM! → increased sIgM level has low sensitivity and specificity as a screening marker for the HIGM syndrome

Hyper-IgM syndrome

- XL: 70% CD40L (CD40LG, or CD154)
  - ‘Activation marker’ on CD4 T cells (PHA/PMA activation followed by flow cytometry - CD69 or CD25 for activation control)
  - Low IgG/A, low memory B (IgD- CD27+)
  - T cell defects: PCP, cryptosporidium, Toxoplasma, Mycobateria
  - Neutropenia (transient or persistent)
  - Autoimmunity (5-15% anemia)
  - Malignancy: pancreas, liver, and biliary tree
- AR: CD40, AID, UNG, PMS2
- IKBKG (aka. NEMO, XL): HIGM syndrome associated with ectodermal dysplasia and immunodeficiency (hypomorphic mutations) → variety of bacterial and opportunistic infections
- Syndromes affecting DNA repair: Ataxia-telangiectasia (AT) and Nijmegen Breakage syndrome (ATM and NBS1 genes)
- BTK deficiency

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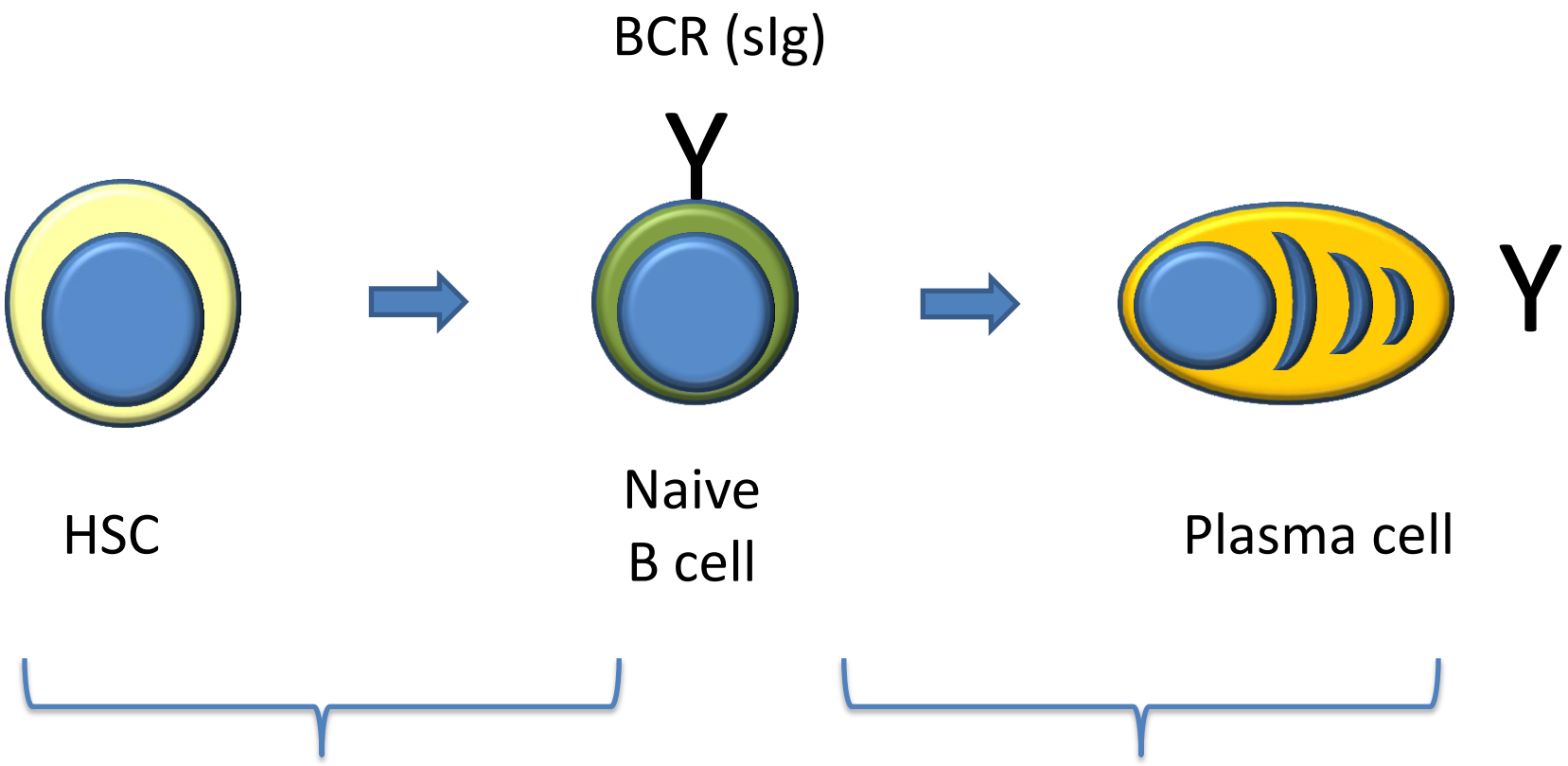


Common Variable Immunodeficiency (CVID)

- Most common symptomatic primary immunodeficiency (1:25,000 to 1:50,000; worldwide)
- Heterogeneous group of late-onset diseases

  characterized by defective immunoglobulin production that leads to recurrent infections
- Part of a spectrum of disorders
  - IgA deficiency (IgA deficiency and CVID in the same families; progression of IgA deficient pts. into CVID)
  - IgG subclass deficiencies (IgG1, IgG2, IgG3, IgG4)
- Complicated by autoimmune and granulomatous diseases, lymphoid hyperplasias, and increased risk of developing malignant neoplasms, especially non-Hodgkin lymphomas

Diagnosis of CVID

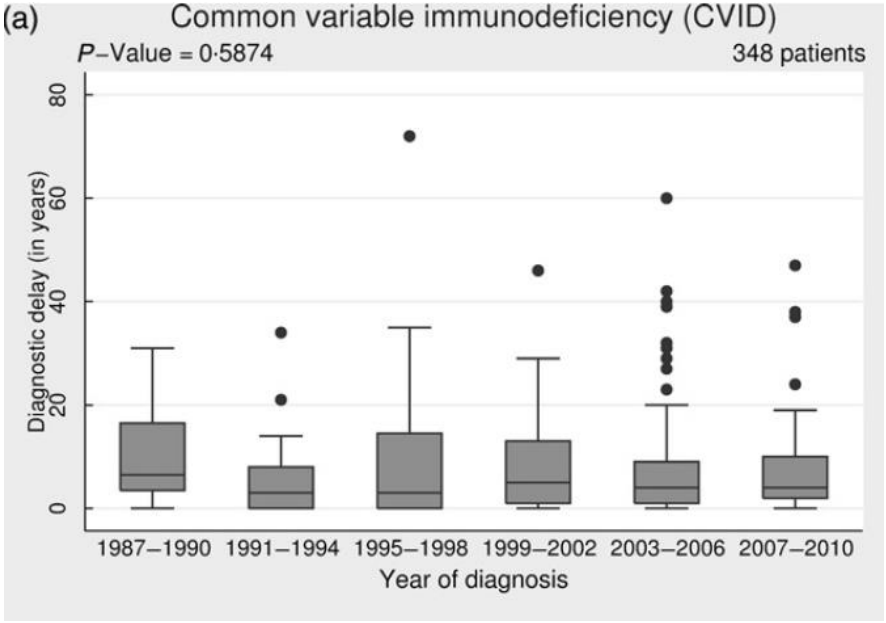
- CVID is characterized by a marked reduction in serum levels of both IgG and IgA
  - about half of these patients also have reduced IgM

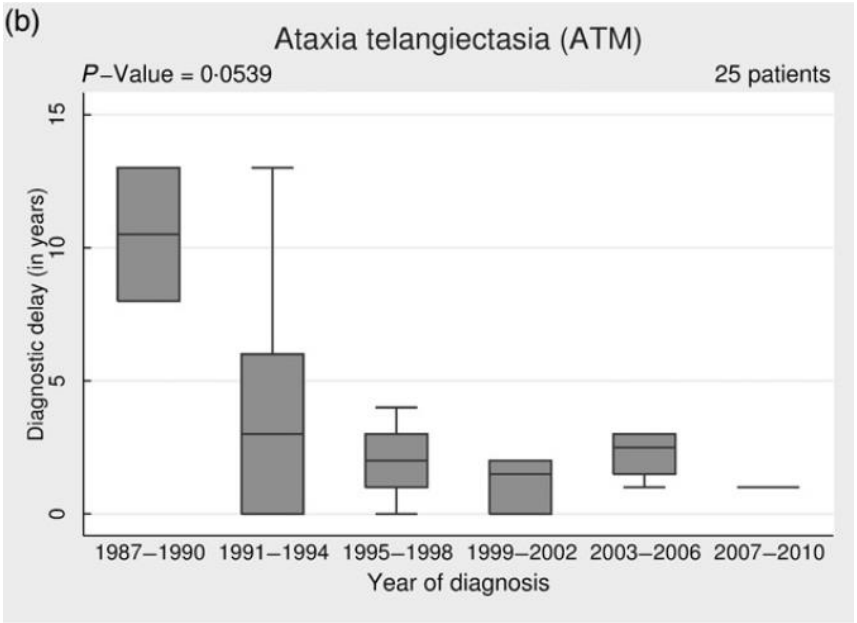
- Diagnosis:
  - Ig deficiency (IgG, IgA /IgM/)
    (overlap/progression)
  - no response to vaccination → Pneumococcus, Tetanus
  - exclusion of other causes of low Ig (genetic and acquired)

- Therapy: replacement

CVID

- Difficult diagnosis:
  - largely based on exclusion
  - PID are zebras in adults
  - progressive disease





Gathmann et al. Clin Exp Immunol 2013

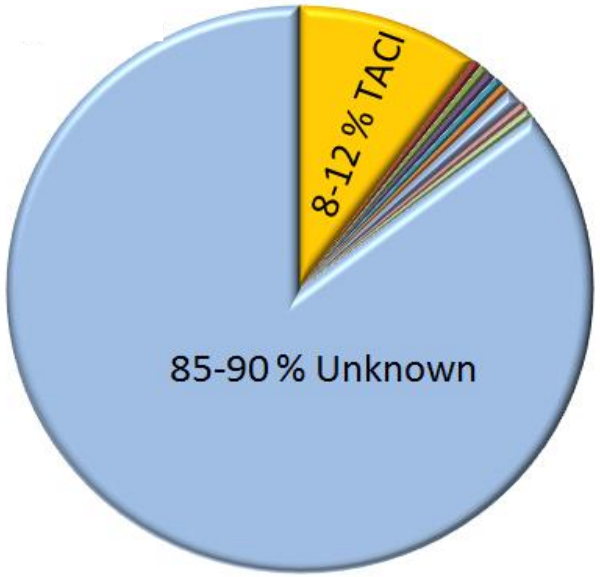
Genetics of CVID

- 90 % sporadic cases
- 10 % familial:

  - AD with variable penetrance (80%)

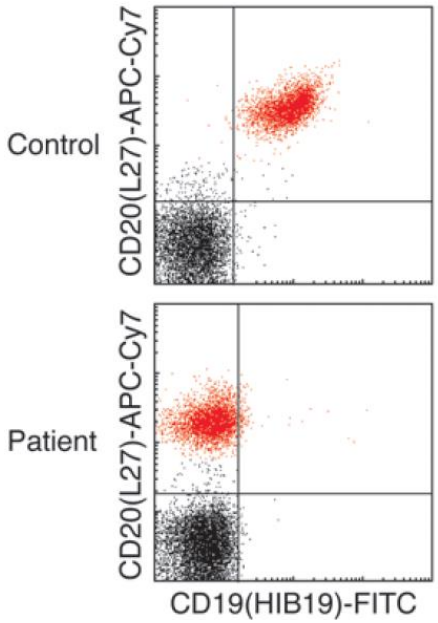
  - AR (20%)

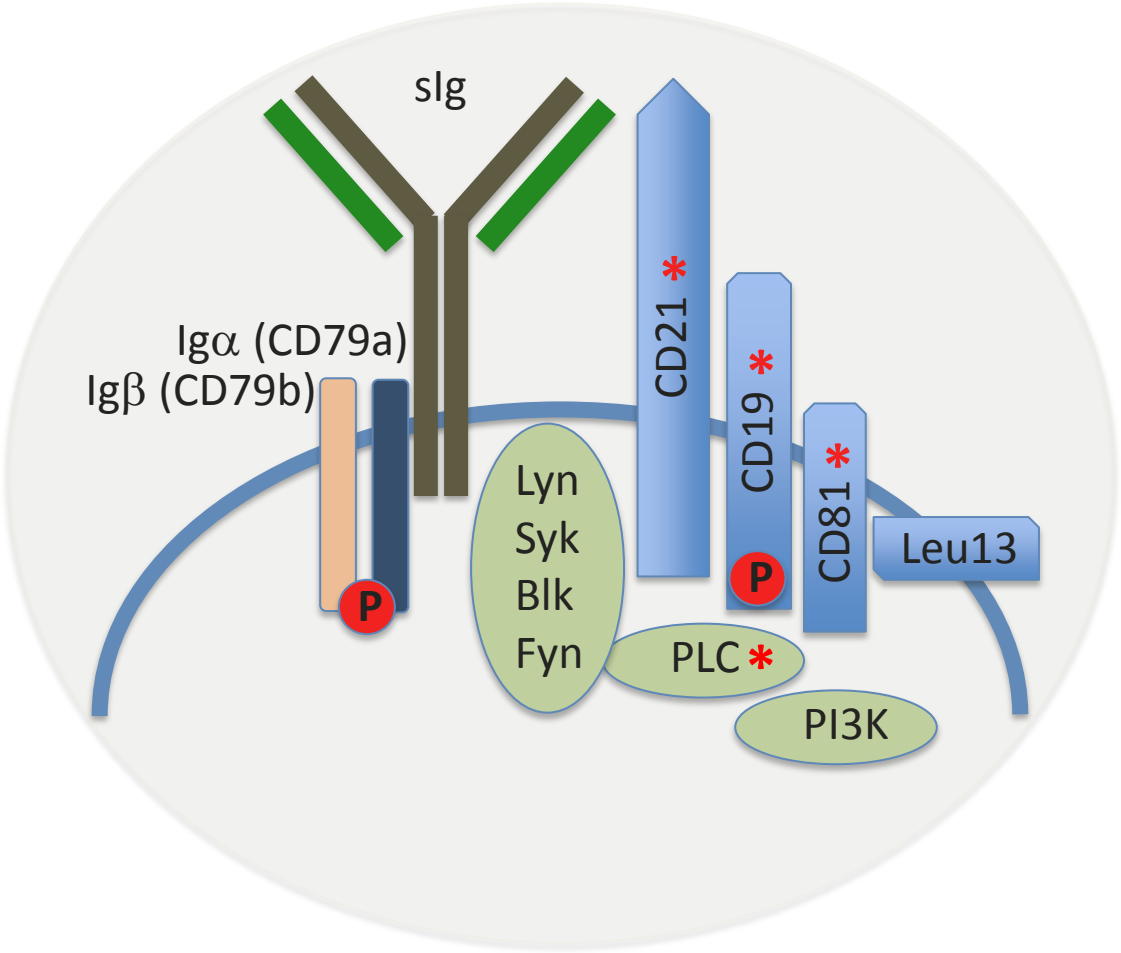
- Genes: BAFF-R, TACI, ICOS, CD19, CD20, CD21, CD81, LRBA, PLCG2, PRKCD, NFKB2



Genetics of CVID

- BAFF-R
- **CD19, CD21, CD81**
- CD20
- TACI
- ICOS





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IgA deficiency

- Serum IgA level of less than 7 mg/dL (0.07 g/L) is considered as selective IgA deficiency (the lowest detectable limit established by most of the laboratories)
- > 7 mg/dL but < two SD below normal for age, the condition may be referred to as partial IgA deficiency (quite common)
- Europe 1:150 and 1:900, incidence is lower in Asian populations

  (Spain 1:150 - Japan 1:18,000, US 1:300-3000 in blood donors)
- Genetics ??? (HLA)
- Often diagnosed by accident as part of a laboratory evaluation for celiac disease, allergy, or autoimmune disease (90%)

IgA deficiency

- Minority of patients develop recurrent lower respiratory tract infections and/or bronchiectasis.

  - Patients with sIgAD are especially at risk of chronic diarrhoea and giardiasis because of their defect in mucosal immunity

- Allergic diseases (atopy ~50%) and autoimmunity (~25%) is more common in IgAD
- Secretory IgA (dimeric), is the prominent immunoglobulin in luminal secretions of the respiratory and gastrointestinal tract and as such an important component of mucosal immunity.
  - cannot be measured in the serum; the serum level of monomeric IgA is rather an indirect measure of IgA in the body

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Genetics of primary antibody deficiencies

- X-linked/AR agammaglobulinemia
  → 7 genes (XL vs. AR)
  → transient hypogammaglobulinemia of infancy
  → other primary antibody deficiencies

- Class switch deficiency / Hyper-IgM syndrome
  → 6 genes (XL vs. AR),
  → DNA repair: ATM, PMS2, Nijmigen
  → other primary antibody deficiencies (BTK)

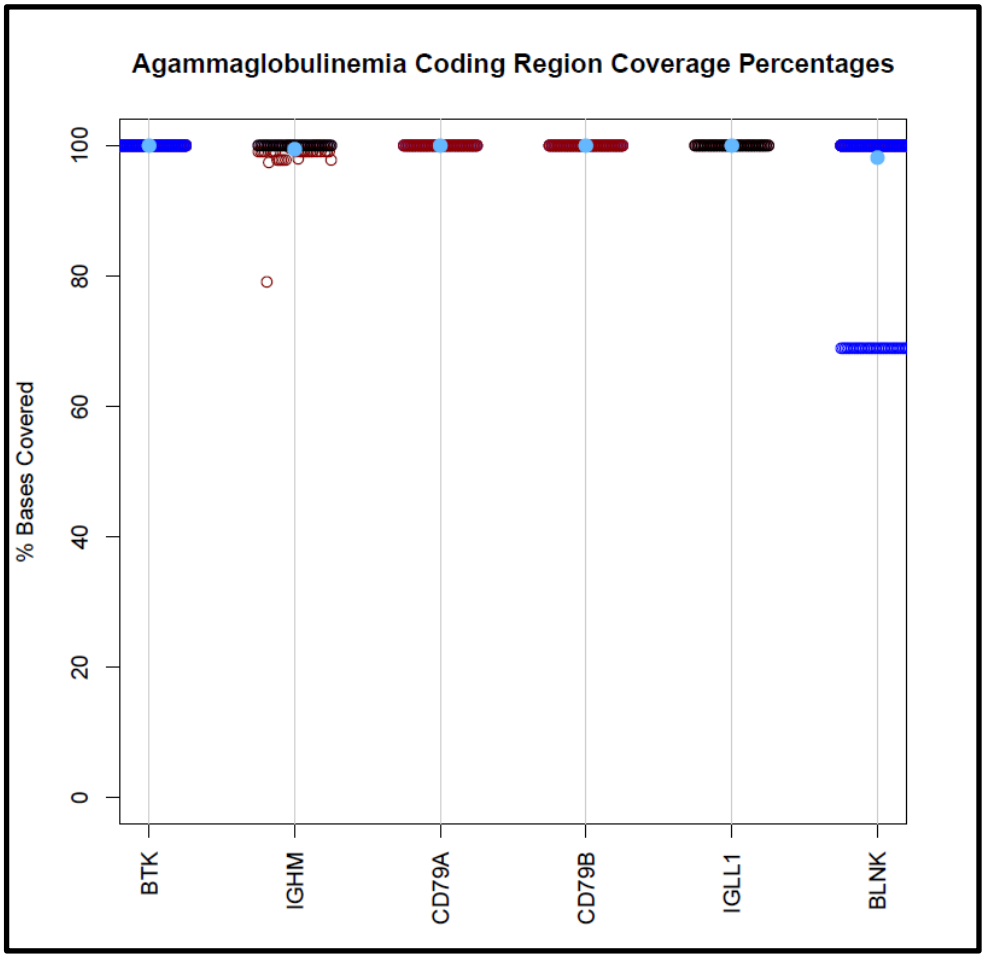
- Common Variable Immunodeficiency
  → 10+ genes
  → other primary antibody deficiencies (IgA, Isolated subclass def.)

- “Mild SCID”/CID, DiGeorge syn., X-linked lymphoproliferative syn.

- Unknown genetics: CVID, IgA, IgG subclass, IgM, Selective Anti-polysaccharide deficiencies

Gene panels

- Overlapping phenotypes
- >30 genes to consider → single gene testing vs. gene panels



Average Coverage

Exons

8 read cutoff

References

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- IgA deficiency
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