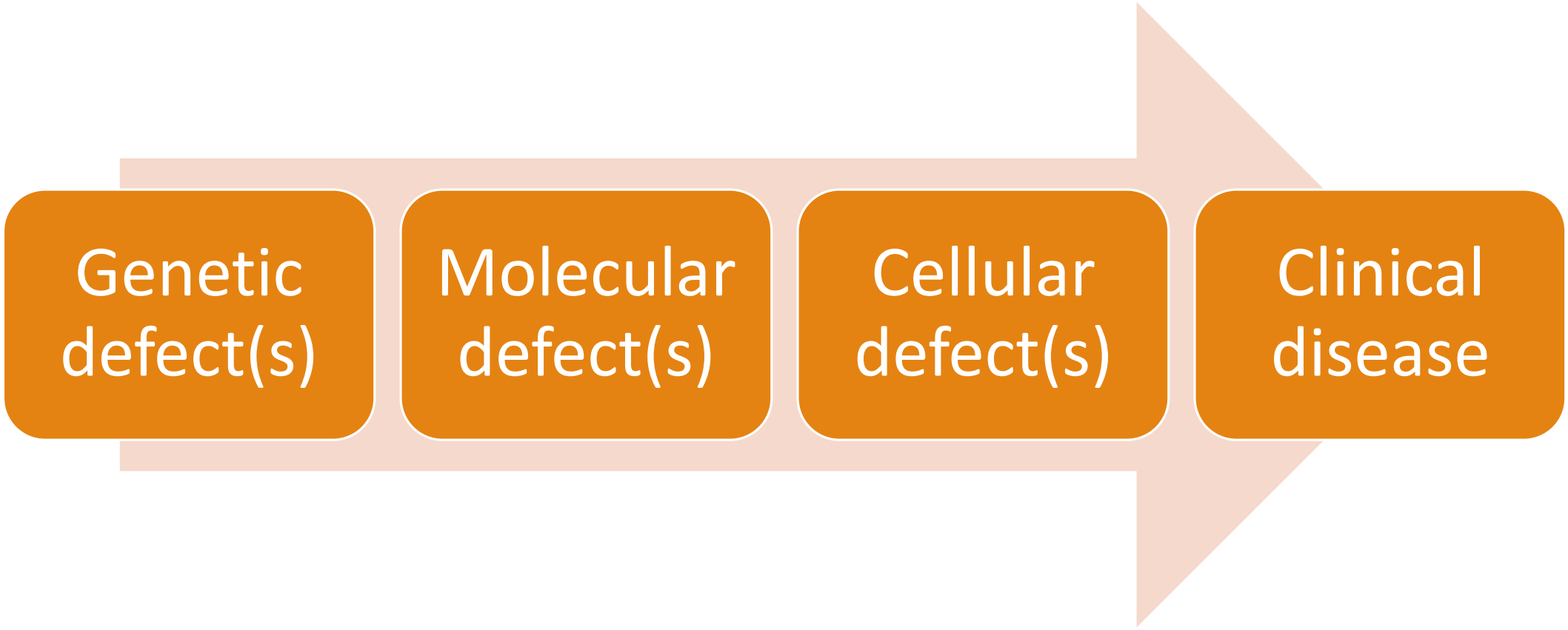
Is it CVID?
Not Necessarily

HAIG TCHEUREKDJIAN, MD

Current Paradigm of Pathogenesis



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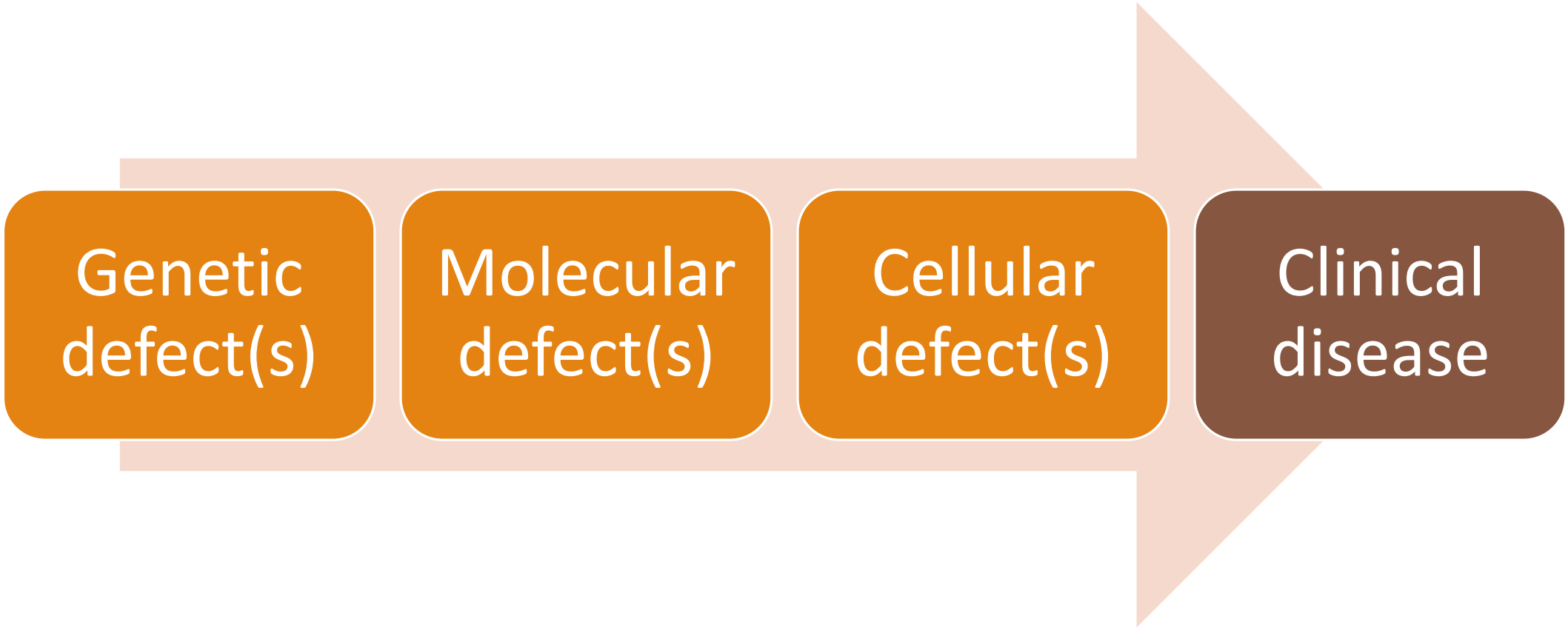


Clinical Disease

PAGID 1999

Immunodeficiency

AMERATUNGA, ET AL 2013

Recurrent, severe, or unusual infections

Poor response to antibiotics

Breakthrough infections despite prophylactic antibiotics

Infections in spite of appropriate immunization

Bronchiectasis or chronic sinus disease

Inflammatory disorder or autoimmunity

ICON 2015

Infection

Autoimmunity

Lymphoproliferation

None of the above

Laboratory Phenotype

PAGID 1999

Marked decrease in IgG and IgA (or IgM)

Absent isohemagglutinins and/or poor vaccine responses

AMERATUNGA, ET AL 2013

IgG < 500 mg/dL

Low IgA (<80 mg/dL) and/or IgM (<40 mg/dL)

B cells present but low # $CD27^{+}$ and/or increased $CD21^{low}$ B cells

IgG3 deficiency (<20 mg/dL)

Poor vaccine response

Transient responses to vaccines

Absent isohemagglutinins

Serological support for autoimmunity

Sequence variations in predisposing genes

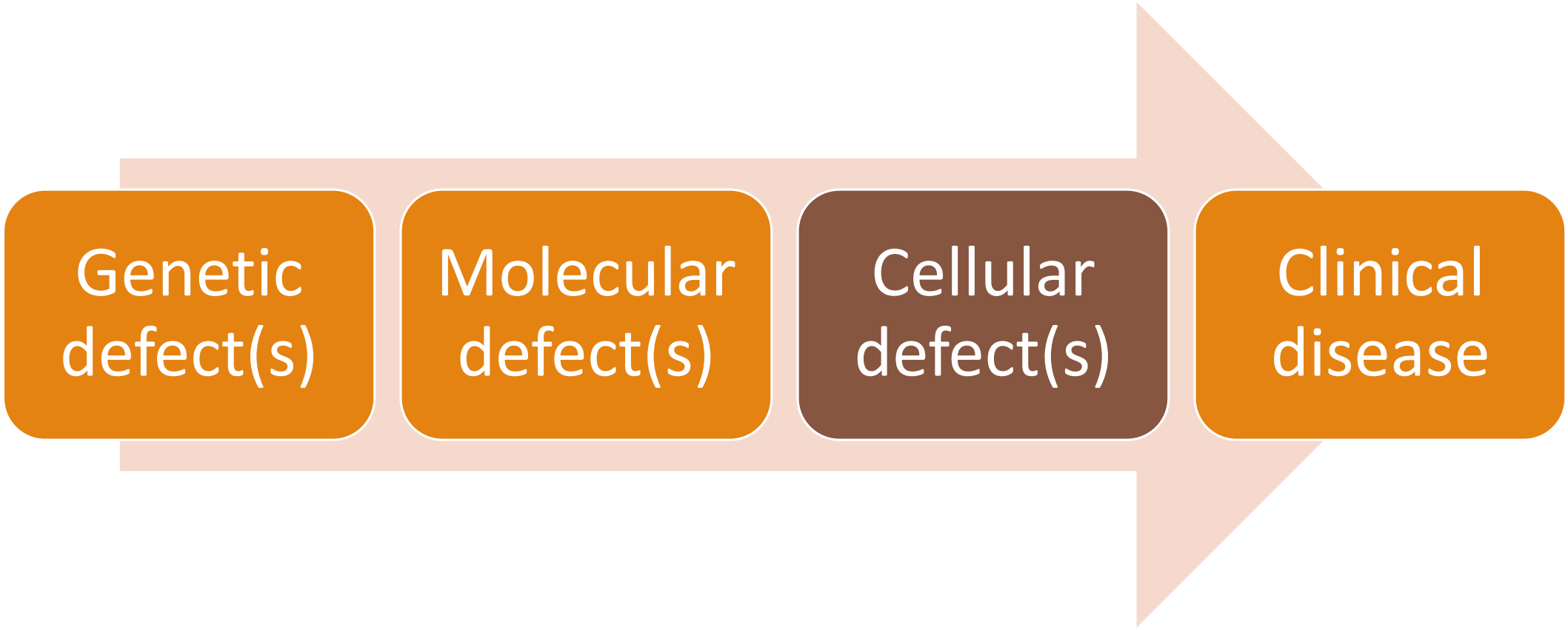
ICON 2015

IgG < 450 mg/dL (although near normal still consistent)

Low IgA or IgM

Poor vaccine responses

Current Paradigm of Pathogenesis



sine qua non of CVID

Maybe a B cell defect?

Not necessarily an Ig production defect

Function by Immunoglobulin Isotype

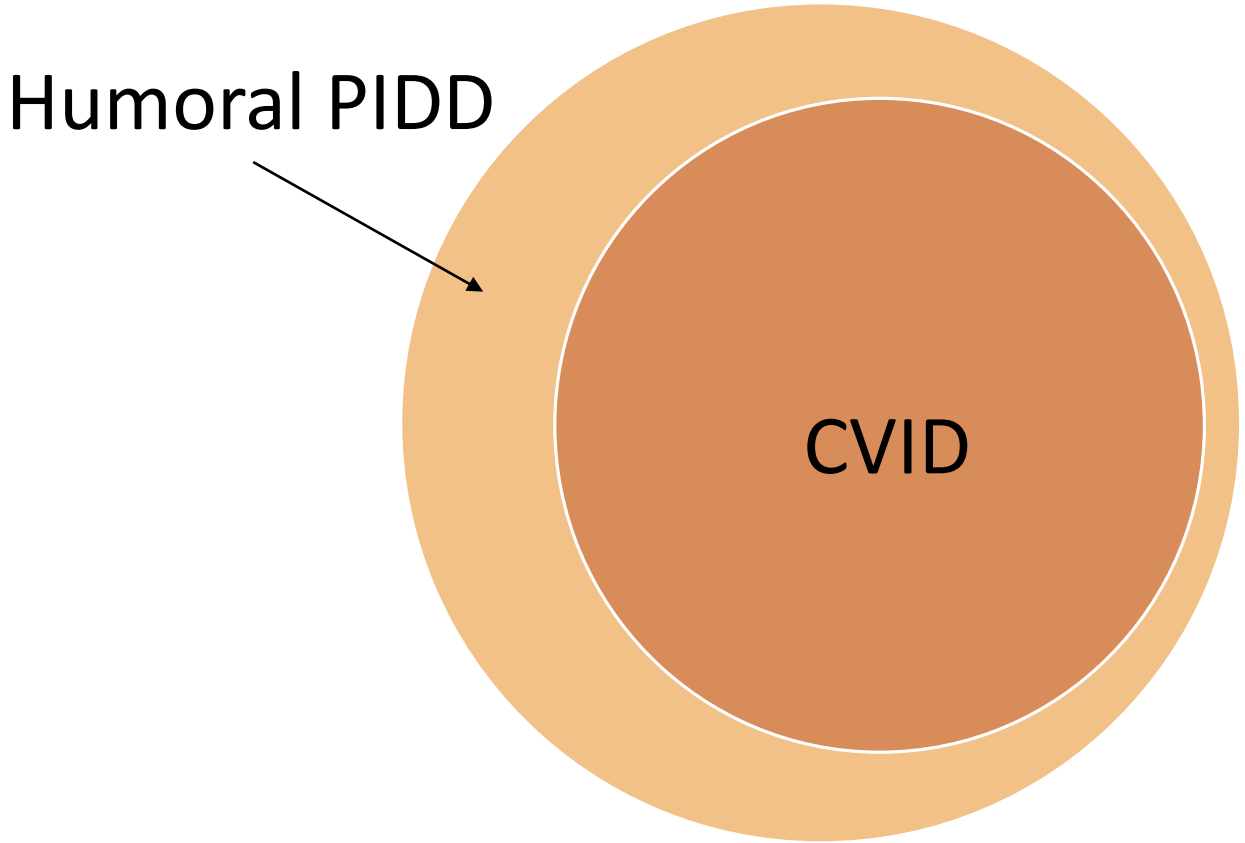
Functional Activity	IgM	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	++	++	++	++	++	
Opsonization		+++	Genotype dependent	++	+	+	
Sensitization for killing by NK cells		++		++			
Sensitization of mast cells		+		+			+++
Complement activation	+++	++	+	+++		+	

Maybe a T cell defect?

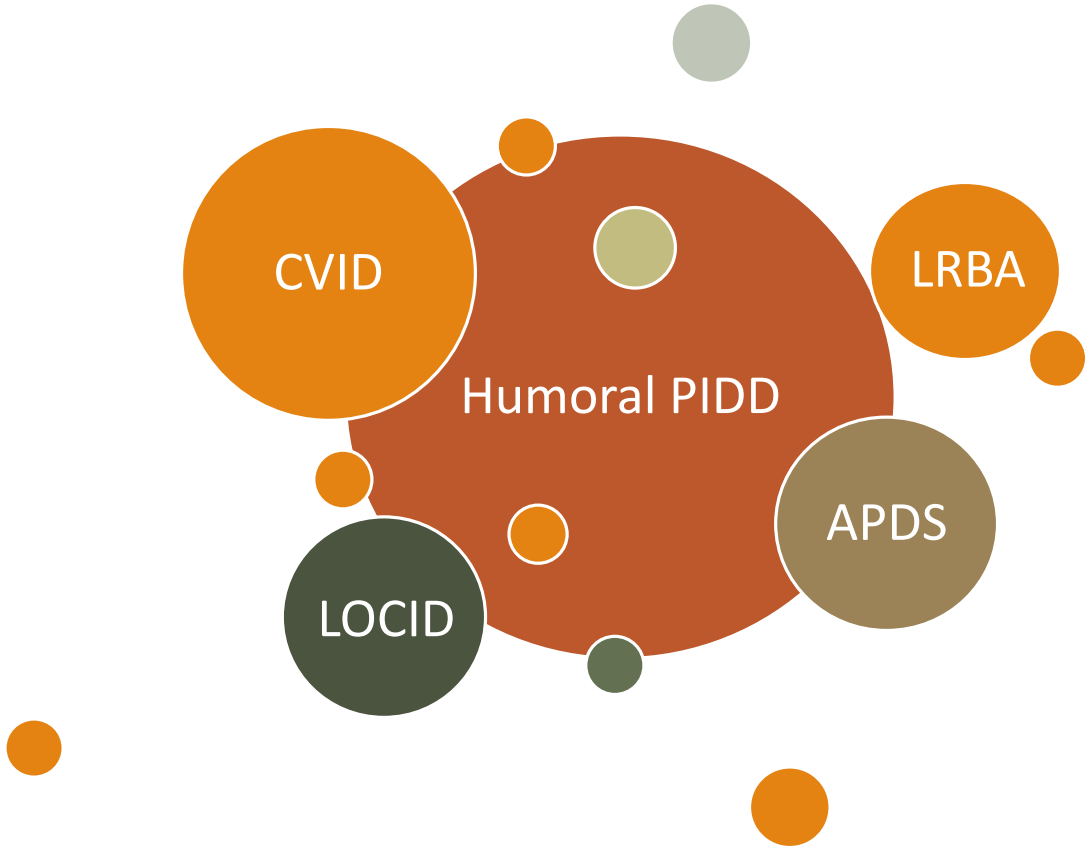
Maybe a dendritic cell defect?

Likely multicellular defect

Historical model



Current/Evolving model



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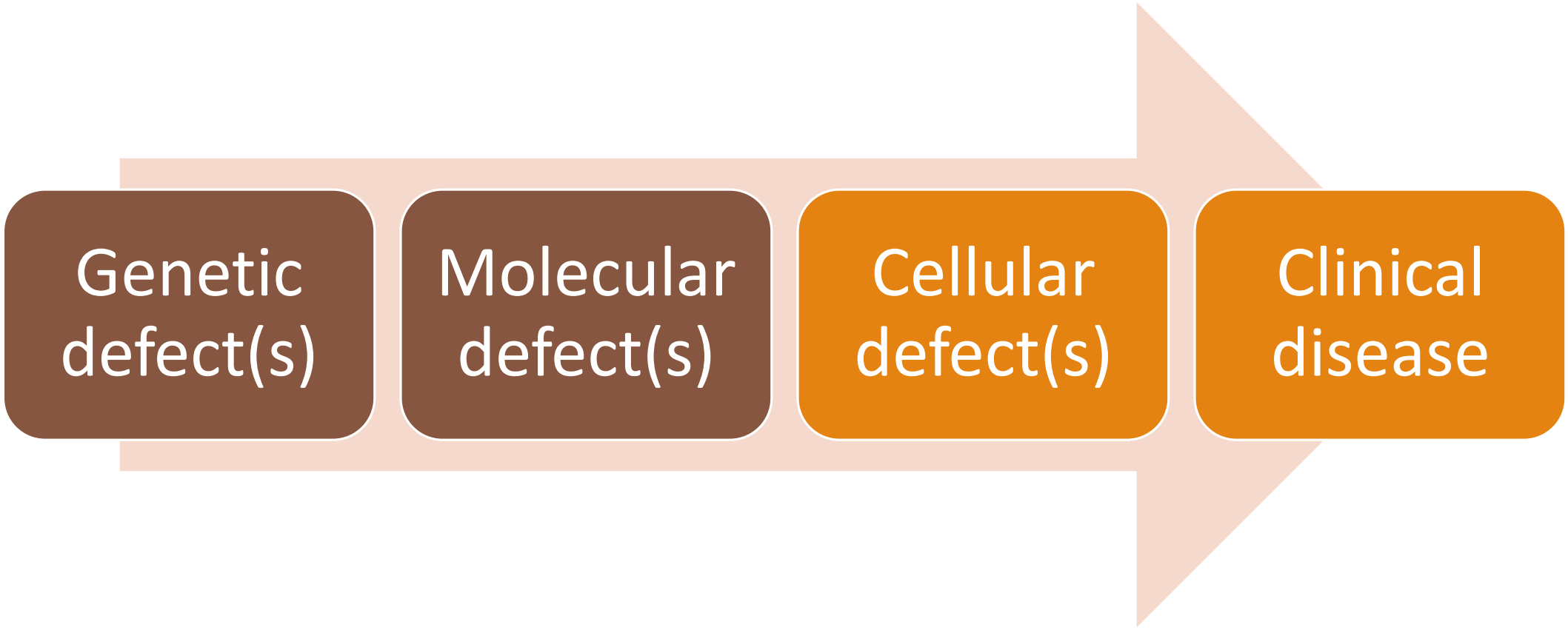

Genetic defects

Bogaert, et al. J Med Genetics. 2016;53:575-590.

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Inducible T cell co-stimulator (ICOS)

- ICOS expression
  - T cells
  - Dendritic cells
- ICOS ligand expression
  - B cells
  - Dendritic cells
- ICOS - ICOS ligand interactions
  - Germinal center formation
  - Terminal B cell differentiation
  - Effector T cell responses
  - Immune tolerance

ICOS Deficiency Clinical Features

- Autosomal recessive loss of function mutations
- Presents at any age
- Infections
  - Sinopulmonary
  - Gastrointestinal
  - Opportunistic
    - CMV viremia
    - Pneumocystis jirovecii pneumonia
- Immune Dysregulation
  - Autoimmune disease
  - Lymphoid hyperplasia
  - Granulomatous disease
  - Hepatosplenomegaly
  - Inflammatory bowel disease

ICOS Deficiency Laboratory Findings

- Low IgG (variable IgA and IgM)
- Impaired responses to protein and polysaccharide vaccines
- Absent to near absent memory B cells
- Absent plasma cells in marrow

ICOS Deficiency Therapy

- B-cell, T-cell, and Dendritic cell defects must be weighed
- Immunoglobulin replacement
- Prophylaxis against opportunistic infections
  - Trimethoprim/sulfamethoxazole
  - Acyclovir
- Hematopoietic stem cell transplantation
  - Infections
  - Inflammatory bowel disease

Who to genotype?

- Opportunistic infections
- Difficult to control inflammatory disease, especially enteropathy
- Absence or near absence of memory B cells
- Absence of marrow plasma cells
- Family history

Benefits of genotyping

- Opportunistic infection prophylaxis
- Consider HSCT in severe cases including enteropathy
- Family planning

TACI

- Transmembrane activator and calcium modulator and cyclophilin ligand interactor
- Expressed on B cells
- Ligands
  - B-cell activating factor (BAFF) or B Lymphocyte Stimulator (BLyS)
    - Membrane bound and soluble
  - A Proliferation Inducing Ligand (APRIL)
    - Soluble
  - Produced by
    - Dendritic cells
    - Monocytes
    - Neutrophils
    - Bone marrow stromal cells

TACI Function

- Class switch recombination
- Differentiation of plasma cells
- Survival of plasma cells
- T-independent responses to polysaccharide antigens
- Central B-cell tolerance and peripheral B-cell expansion

TACI Mutation Clinical Features

- Biallelic mutations are disease causing
- Monoallelic mutations are disease predisposing
- Loss of function mutations
- Clinical phenotype
  - Common variable immunodeficiency
    - Sinopulmonary infections, granulomatous disease, lymphoid hyperplasia
    - Autoimmune disease primarily in heterozygous patients
  - Selective IgA deficiency
  - IgG subclass deficiency

TACI Mutation Laboratory Findings (in CVID)

- Low IgG (variable IgA and IgM)
- Impaired responses to polysaccharide vaccines
- Variable memory B cell numbers

TACI Mutation Therapy in CVID

- Traditional CVID therapy
  - Immunoglobulin replacement
  - Antimicrobial prophylaxis when appropriate
  - Management of inflammatory and autoimmune diseases
  - Malignancy surveillance

Phosphoinositide 3-kinase (PI3K)

- PIK3CD gene encodes the catalytic p110δ subunit of phosphoinositide 3-kinase (PI3K)
- Intracellular molecule in leukocytes including B-cells and T-cells
- Activated by binding of ligands to various cell surface receptors
  - Antigen receptors
  - Cytokine receptors
  - Surface integrins
- Modulates signaling through multiple downstream pathways including mechanistic target of rapamycin (mTOR) modulating
  - Gene expression
  - Regulation of protein and organelle function
  - Cellular metabolism

Immunodeficiency secondary to PIK3CD mutation

- Activated PI3Kδ Syndrome (APDS) OR p110δ Activating mutation causing Senescent T cells, Lymphadenopathy, and Immunodeficiency (PASLI Disease)
- Autosomal dominant
- Gain of function mutations

APDS Infectious Complications

Recurrent respiratory tract infections	51/53 (98)
Pneumonia†	39/46 (85)*
Bronchiectasis‡	32/53 (60)
Chronic rhinosinusitis	24/53 (45)
Recurrent otitis media	26/53 (49)
(with permanent hearing loss)	4/53 (8)
Severe or persistent herpesvirus infection	26/53 (49)
EBV	14/53 (26)
CMV	8/53 (15)
HSV and VZV	11/53 (21)
Tonsillitis	15/53 (28)
(with tonsillectomy)	7/53 (13)
Ocular infections	10/53 (19)

*

J Allergy Clin Immunol 2017;139:597-606

APDS Non-infectious Features

Lymphadenopathy§	34/53 (64)
Splenomegaly	31/53 (58)
Hepatomegaly	24/53 (45)
Autoimmune disease	22/53 (42)
Nodular mucosal lymphoid hyperplasia	17/53 (32)
Enteropathy‖	13/53 (25)
Developmental delay	10/53 (19)
Lymphoma	7/53 (13)

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APDS Immunoglobulin levels

	Reduced, n/total (%)	Normal, n/total (%)	Increased, n/total (%)
IgG	21/49 (43)	26/49 (53)	2/49 (4)
IgA	25/50 (50)	24/50 (48)	1/50 (0.5)
IgM	0/50 (0)	12/50 (24)	38/50 (76)
Pneumococcal vaccine response*	25/28 (89)	3/28 (11)	

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APDS T cell phenotype

- Decreased CD4/CD8 ratio
- Increased number of terminally differentiated memory T cells (poor proliferative capacity)
- Increased number of senescent CD8+ memory T cells (poor functional capacity)

Nat Immunol. 2014 January ; 15(1): 88–97

APDS B cell phenotype

Reduced B-cell counts ($CD19^+$)	32/48 (67)
Increased transitional B-cell counts ($CD19^+IgM^{++}CD38^{++}$)	24/32 (75)
Reduced nonswitched memory B cells ($CD19^+IgD^+CD27^+$)	15/30 (50)
Reduced class-switched memory B-cell counts ($CD19^+IgD^-CD27^+$)	17/30 (57)

J Allergy Clin Immunol 2017;139:597-606

APDS Therapy

- Immunoglobulin replacement
- Antibacterial, antiviral, and/or antifungal prophylaxis in selective patients
- Frequent screening for lymphoma
- Rituximab for non-neoplastic lymphoproliferation and other autoimmune disease
- Rapamycin (sirolimus) for non-malignant lymphoproliferation and hepatosplenomegaly
- Consider selective PI3Kδ inhibitors
- Consider HSCT

Cellular effects of sirolimus therapy

Nat Immunol. 2014 January ; 15(1): 88–97

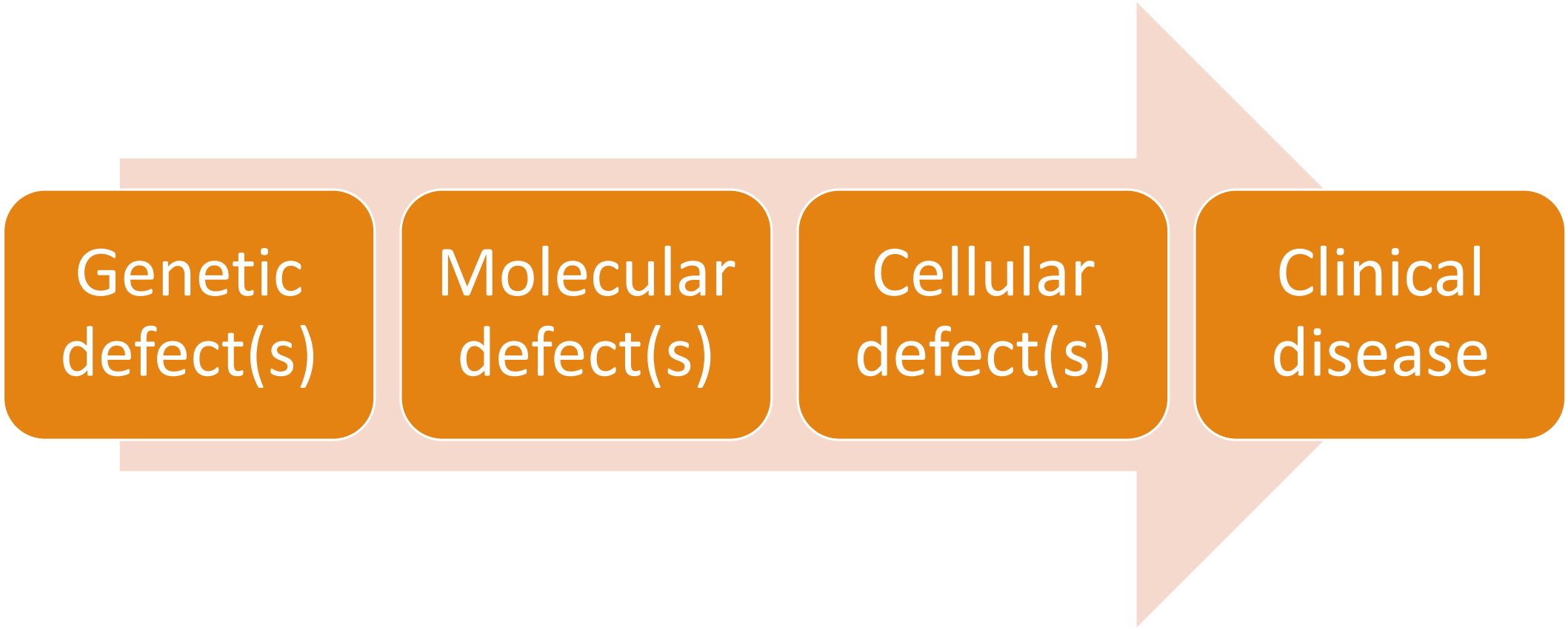
Who to genotype?

- Hyper IgM
- Severe non-malignant lymphadenopathy
- Herpes family viremia
- Increased number of terminally differentiated (CCR7-) memory (RA-) T cells
- Increased number of senescent (CD57+) CD8+ T cells
- Family history

Benefits of genotyping

- Consider antiviral prophylaxis
- Consider sirolimus for non-malignant lymphoproliferation
- Implement aggressive lymphoma screening
- Consider HSCT in severe cases
- Family planning

Current Paradigm of Pathogenesis



III. Predominantly antibody deficiencies

Recurrent bacterial infections eg : Otitis, pneumonia, sinusitis, diarrhea, sepsis

Serum Immunoglobulin Assays : IgG, IgA, IgM

IgG, IgA and/or IgM ↓ ↓

Exclude 2^0 causes: drugs [Hx], myeloma [bone marrow], Lymphoma . Ig loss (not hypo-IgM) in urine, GI or skin

B Lymphocyte (CD19+) enumeration (CMF)

B absent

X-Linked Agammaglobu-linaemia (*BTK*)

AR
Agammaglobulinaemias

μ heavy chain Def (*IGHM*)
Igα (*CD79A*)
Igβ (CD79B)
BLNK (*BLNK*)
I5 (*IGLL1*)
PI3KR1 def (*PIK3R1*)

AD
E47 transcription factor def (*TCF3*)

B >1 %

Common Variable Immunodeficiency Disorders (CVID)

Very rare AR disorders: *TACI,BAFF-R, CD19 , CD81, CD20, CD21, TWEAK, NFKB2*

Thymoma with immunodefciency
Bacterial/ opportunisitc infections, autoimmunity

Myelodysplasia with hypogammaglobulinemia (Monosomy 7, trisomy 8 or DKC, GATA2)

Congenital sideroblastic anemia, deafness, developmental delay : TRNT1 def (*TRNT1*)

Trichorrhexis nodosa TTC37 def (*TTC37*)

Dysmorphic facial features, Hypotonia, neurologic disorder; severe hypogammaglobulinemia
CDG-IIb (*MOGS*)

IgG (↓) ,IgA(↓) and IgM(N / ↑) : HIGM

Healthy infant, no increased bacterial infections. Normalisation at 36-60 months

Transient hypogamma-globulinemia of infancy

AR hyper-IgM disorders, with lymphoid hyperplasia:

AID def (*AICDA*)
UNG def (*UNG*)

Others

INO80 def (*INO80*)

MHS6 def (*MHS6*) (cancer)

Growth retardation. EBV. CMV viremia.

PIK3R1 loss-of-function (PI3KR1)

IgA↓

1 IgG subclasses 1,2,3 levels (measure at least two)

2 Specific antibody responses (anti-PPS antibodies and Tet/dip/hib)

Selective IgA def

Low IgG Sub classes

IgA with IgG subclasses def

Low Specific antibody responses

IgA with Specific Ab deficiency

Normal IgA,IgG,IgM

1 IgG subclasses 1,2,3 levels (measure at least two) ?

2 Specific antibody responses (anti-PPS antibodies and Tet/dip/hib) ?

IgG subclasses Low +/- poor Specific Ab response :
Isolated IgG subclass

IgG2 Low + impaired response to PPS and hib :
Bronchiectasis, autoimmunity, chronic EBV, CMV infection

Activated PI3K-δ (*PIK3CD, p110*)

IgG subclasses +/-IgA, absent IgE, asymptomatic : Ig heavy chain mutations or deletion (mutation or chromosomal deletion 14q32)

All have lambda chain, asymptomatic

K chain def (IGKC)

Congenital B cell lymphocyto sis

AD, SPM, Adp.

Bacterial and viral infections, EBV chronic infection, Autoimmune cytopenia

CARD11 gain of function mutations (*CARD11*)

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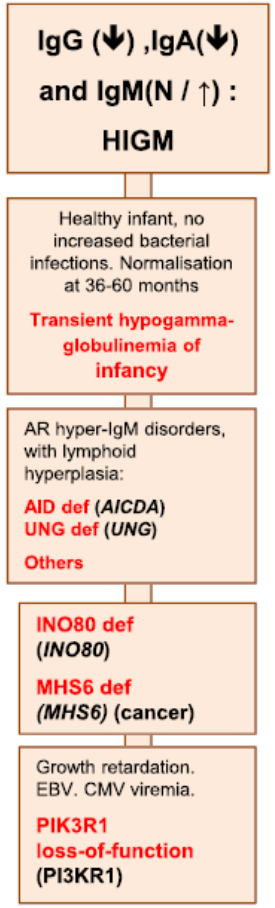

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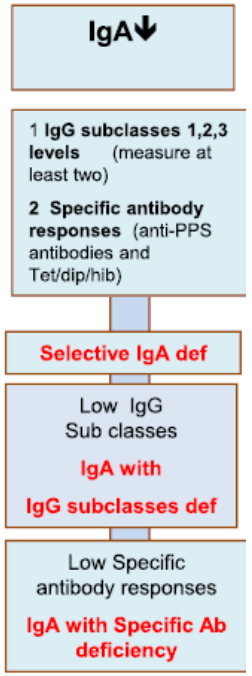

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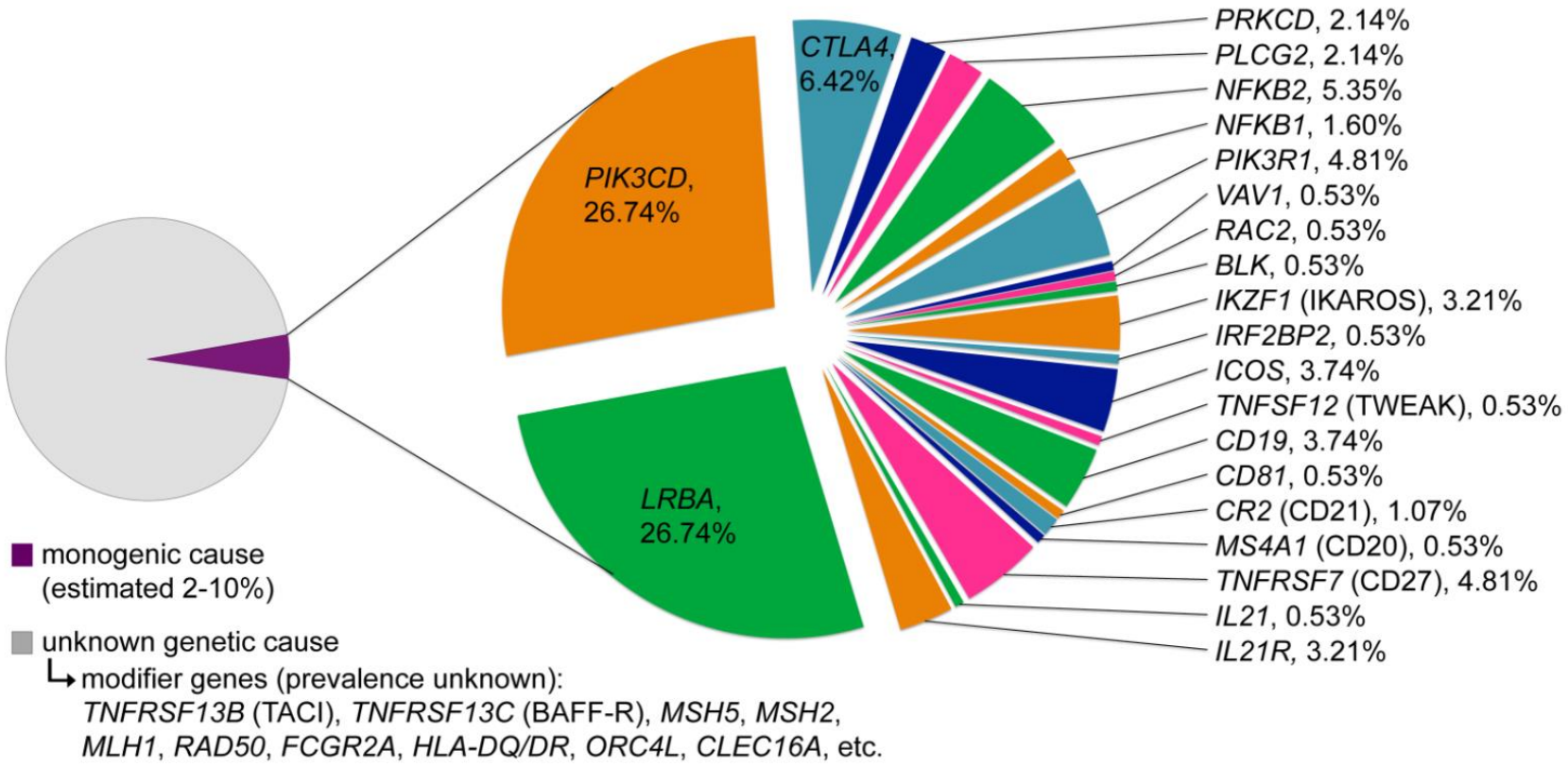

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