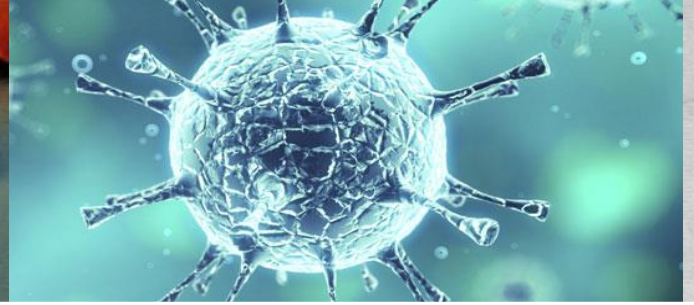
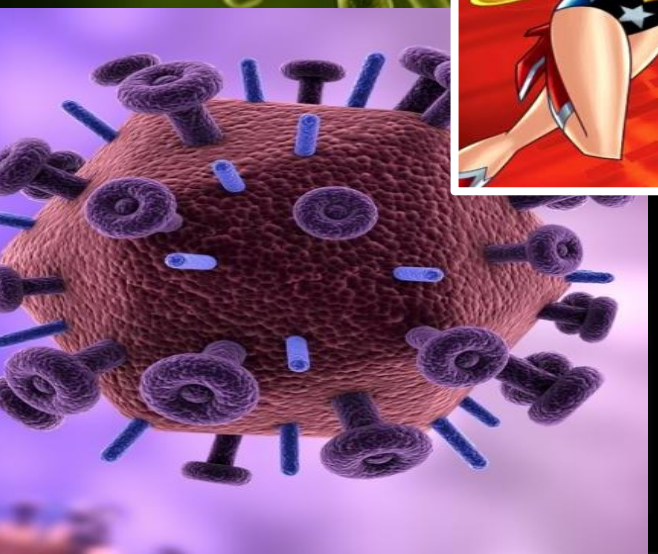
Primary Immunodeficiency Diseases in children and adults

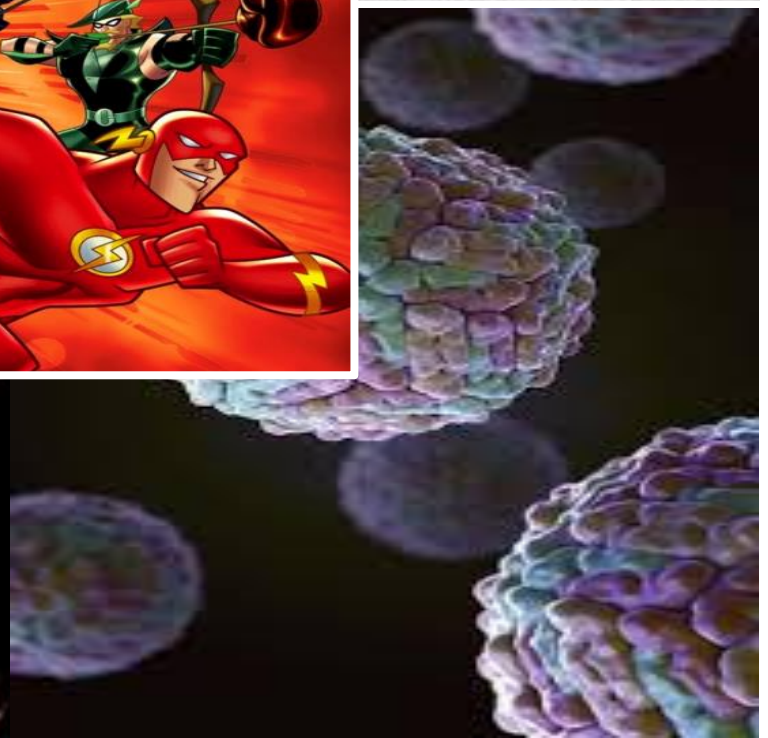
INDIAN COUNCIL OF MEDICAL RESEARCH

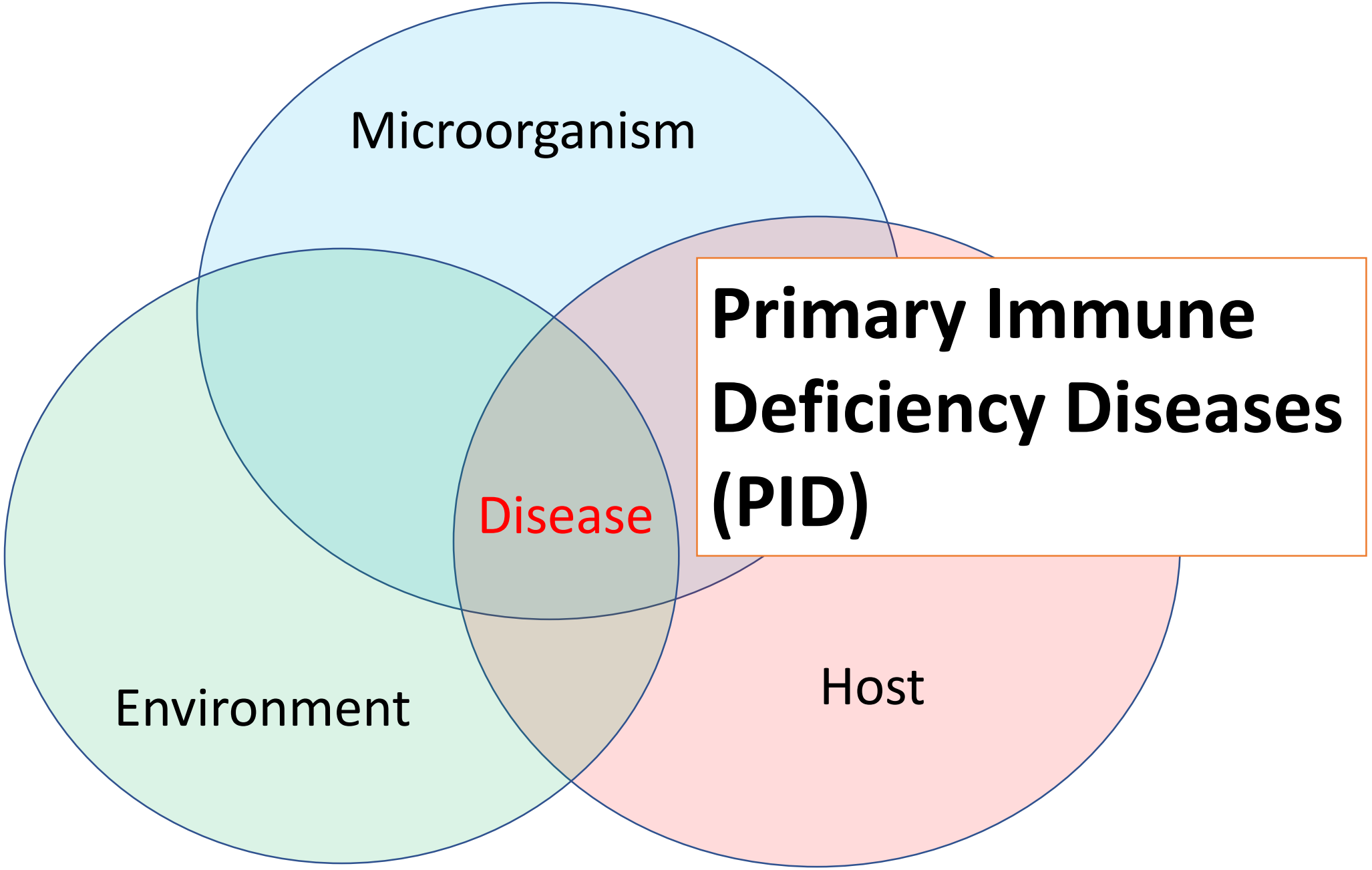
NATIONAL INSTITUTE OF IMMUNOHAEMATOLOGY








Microorganism
Environment
Host
Disease
Primary Immune Deficiency Diseases (PID)

- Background
- Approach to diagnosis of PID
- Genetic diagnosis of PID
- Lack of focus is good thing
- Looks like duck but not a duck

Primary Immunodeficiency diseases

- Inherited diseases of immune system
- Affect different components of the immune system
- Clinically heterogeneous

Why do we need to diagnose PIDs?

- Collective Prevalence of high as 1 in 10000 suggesting a very high burden of disease
- Often missed causing significant morbidity and mortality
- Multiple family members may get affected leading to financial burden on the family and society
- Early diagnosis and adequate management can lead to significant reduction in morbidity and mortality

Group	Category
Group I	**Combined immunodeficiencies**

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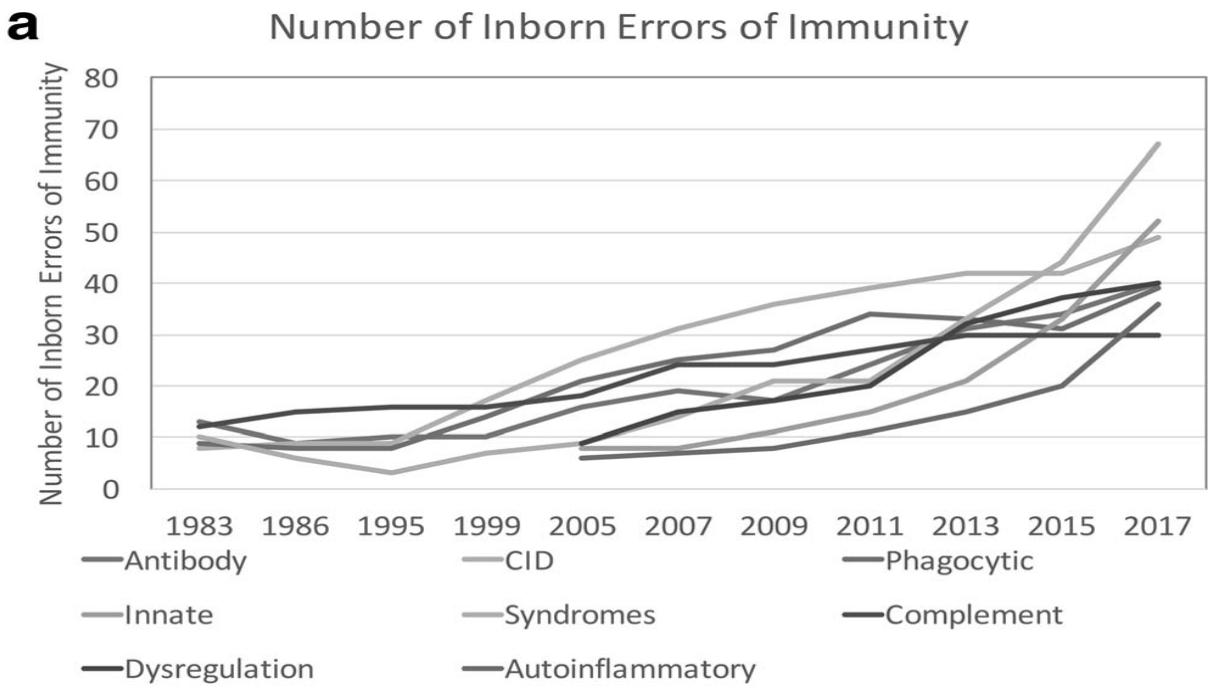
https://doi.org/10.1007/s10875-017-0464-9

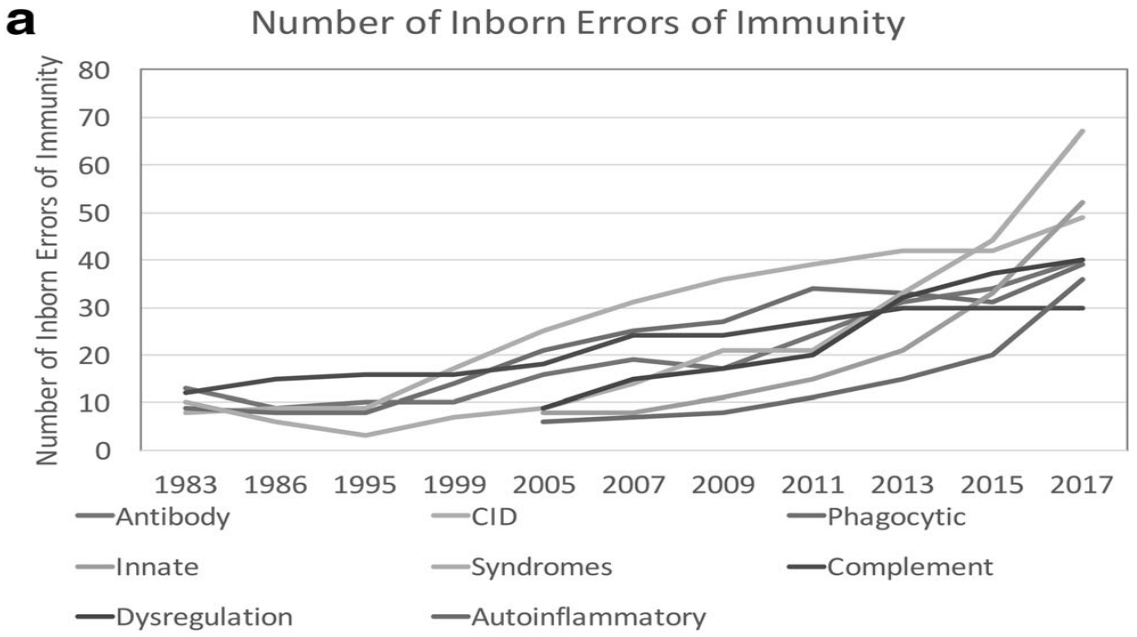
ORIGINAL ARTICLE

International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity

Group VI	**Defects in innate immunity.**
Group VII	**Autoinflammatory disorders.**
Group VIII	**Complement deficiencies.**
Group IX	**Phenocopies of PID**

- International Union of Immunological Societies (IUIS):
- 354 distinct disorders
- 344 different gene defects listed (Feb2017)





Group I	**Combined immunodeficiencies**
Group II	**Combined immunodeficiencies with associated or syndromic features.**
Group III	**Predominantly antibody deficiencies.**
Group V	**Congenital defects of phagocyte number, function, or both.**
Group VI	**Defects in innate immunity.**
Group VIII	**Complement deficiencies.**

Group IV	**Diseases of immune dysregulation.**
Group VII	**Autoinflammatory disorders.**
Group VIII	**Complement deficiencies.**

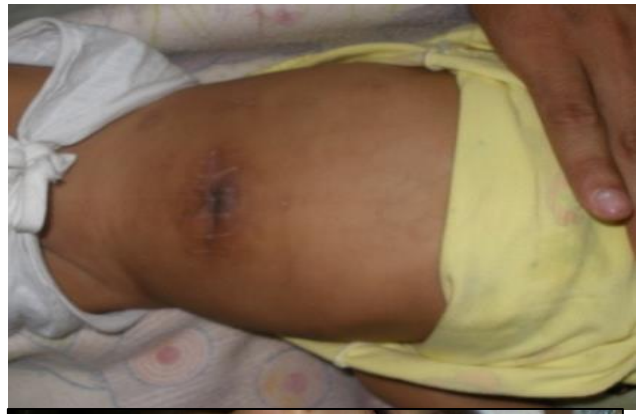
- Autoimmunity
- Auto-inflammation

Inborn errors of immunity

- Recurrent infections
- Malignancies

PID in children

- PID presenting early neonatal period
  - LAD-I
  - Omenn syndrome
  - Di George Syndrome
  - SCN
  - Reticular dysgenesis



PID in children

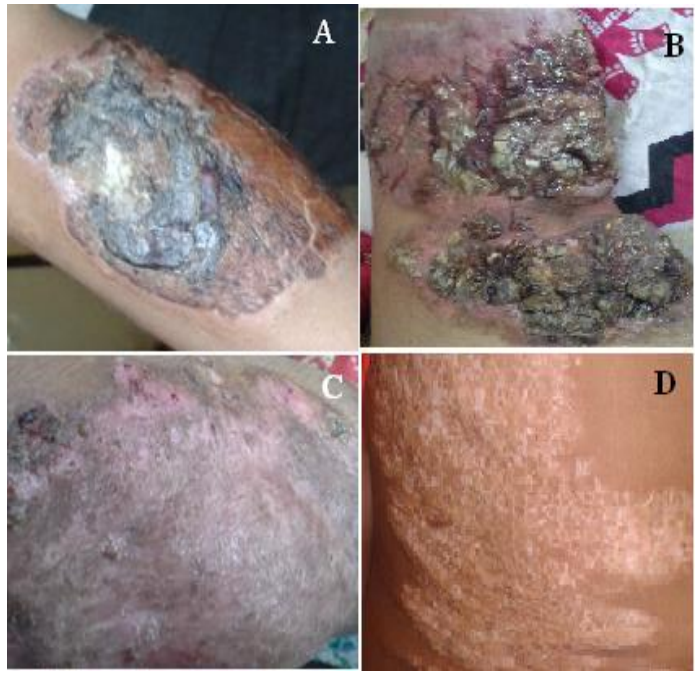
- PID presenting within first 6 months of life
  - SCID
  - CID
  - Di George Syndrome
  - Diseases of immune dysregulation
  - CGD
  - HIGM: CD40-CD40L deficiency
  - MSMD
  - HLH

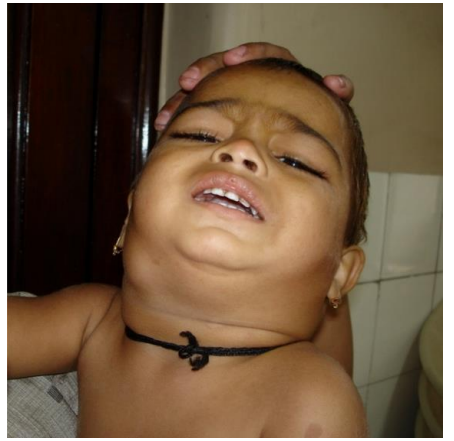
PID in children

- PID presenting between 6 months-1 year
  - XLA
  - Other agammaglobulinemia
  - Wiskott–Aldrich syndrome
  - DiGeorge syndrome
  - Chronic mucocutaneous candidiasis
  - Hypogammaglobulinaemia
  - Phagocytic defect - CGD

PID in children

- PID presenting after the age of 5 year
  - AT, other DNA repair disorder
  - Common variable immunodeficiency
  - Specific antibody deficiency
  - Complement disorder
  - Milder forms of PID





10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

Presented as a public service by:

Jeffrey Modell Foundation | Curing PI. Worldwide.

Funding was made possible in part by a grant from the U.S. Centers for Disease Control and Prevention (CDC).

National Heart, Lung, and Blood Institute (NHLBI)

National Cancer Institute

PPTA Plasma Protein Therapeutics Association

National Institute of Allergy and Infectious Diseases (NIAID)

NICHD

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PIDs in adults

- Antibody deficiencies:
  - Common Variable Immune Deficiency : CVID
  - Specific antibody deficiencies
  - IgG subclass deficiency
- Autoimmune lymphoproliferative syndrome
- Hypomorphic forms of many severe PID
- Phenocopies of PID

10 FOR ADULTS Warning Signs of Primary Immunodeficiency

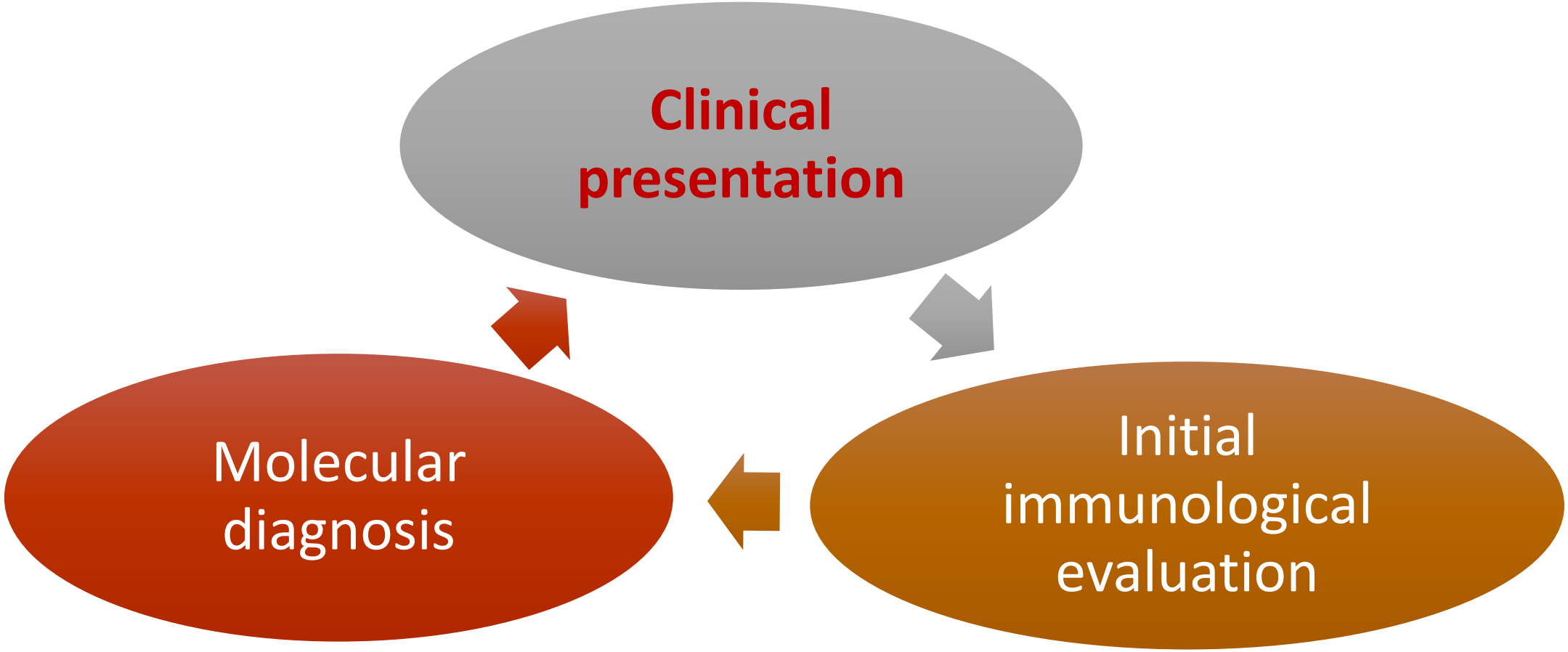
Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
9. Infection with normally harmless tuberculosis-like bacteria.
10. A family history of PI.

Clinical clues:

- Age of presentation
- Pattern of infections: organism and the site involved
- Associated clinical manifestations
  - Autoimmunity and autoinflammation
  - Endocrine manifestations
  - Malignancies
  - Skeletal abnormalities
  - Skin manifestations
- Family history:
  - Early sibling death due to similar illness
  - Consanguinity
  - X-linked pattern

Approach diagnosis of PID



Complete blood count:

- **Absolute counts:**
  - **ANC**
    - Neutropenia: ANC<500 (Severe congenital neutropenia/cyclic neutropenia)
    - Neutrophilia: Leukocyte Adhesion Deficiencies (LAD)
  - **ALC**
    - Lymphopenia: Combined Immunodeficiency (CID)
    - Lymphocytosis: Autoimmune lymphoproliferative Disorders
  - **AEC**
    - Eosinophilia: Hyper IgE syndromes/ Omenn's syndrome
  - **AMC**
    - Monocytopenia in GATA2 deficiency
- **Platelet count with MPV:**
  - Wiskott Aldrich Syndrome (WAS)

Immunological evaluation:

- Total number of cells
- Function of cells:
  - T cell proliferation
  - Antibody production
  - DHR assay
- Assays for specific diagnosis:
  - CD18 expression
  - Perforin expression

Initial evaluation:

- Serum immunoglobulin levels
- Lymphocyte subset analysis
- NBT test
- Complement levels

J Clin Immunol
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ORIGINAL RESEARCH

The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies

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Spectrum of infections: CID

Early onset (<6 months)

Common Microorganisms

Viruses
- CMV
- Vaccinia
- Adenovirus, HSV,
- Measles

Pyogenic bacteria

Mycobacteria:

BCGiosis

Fungi
- Candida,Aspergillus, PCP

Protozoa
- Cryptosporidium

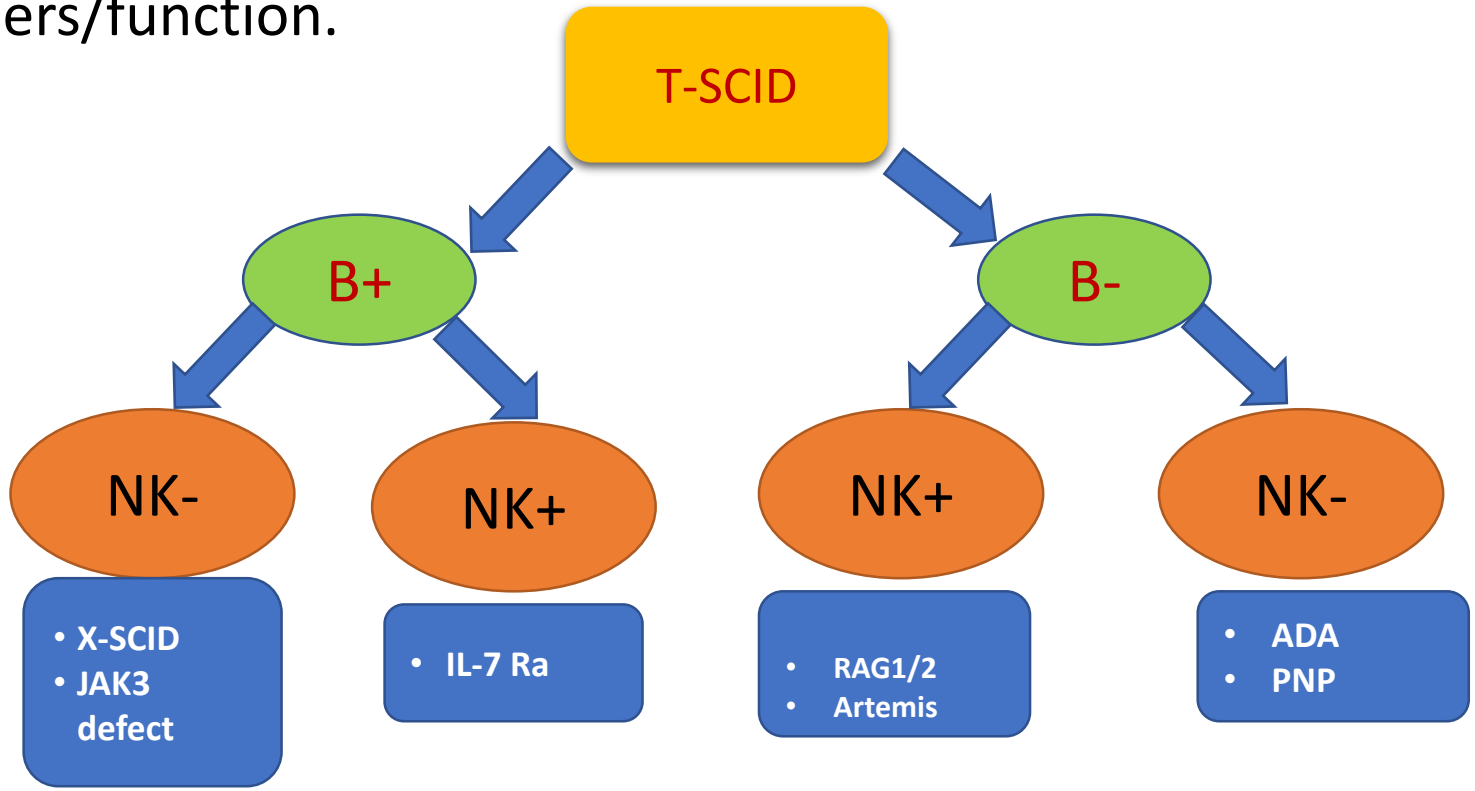
- Failure to thrive
- Oral candidiasis
- Protracted diarrhea
- Skin rash
- Respiratory Tract
- Systemic viral infections
- Gastroenteritis
- Opportunistic infections
- GVHD
- Hepatospenomegaly (Omenn syndrome)

Less common Microorganisms

Bacteria
- Campylobacter
- Mycobacteria
- Listeria

1. Evaluation of defects with altered T lymphocyte population

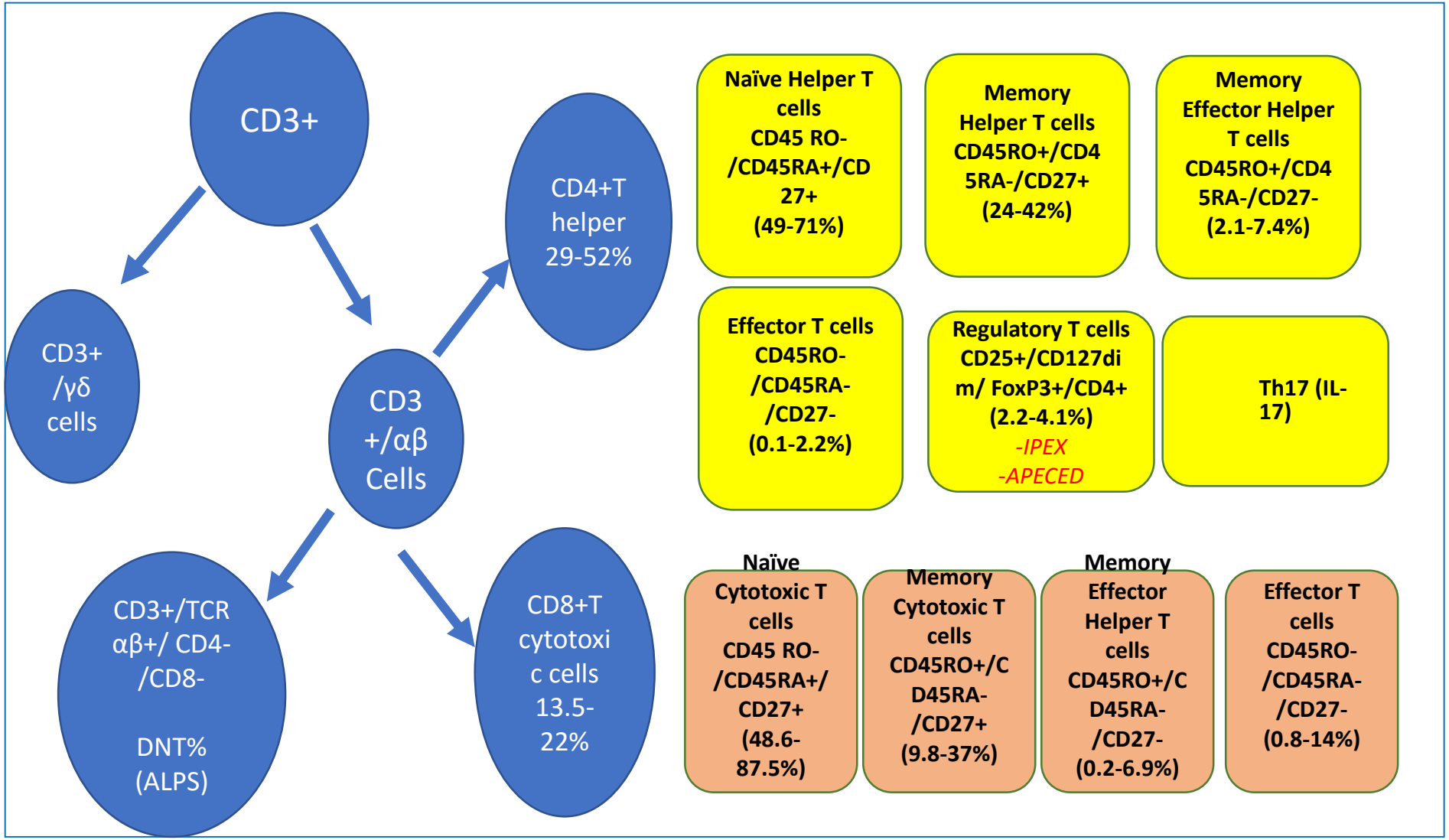
•Severe Combined Immunodeficiency (SCID) disorder characterized by CD3+ T cell lymphopenia. Further classification based on B and NK cell numbers/function.



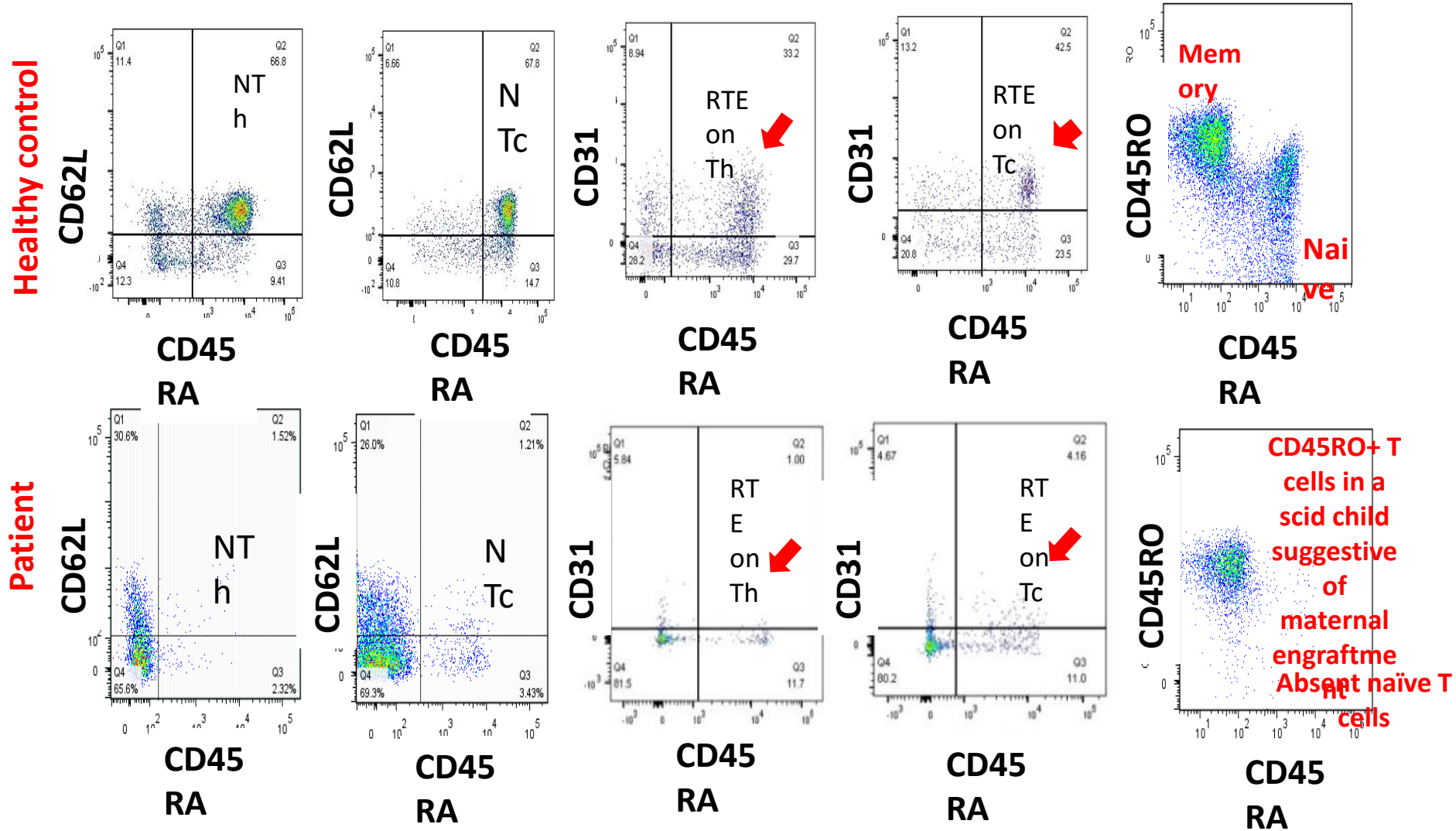
Interpretation of lymphocyte subset analysis

- Check % as well as absolute counts
- The normal ranges vary significantly depending on the age of the patient
- In infants under 4 months of age, a CD4 count of <1000/mm3 is generally associated with impaired cellular immunity, whereas it is <500/mm3 in children over 2 years of age and in adults.
- Immunosuppressive therapies like steroids also significantly alter the values of T and B cell subsets and should be interpreted carefully.
- Do not rely on single observation, repeat counts or compare with the previous counts if available

Immunophenotyping T Lymphocytes



Measurement of Naïve T cell subsets (CD45RA+ CD62L+ T cells) Recent Thymic emigrants (RTE) and Memory T cells (CD45RO+ T cells)



T+ Severe combined Immunodeficiency

- Activation markers on T cells: **HLA- DR**
- TCR- V beta repertoire analysis
- T cell proliferation response to various stimuli

- T+ B+ NK+: Omen's syndrome

  Elevated HLA- DR expression on CD3+ T cells

  Restricted repertoire of T cells

- CD8+B+NK+: CD4 lymphopenia : MHC class II deficiency

  Lack of HLA- DR expression on B cells, Monocytes

- CD4+B+ NK-: ZAP70 kinase deficiency

  Defective CD4+Th cell proliferation

Spectrum of infections: Antibody deficiency

Onset typically between 4 months-1 year

Common Microorganisms

Pyogenic bacteria
- Staphylococci
- Streptococci
- Hemophilus

- Respiratory tract
  - Otitis media, mastoiditis
  - Chronic sinusitis
  - Broncho and lobar penumonia
  - Bronchiectasis
  - Pulmonary infiltrates (granulomas)
- GI tract
  - Giardia
  - Nodular hyperplasis, ileitis, colitis
- Skin infections
- Sepsis/Meningitis
- Skeletal
  - Arthritis (bactetial, mycoplasma, noninfectiuos)

Less common Microorganisms

Enteroviruses
- Polio
- ECHO
- Salmonella
- Campylobacter
- Mycoplasma

Evaluation of Predominantly antibody deficiency

- B cell function:
  - IgG, A, M and E
  - Specific antibody responses against both protein and polysaccharide vaccines
  - Ig subclass estimation
- B cell numbers: CD19 or CD20
- B-cell immunophenotyping, and other modalities of measuring B-cell function

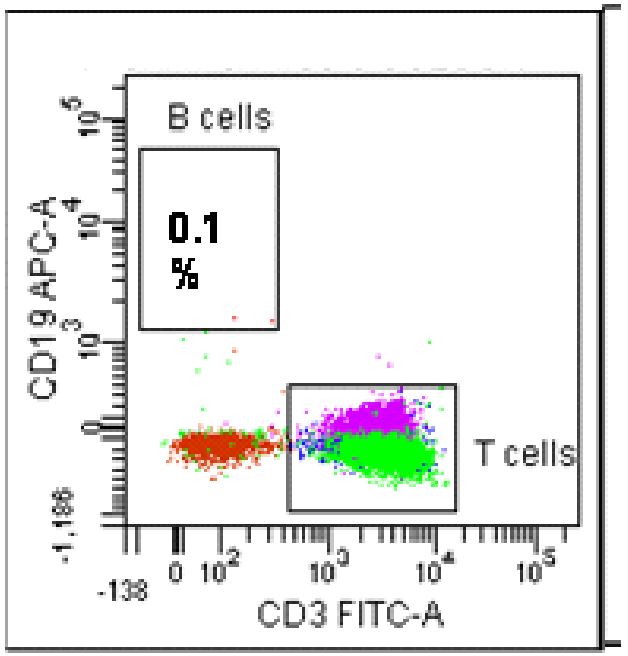
Immunoglobulin levels

- IgG, IgA, IgM, IgE
  - The assay results should be evaluated in the context of the tested patient's age and clinical findings
  - Compare with age related normal ranges
  - Child < 6 months of age has circulating maternal IgG.
- Blood transfusion and immunoglobulin infusion will alter the levels and hence this history needs to be taken.
- Persistence of hypogammaglobulinemia is required for at least 3 months needs to be documented for diagnosis of CVID
- Hypergammaglobulinemia can be the result of HIV-1, CGD, and ALPS

Immunoglobulin levels:

- Always rule out secondary causes of hypogammaglobulinemia
  - Drugs: Steroids, Rituximab, other chemotherapy
  - Myeloma and Lymphoma
  - Loss of Ig (usually IgM is normal) in urine, GI, skin

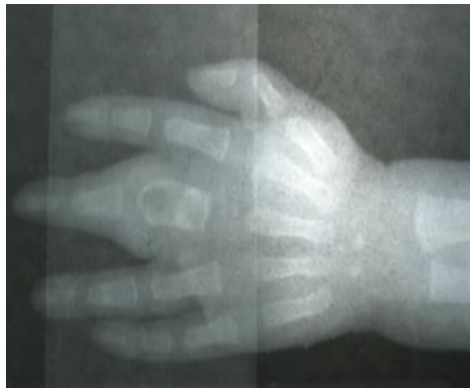
B cell numbers:

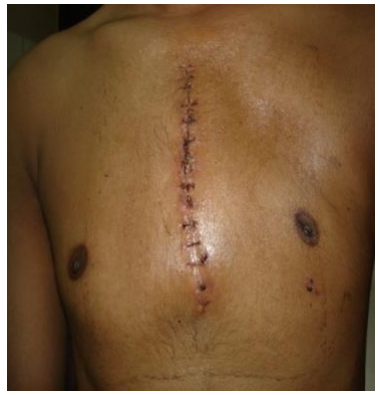


- Check % as well as absolute counts
- Significant variation depending on the age and hence must be compared with age matched controls
- Always interpret along with T cell and NK cell numbers
- Check history of drugs:
  - Rituximab
  - Steroids

B cell immunophenotyping

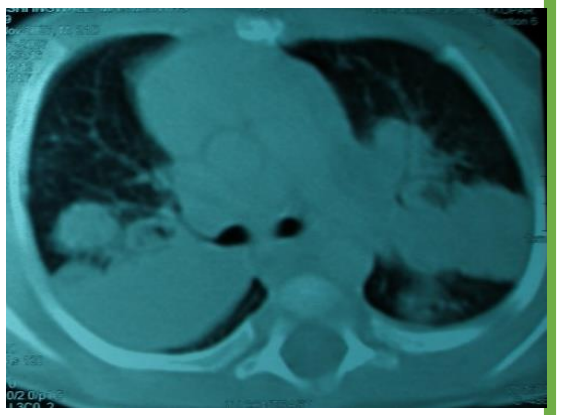
- CD19+=B cells expressing CD19 as a percent of total lymphocytes
- CD19+ CD21-=CD21 low ("immature") B cells
- CD19+ CD21+=mature B cells
- CD19+ CD27+=total memory B cells
- CD19+ CD27+ IgD+ IgM+=marginal zone or non-switched memory B cells
- CD19+ CD27+ IgD- IgM+=IgM-only memory B cells
- CD19+ CD27+ IgD- IgM-=class-switched memory B cells
- CD19+ IgM+=IgM B cells
- CD19+ CD38+ IgM+=transitional B cells
- CD19+ CD38+ IgM-=plasmablasts
- CD19+ CD20+=B cells co-expressing both CD19 and CD20 as a percent of total lymphocytes





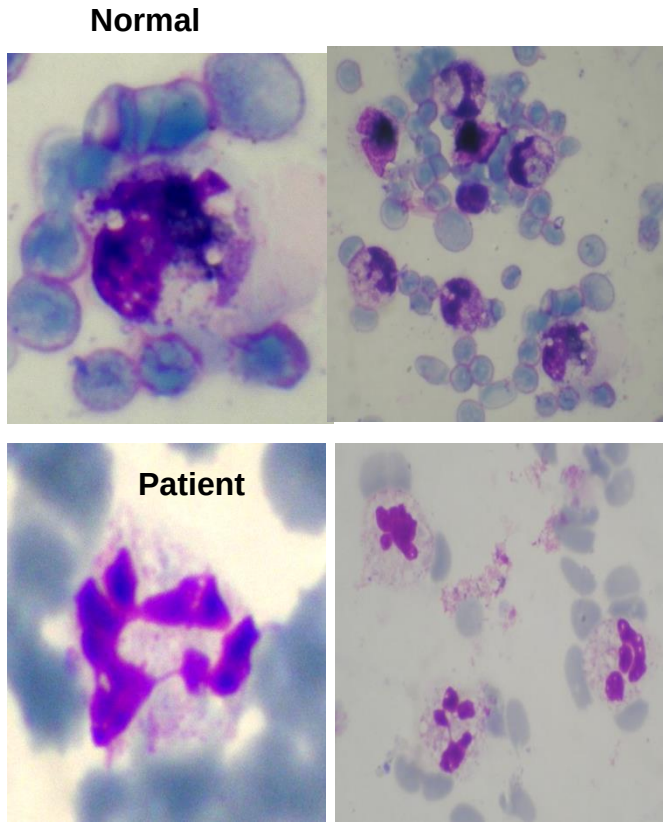
Deep seated abscesses, Fungal Infection Gram negative septicemia

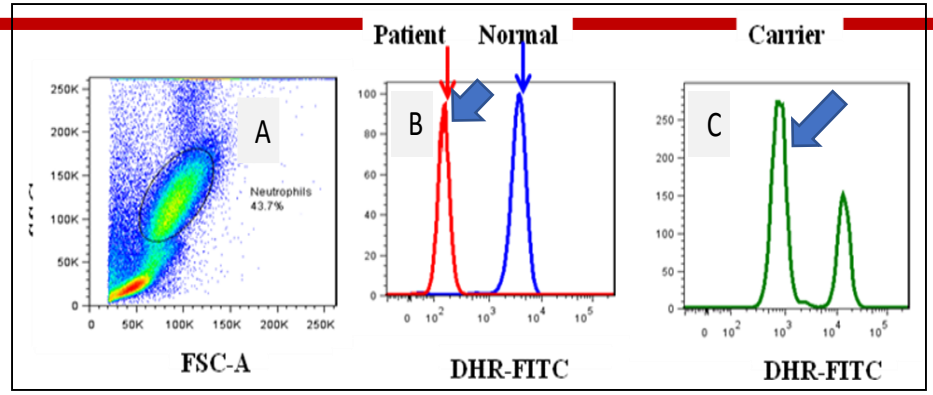
- Hepato-splenomegaly/ lymphadenopathy
- Granulomas

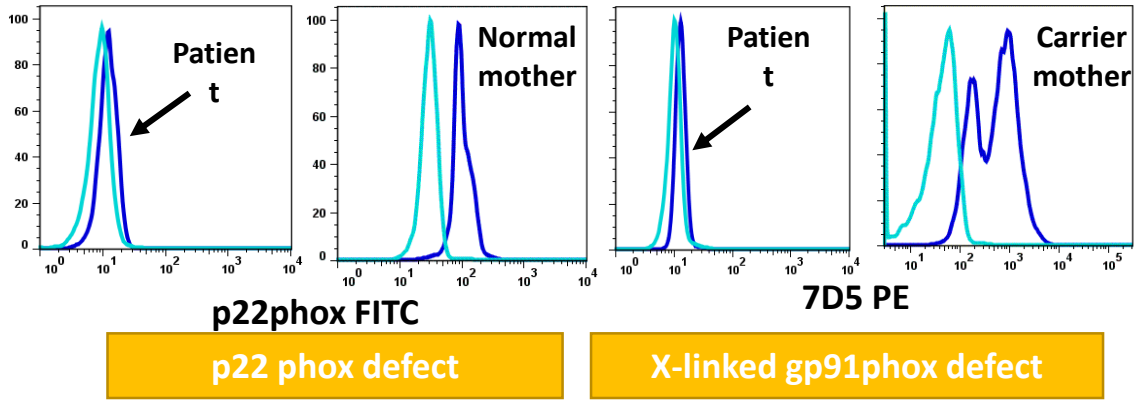


Phagocytic defects CGD

Chronic Granulomatous disease:







p22 phox defect

X-linked gp91phox defect

Interesting cases

Case

- 18 year old male studying engineering :
  - h/o abdominal tuberculosis two times
  - h/o histoplasmosis 4 years back
  - h/o infective diarrhea frequent episodes since last 5years
  - h/o failure to thrive
  - h/o BCGiosis at 4 months of age

- CBC:
  - Lymphopenia ALC 1200/mm3
- Immunoglobulin levels: Normal
- NBT and DHR normal
- Lymphocyte subset analysis:
  - Absolute CD4 counts: 250
  - Other subsets within normal range
  - Memory and naïve T cells within normal range
- Sample sent for NGS
  - IL12R B1 deficiency

Mendelian Susceptibility to Mycobacterial Diseases (MSMD)

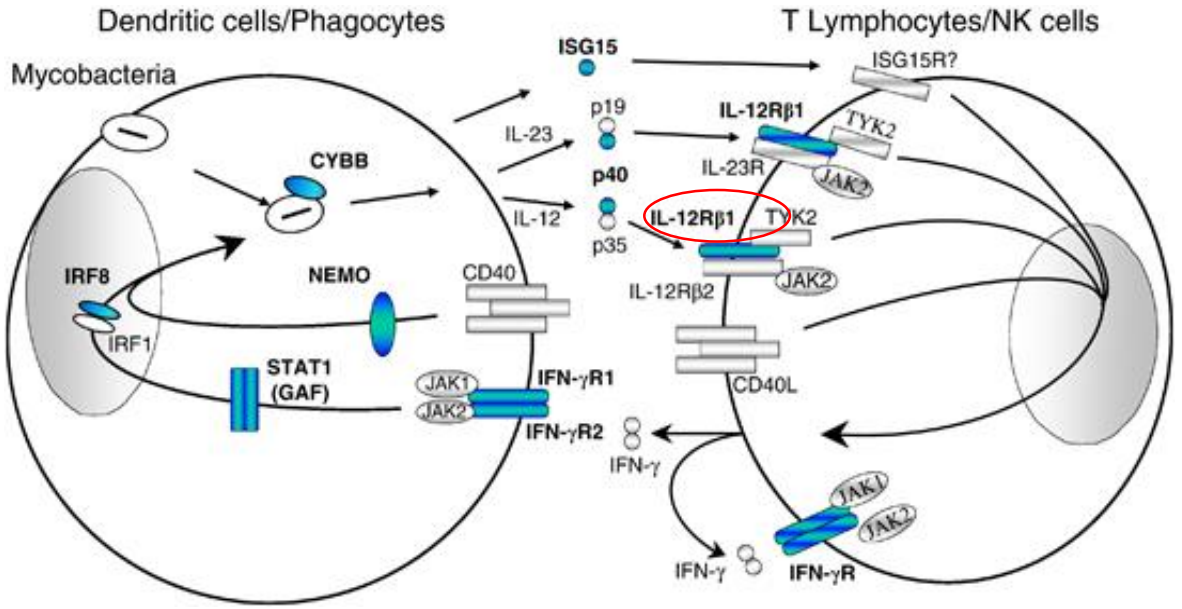
Defect in IFNγ/IL12-23 Axis loop

Clinical Presentation

- BCGiosis
- Recurrent TB
- Infections by non-mycobacterial TB
- Multifocal TB
- Salmonella Infections
- Fungal infections

Diagnosis

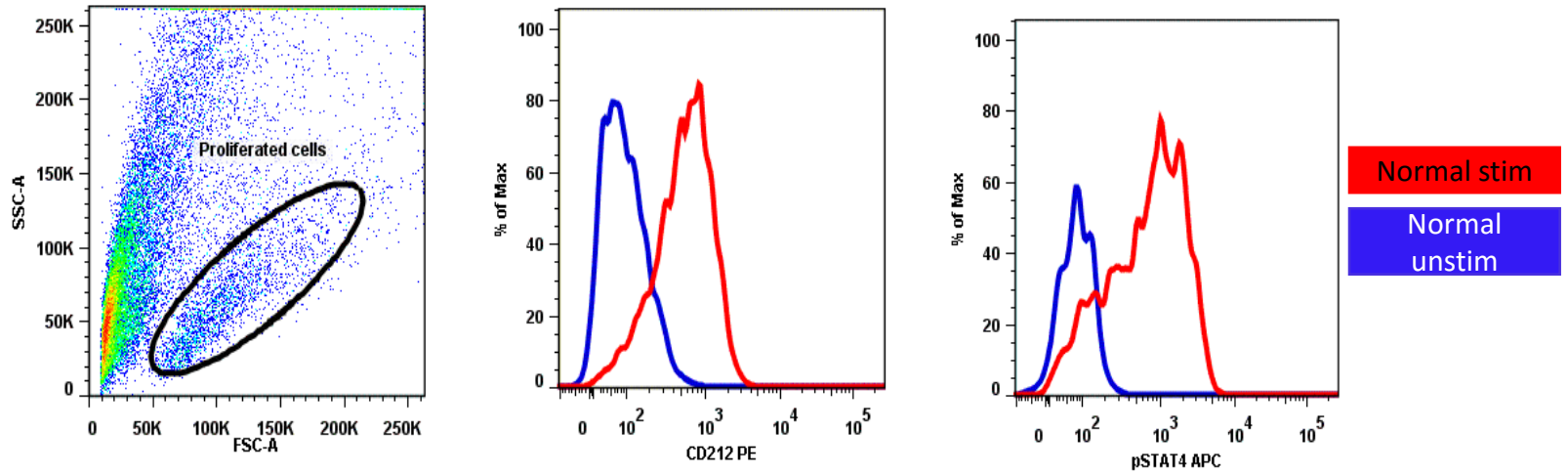
Flow cytometric evaluation of IFNγ/IL12-23 Axis



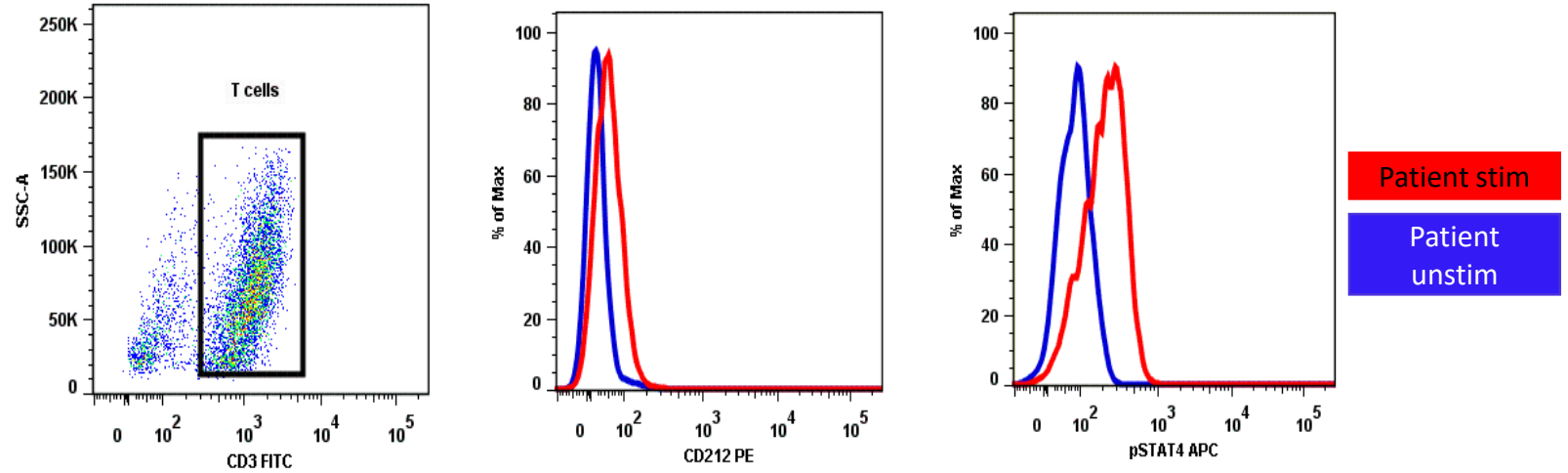
Bogunovic D, Boisson-Dupuis S, Casanova J-L. ISG15: leading a double life as a secreted molecule. *Experimental & Molecular Medicine*. 2013;45(4):e18-. doi:10.1038/emm.2013.36.

Defective molecules in this circuit, including IFN-R1, IFN-R2, IL-12p40, IL-12R-1, STAT-1, NEMO, IKBA

IL12Rβ1 and pSTAT4 expression in Normal



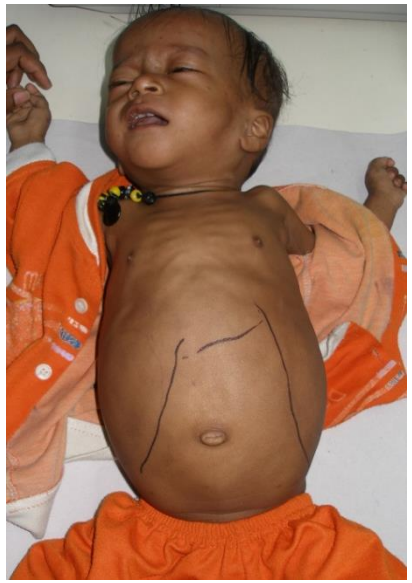
IL12Rβ1 and pSTAT4 expression in patient



Autoimmune Lymphoproliferative syndrome (ALPS)

Clinical presentation

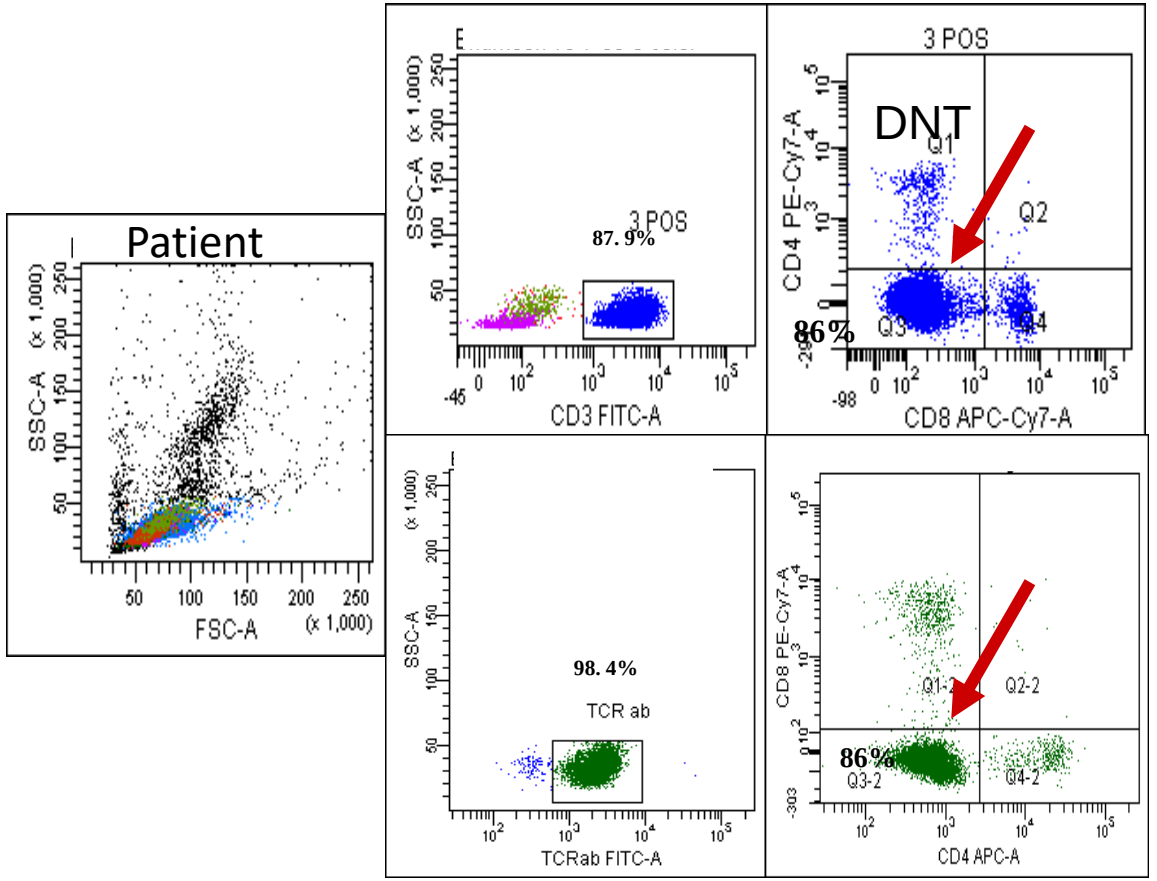
- Chronic nonmalignant lymphadenopathy
- Splenomegaly
- Autoimmunity



Diagnosis of ALPS

Double Negative T cells

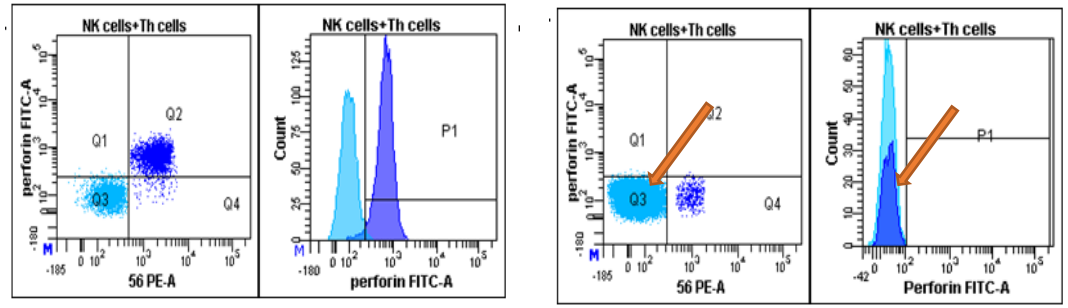
(CD3+TCRab+CD4-CD8- % greater than or equal to 1.5% of total lymphocytes or 2.5% of T lymphocytes, in the setting of **normal** or **elevated lymphocyte counts**



Familial Hemophagocytic Lymphohistiocytosis (FHL) with late onset

- 36year old Male born with non consanguineous marriage and no significant family history
- He had prolonged fever for more than a 3 months with cytopenia and hepatosplenomegaly.

HLH criteria		
Fever	Yes	3/4
Splenomegaly	Yes	
Cytopenia	Yes	
Hepatitis	No	
Hemophagocytosis	yes	3/4
Ferritin (>500mg/ml)	1,00,000ng/ml	
sCD25 levels (1886-13474pg/ml)	ND	
NK cell function	Low	
Triglygerides (>265mg/dl)	365mg/dl	2/2
Fibrinogen (<150mg%)	65mg%	



***PRF1* gene mutation- 694C>T Arg232Cys**

- Treated with HLH protocol 2004 including cyclosporine and dexamethasone. He responded well.
- On tappering the protocol, he again developed fever and hence, the protocol was resumed.
- Maintenance therapy and then was then off steroids for more than 6 months and leading routine life.
- He again had a relapse and inspite of prompt supportive treatment, ***patient succumbed*** to the disease due to multiple organ failure and septic shock

Autoantibody to interferon-gamma in Adult Lymphopenia

- Adult-onset-immunodeficiency a syndrome associated with disseminated infections.

- Cell-mediated immune deficiency in **HIV-negative**, adult-onset immunodeficient patients linked to the **presence of autoantibody to interferon-gamma (IFN-γ).**

Autoantibody to Interferon-gamma Associated with Adult-Onset Immunodeficiency in Non-HIV Individuals in Northern Thailand

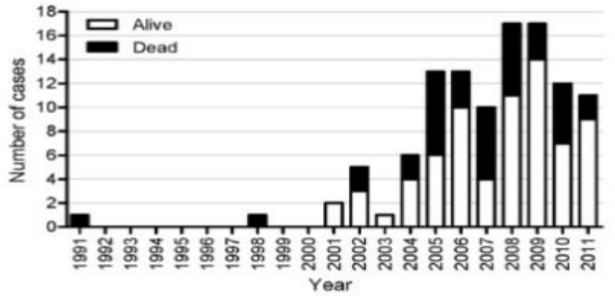


Figure 1. Patients with adult-onset immunodeficiency in northern Thailand (1991 to 2011).

Immunobiology 218 (2013) 762–771

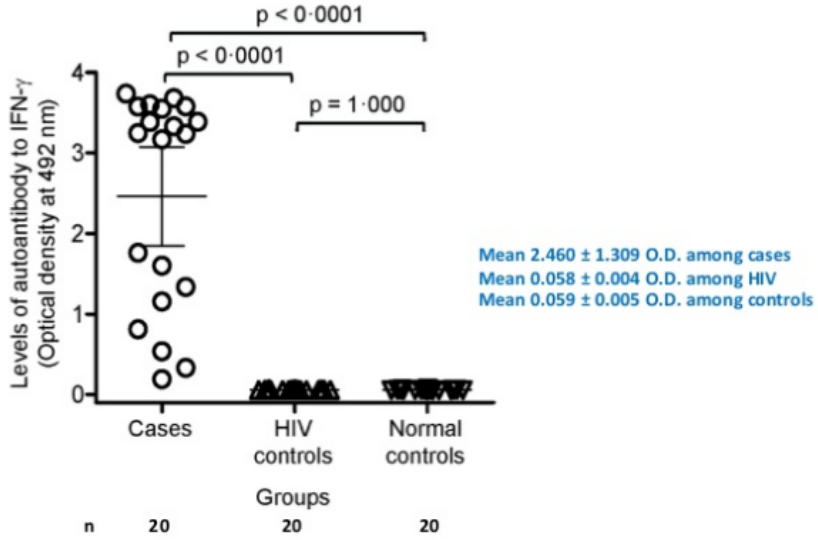
Contents lists available at SciVerse ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Patients with inhibitory and neutralizing auto-antibodies to interferon-γ resemble the sporadic adult-onset phenotype of Mendelian Susceptibility to Mycobacterial Disease (MSMD) lacking Bacille Calmette–Guerin (BCG)-induced diseases

Wen-I. Lee[a,b,*], Jing-Long Huang[a,b], Ting-Shu Wu[c], Ming-Hsun Lee[c], I.-Jung Chen[d], Kuang-Hiu Yu[d], Chien-Ying Liu[e], Chih-Hsun Yang[f], Meng-Ying Hsieh[g], Yi-Ling Lin[a], Ying-Fan Shih[a], Tang-Her Jaing[a,h], Shih-Chiang Huang[i], Tseng-Tong Kuo[i], Cheng-Lung Ku[j]



Wongkulab P. et al. PloS One 2013;8:e76371

Genetic Diagnosis of PID

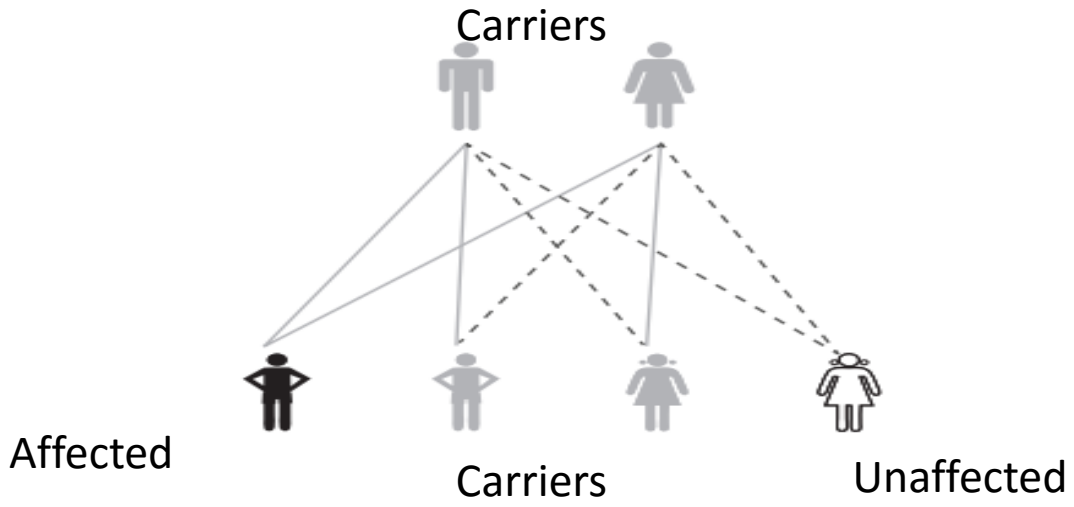
Genetics of PID

- >354 distinct disorders with 344 different gene

- Inheritance model:
  - Autosomal Recessive (AR),
  - Autosomal Dominant (AD)
  - X-Linked (XL)

Inheritance Model: Autosomal Recessive (AR)

- Parents are carriers.
- Risk of having an affected child is ¼ or 25% percent chance
- Risk of having an affected child is increased in consanguineous marriages.



Some PID following AR inheritance	Gene
Severe Combined Immunodeficiency	*ADA,RAG1,RAG2,PNP,IL7RA,JAK3*
Chronic Granulomatous disease	*CYBA, NCF1, NCF2, NCF4.*
Leukocyte Adhesion Defect	*ITGB2*
Familial Hemophagocytic lymphohisticytosis	*PRF, UNC13D*

Leukocyte Adhesion defect (LAD-I)

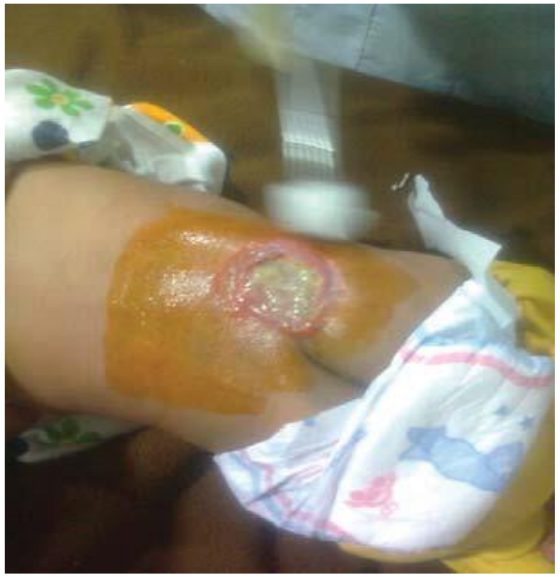
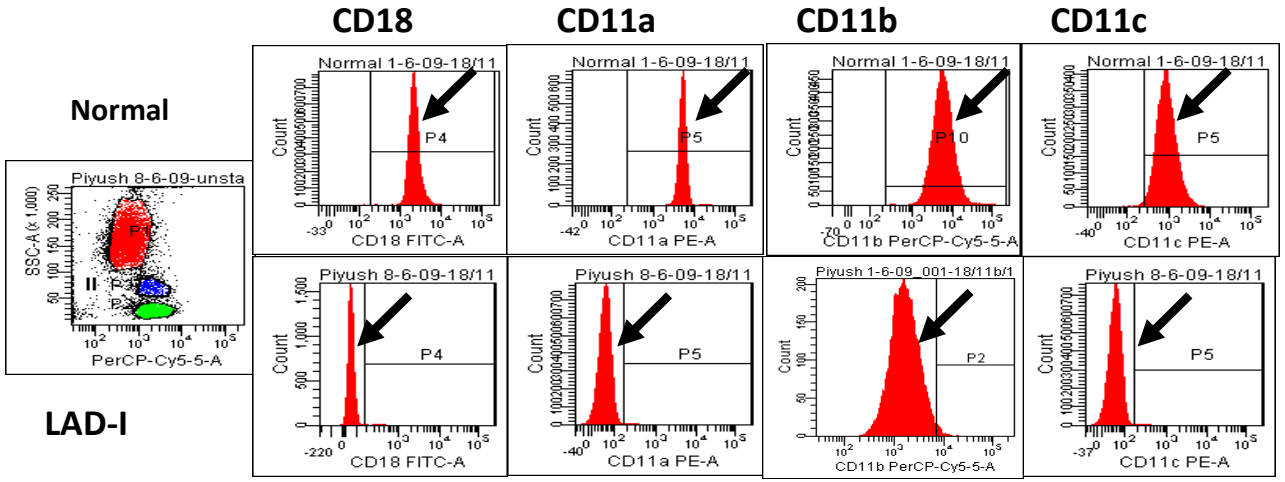
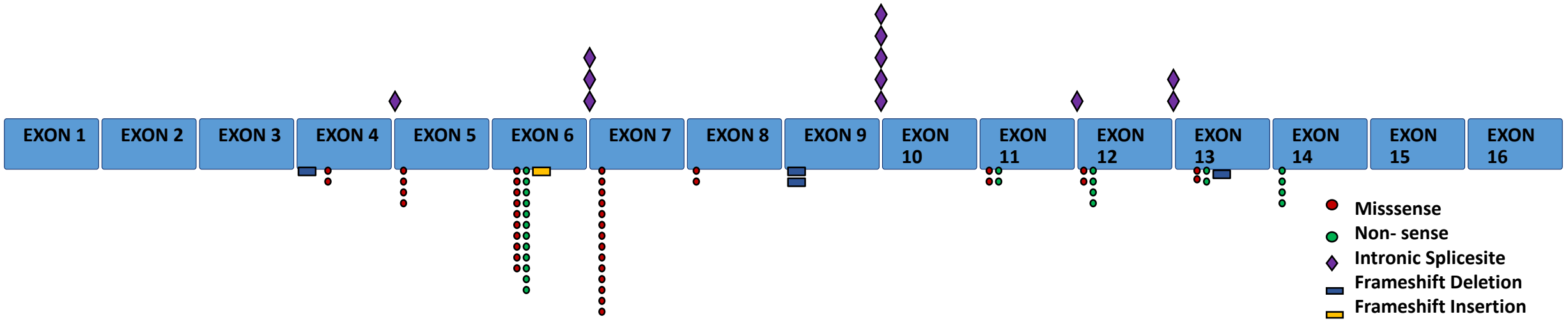


Photo from Dr Mukesh Desai

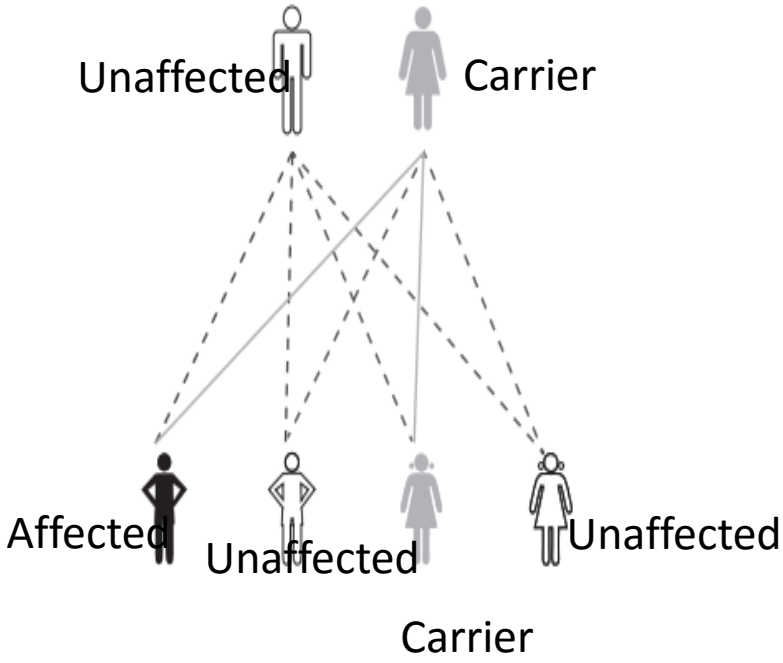


Different mutations observed in *ITGB2* gene



X-Linked Inheritance

- Mutation is in a gene on the X chromosome.
- Females and males manifest the condition differently. Females with single copy mutation are usually carriers; males with one mutated copy are affected.
- Females carrier has 1 in 2 or 50% risk of having an affected boy and the same chance of having a carrier daughter.
- Family pedigree shows strong history of male children affected.
- Skewed X-inactivation can result in carrier females displaying symptoms of the condition as a larger proportion of their normal X chromosomes are inactivated



Some PIDs inherited in X-Linked model	
X-linked agammaglobulinemia (XLA; Bruton's disease)	*BTK*
X-linked severe combined immunodeficiency (X-SCID)	*IL2RG*
X-linked hyper IgM syndrome (CD40 ligand deficiency)	*CD40L*
X-linked lymphoproliferative disease (XLP)	*SH2DIA*
X-linked inhibitor of apoptosis (XIAP) deficiency	*XIAP*
X-linked chronic granulomatous disease (X-CGD)	*CYBB*
Wiskott-Aldrich syndrome (WAS)	*WASP*

X-linked agammaglobulinemia (XLA; Bruton's disease)

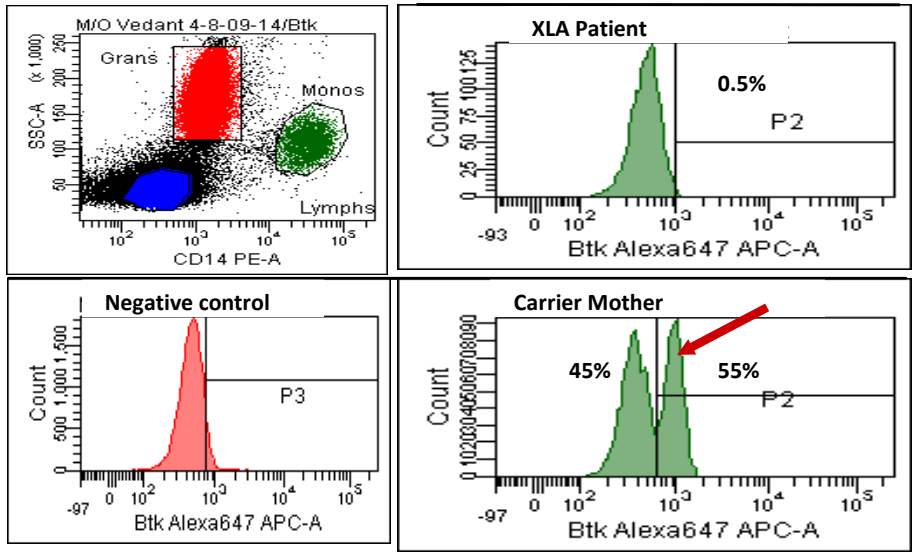
Laboratory Findings

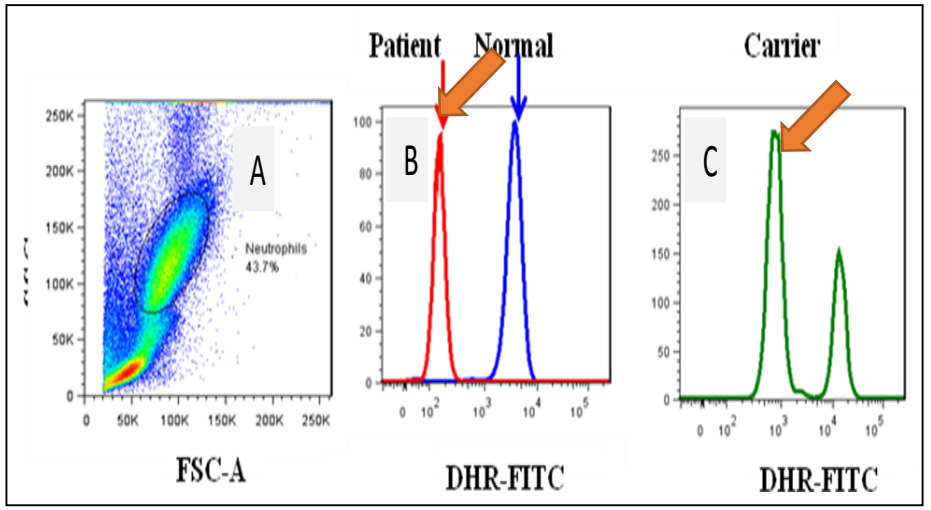
- All Ig low with absent B cells

XLA?

- Analysis of Bruton Tyrosine Kinase on Monocytes

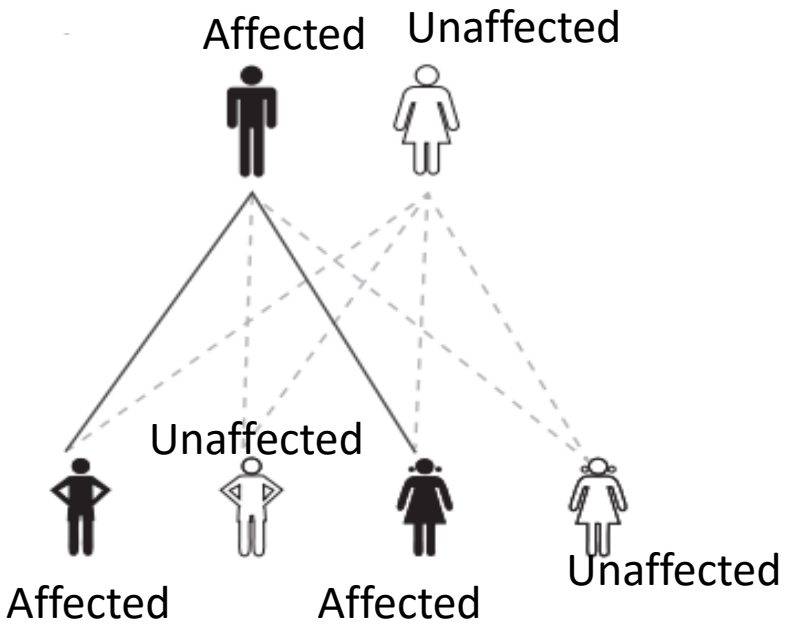
- Mother shows a classical carrier pattern of BTK expression





Autosomal Dominant Inheritance model

- Affected individual has one affected copy and normal functioning copy
- One copy of mutation sufficient to cause the condition
- 1 in 2 or 50% risk of passing the mutation on to offspring who will then also be affected.
- Same mutation – degree of disease phenotype differs
  (variable expressivity)
- Same mutation – may not result in disease phenotype in all individuals (incomplete penetrance).



Some PIDs that follow AD inheritance	Gene
Hyper IgE	*STAT3*
Hereditary neutropenia	*ELA2*
Di George Syndrome	*deletions on chromosome 22q11.2*
Mendelian susceptibility to mycobacterial diseases	*Partial IFNgR1 deficiency STAT1*

Hyper IgE Syndrome, due to mutations in STAT3 (Jobs syndrome)

Typical features in AD HYPER IgE:

Eczema,

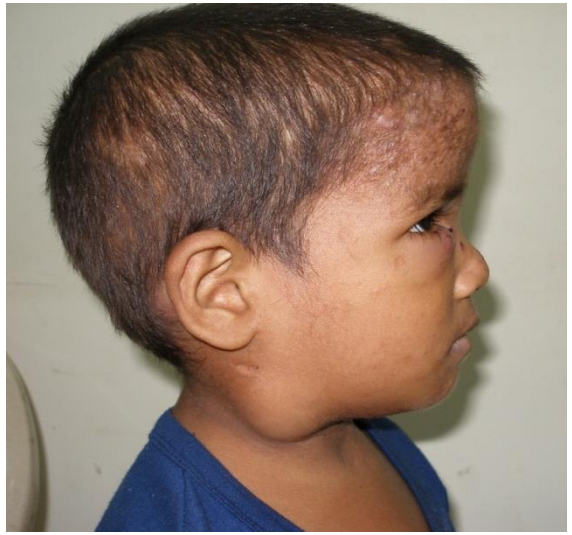
Repeated staphylococcal skin abscesses,

Staph pneumonia with pneumatocele formation

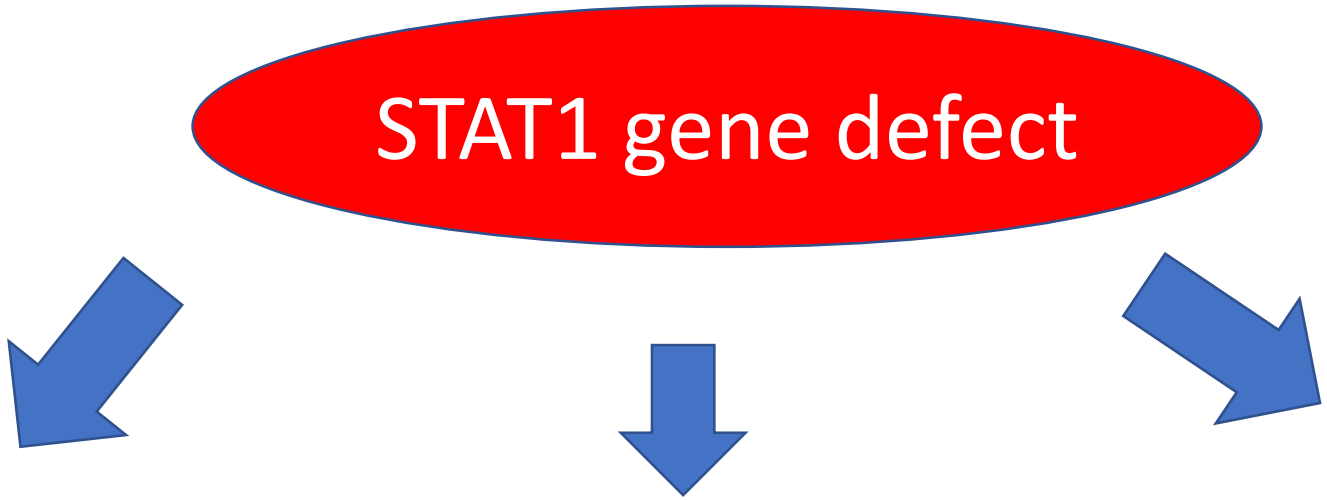
Skeletal abnormalities and fractures

Laboratory finding of Increased IgE levels

Immunoglobulin	Values	Normal Range
IgG	22.9 g/L	3.5 to 16.2g/L
IgA	0.8 g/L	0.17 to 3.18 g/L
IgM	1.42g/L	0.30 to 2.65 g/L
IgE	**50800 IU/mL**	3.0 - 423 IU/mL



One gene, multiple phenotypes



AD STAT1 deficiency:
Loss of function mutation

susceptibility to mycobacterial and salmonella infections

AD STAT1 deficiency: gain-of-function mutation

chronic mucocutaneous candidiasis

Complete/ Partial **AR STAT1 deficiency**: loss-of-function mutation

susceptibility to severe viral and mycobacterial disease

Different genes →similar phenotype

IL-17RA, IL-17F, STAT1, DECTIN1, CARD9, STAT3, DOCK8, AIRE

Chronic Mucocutaneous Candidiasis

IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1, NEMO, CYBB, IRF8, ISG15, TYK2

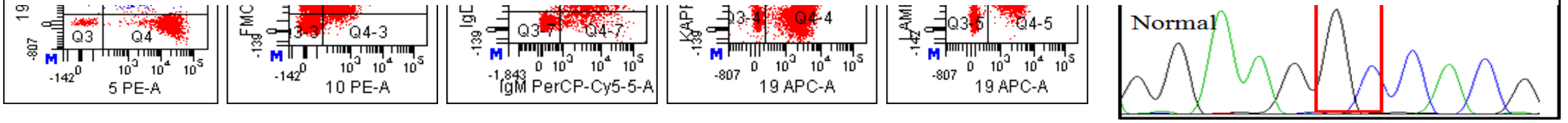
Mendelian Susceptibility to Mycobacterial Diseases

frontiers in Immunology

ORIGINAL RESEARCH
published: 14 June 2018
doi: 10.3389/fimmu.2018.01049

Clinical, Immunological, and Molecular Findings in Four Cases of B Cell Expansion With NF-κB and T Cell Anergy Disease for the First Time From India

*Maya Gupta[1], Jahnavi Aluri[1], Mukesh Desai[2], Madhukar Lokeshwar[3], Prasad Taur[2], Michael Lenardo[4], Jenna Bergerson[4], Aparna Dalvi[1], Snehal Mhatre[1], Manasi Kulkarni[1], Priyanka Kambli[1] and Manisha Madkaikar[1]**



What strategy do we use for molecular diagnosis?

- Sanger sequencing/ targeted gene analysis

- NGS:
  - PID panel
  - Clinical exome
  - Whole exome
  - Whole genome

No shoe that fits all

- Diseases for Sanger sequencing/ specific gene analysis is preferred:
  - LAD-I
  - Perforin deficiency
  - X-HIGM
  - XLA
  - CGD

Lack of focus is good thing

- 10 months old male child
- 2nd by order born of 3rd degree consanguineous marriage,
- Symptomatic since day 7 of iife with fever and loose stools and respiratory distress
- Elder female sibling death at 6 months of age due to respiratory illness.
- Elevated absolute lymphocyte count (ALC23023/cu mm)
- Lymphocyte subset analysis elevated CD8
- Sample sent for NGS analysis

Lack of focus is good thing

- Targeted NGS analysis by Medgenome laboratory revealed previously reported homozygous mutation in exon 8 at c.847C>T; p.Arg283Ter of *ZAP -70* gene
- 90% of CD8 positive cells were HLA-DR + and naïve CD8T cell % was very low

Limitations of Sanger sequencing

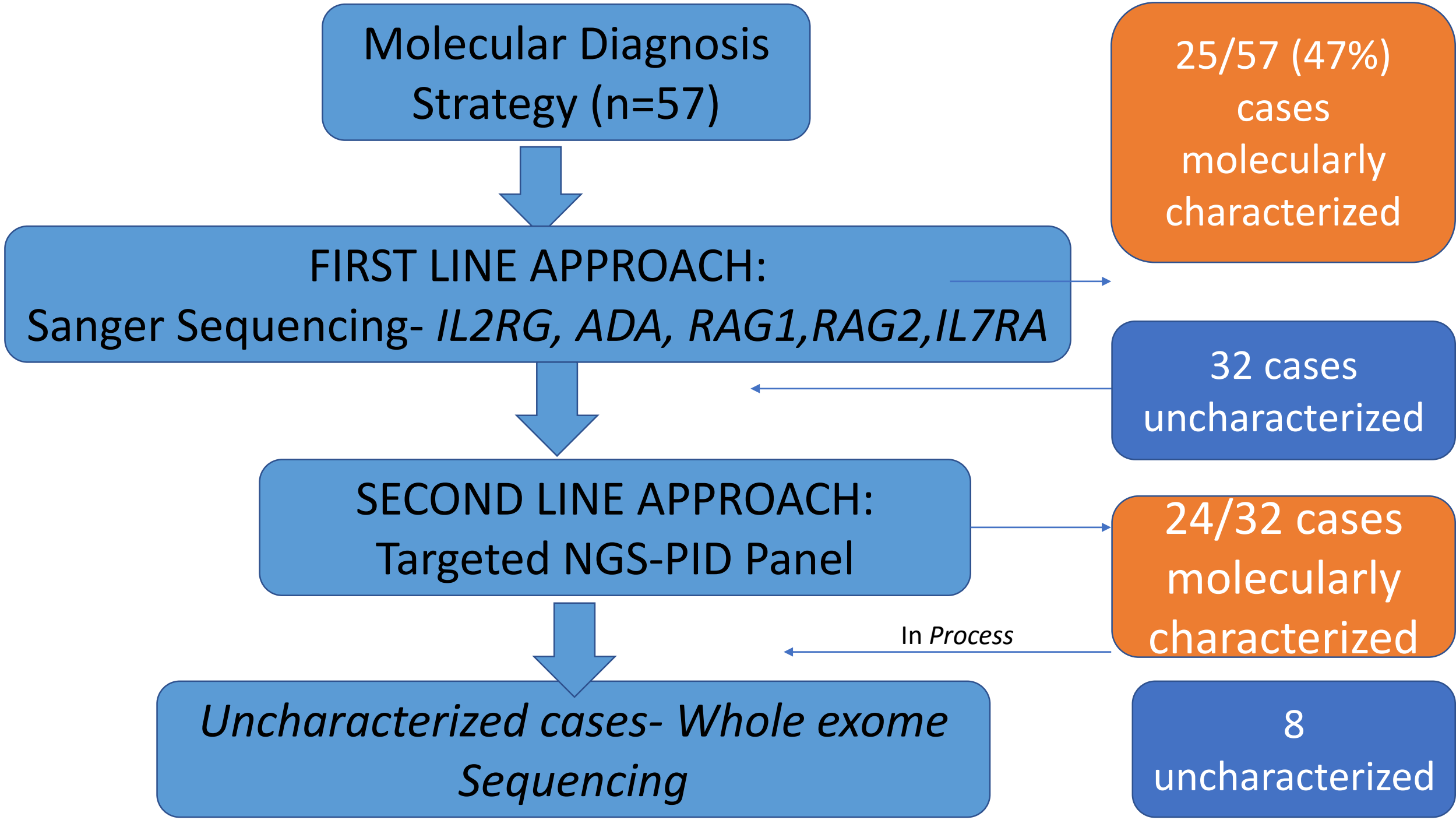
- **One-by one analysis of single genes or candidate genes**.

  PID diagnosis complicated due to genetic heterogeneity and a clinical overlap among various PID categories. In some cases, many genes are involved in the pathogenesis of a specific PID form. For eg: SCID can result from a defect in any of the 15-20 genetic defects.

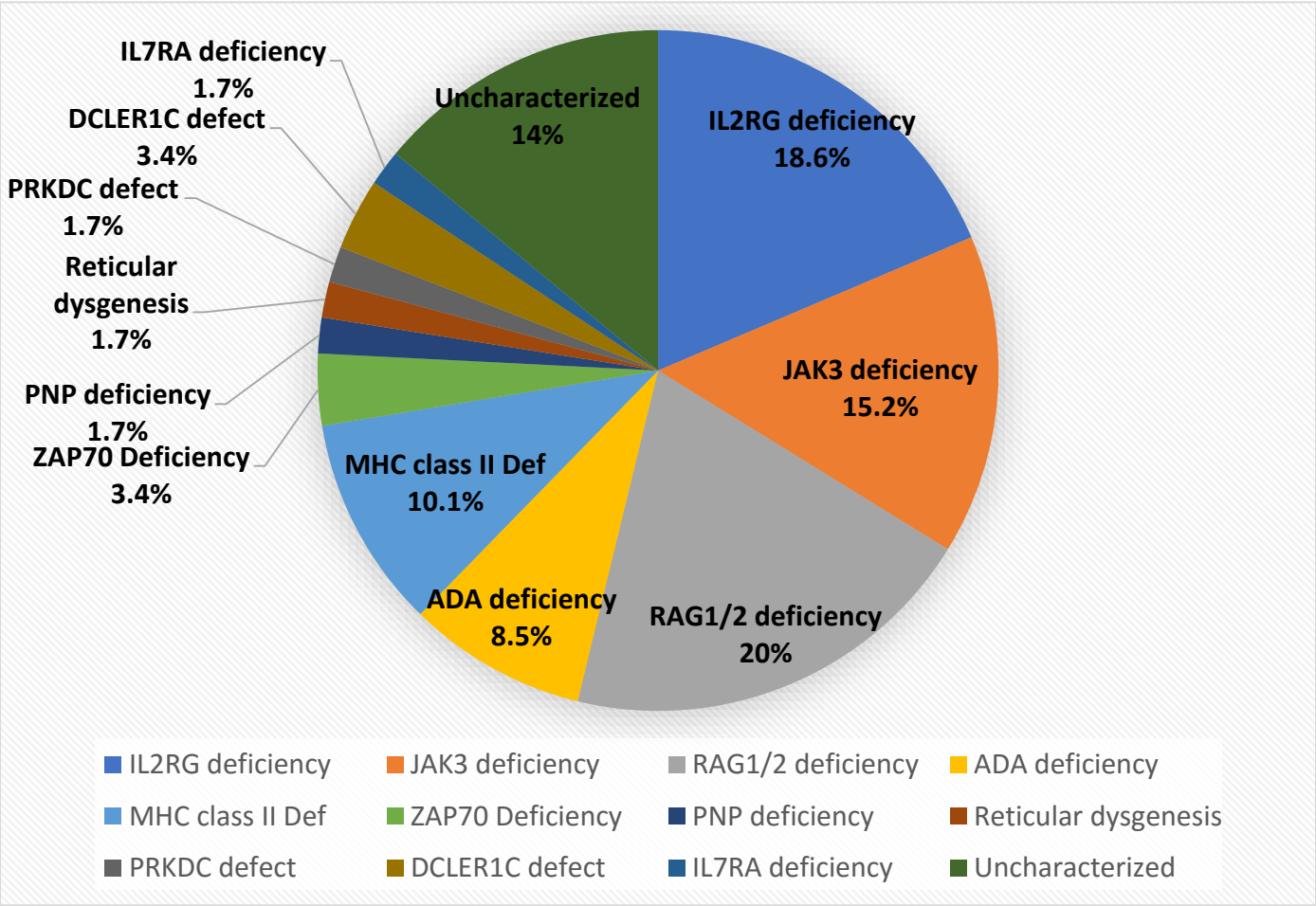
- **Cost and time consuming to identify the molecular etiology**.
- **The immunophenotype pattern may not always correlate with the genetic etiology.**

  May cases remain unresolved due to lack of phenotype-genotype correlation. Screening the candidate gene does not give the molecular answer.

- **Does not detect large deletions or duplications**


Molecular Diagnosis Strategy (n=57)
25/57 (47%) cases molecularly characterized
FIRST LINE APPROACH:
Sanger Sequencing- IL2RG, ADA, RAG1,RAG2,IL7RA
32 cases uncharacterized
SECOND LINE APPROACH:
Targeted NGS-PID Panel
24/32 cases molecularly characterized
In Process
Uncharacterized cases- Whole exome Sequencing
8 uncharacterized

Spectrum of genetic defects in our cohort (n=57)



SCID gene defect	Percentage (%)
IL2RG deficiency	18.6
JAK3 deficiency	15.2
RAG1/2 deficiency	20
ADA deficiency	8.5
MHC class II Def	10.1
ZAP70 Deficiency	3.4
PNP deficiency	1.7
Reticular dysgenesis	1.7
PRKDC defect	1.7
DCLER1C defect	3.4
IL7RA deficiency	1.7
Uncharacterized	14

Next generation sequencing

- High throughput, massively parallel technology involving simultaneous sequencing of a large number of template DNA or cDNA fragments in parallel.
- DNA sequencing can be performed on the entire genome or targeted to specific regions.
- Rapid, cost-efficient, accurate, and high-throughput sequencing of millions of DNA fragments in a reasonably short time.

Strategy for NGS for PID

Patients affected with clinical phenotypes highly suggestive of a PID, Targeted Sequencing restricted only to specific genes or to specific regions of interest (specific panels or clinical exome)

Whole exome sequencing

Whole genome sequencing

What looks like a duck but not a duck

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-018-0567-y

ORIGINAL ARTICLE

Approach to Molecular Diagnosis of Chronic Granulomatous Disease (CGD): an Experience from a Large Cohort of 90 Indian Patients

Manasi Kulkarni[1] &Gouri Hule[1] &Martin de Boer[2] &Karin van Leeuwen[2] &Priyanka Kambli[1] &Jahnavi Aluri[1] & Maya Gupta[1] &Aparna Dalvi[1] &Snehal Mhatre[1] &Prasad Taur[3] &Mukesh Desai[3] &Manisha Madkaikar[1]

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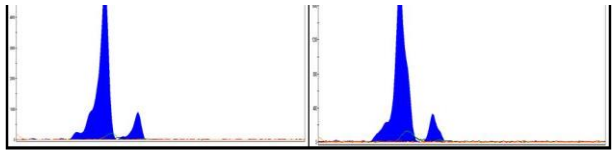


Distribution of PID cases

IUIS 2017 Classification of PID	Diagnosed Cases Till Date		Daignosed Cases 2017-2018	
	No.	%	No.	%
I. IMMUNODEFICIENCY AFFECTING CELLULAR & HUMORAL IMMUNITY	147	20	47	18
II. CID WITH ASSOCIATED OR SYNDROMIC FEATURES	59	7.8	21	8
III. PREDOMINANTELY ANTIBODY DEFICIENCY	136	18	61	24
IV. DISEASE OF IMMUNE DYSREGULATION	151	20	70	27
V. CONGENITAL DEFECTS OF PHAGOCYTE NO. FUNCTION	234	31	55	21
VI. DEFECT IN INTRENSIC AND INNATE IMMUNITY	24	3	5	2
VII. AUTOINFLAMATORY	1	0.1	0	0
VIII. COMPLEMENT DEFICIENCY	1	0.1	1	0.4
IX PHENOCOPIES OF PID	0	0	0	0
Total	753		260	

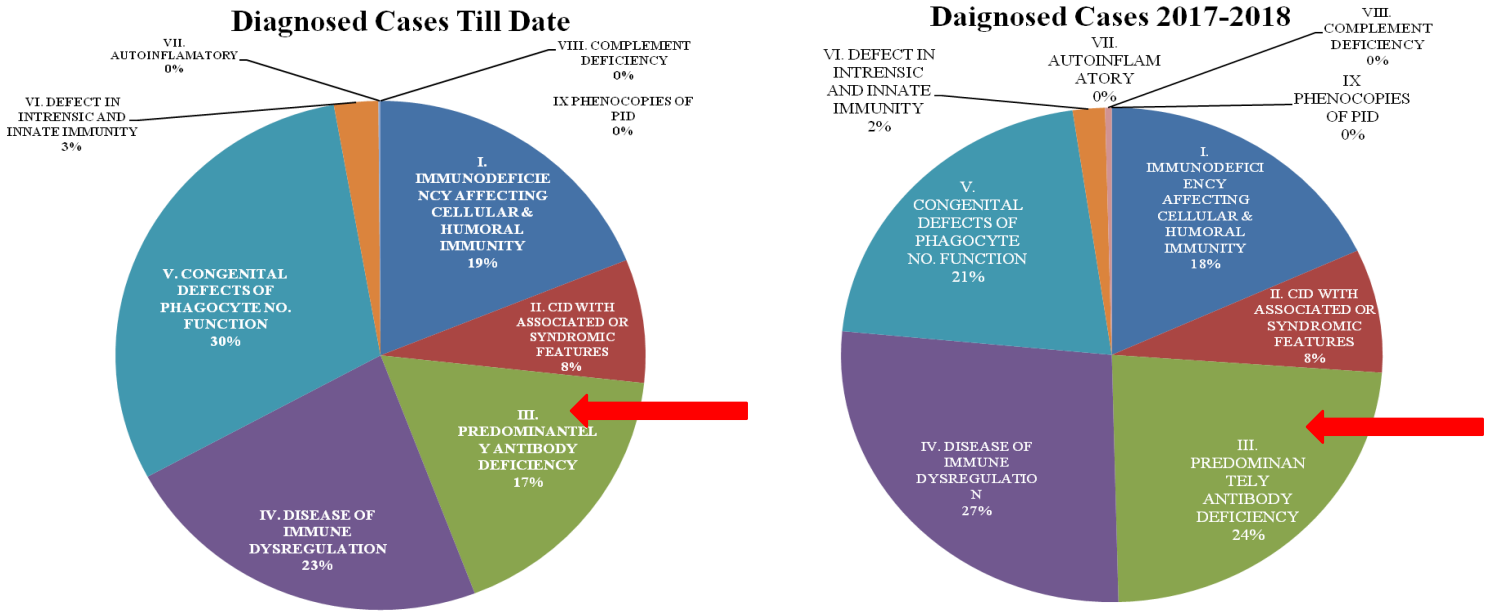
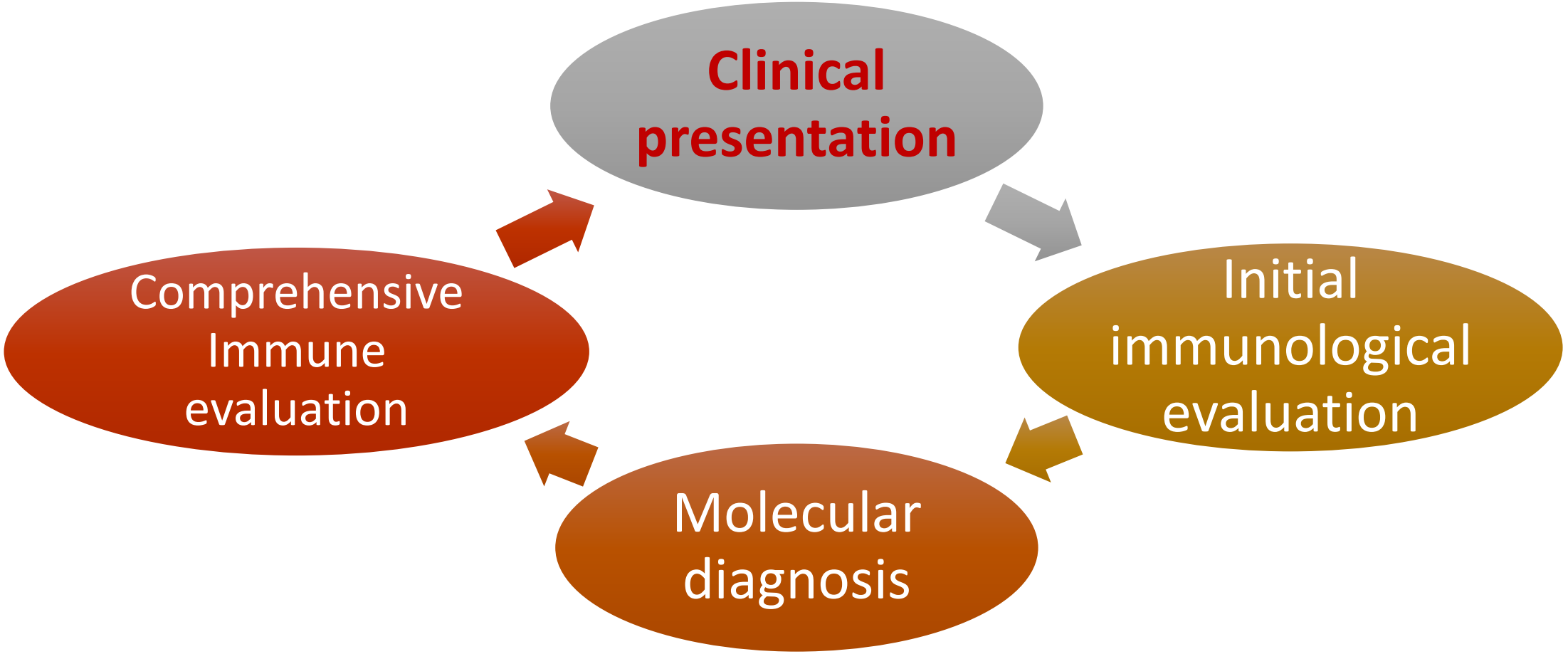
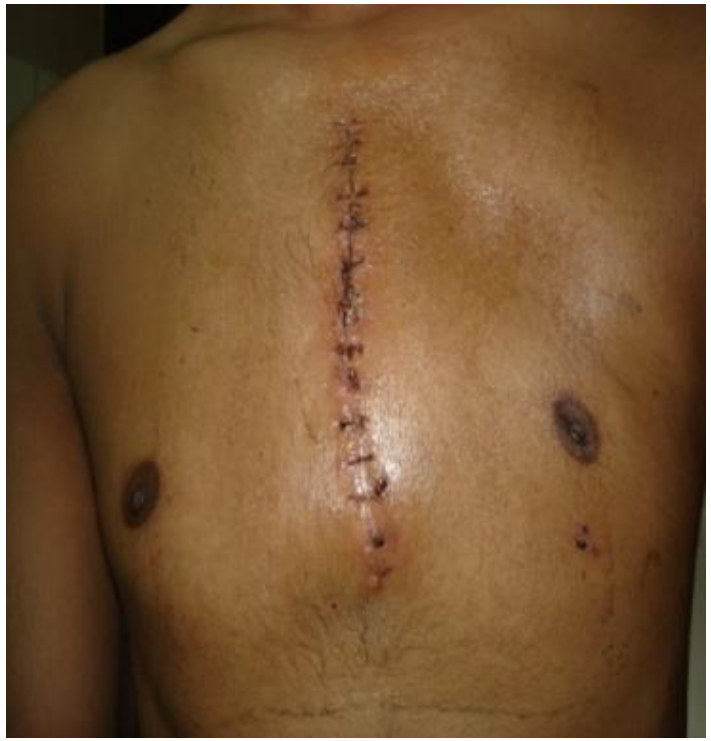
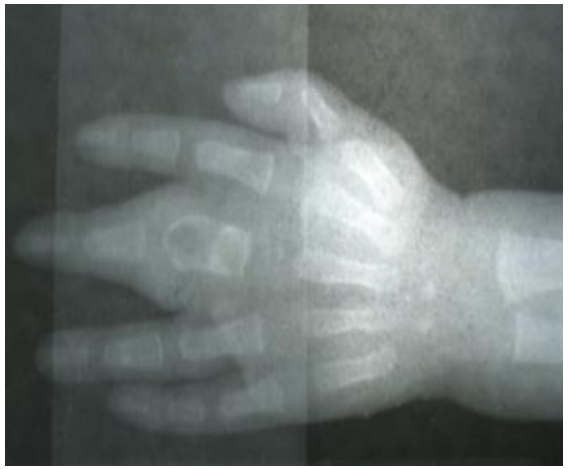


Figure 3: Distribution of Primary Immunodeficiency Disorders diagnosed a) over last 11 years and b) during the period of Jan 2017 – Dec 2018

Approach diagnosis of PID







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Laboratory group

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Department of Laboratory Medicine, NIH Clinical Center,
Bethesda, MD, United States.

- **Fellowship in Genetic Diagnostics**
  - 6 months
  - For Post-graduate degree (MD/MS/DNB) in Pediatrics, Medicine or Obstetrics &Gynaecology, Pathology, Microbiology, Biochemistry, Laboratory Hematology, Laboratory Medicine, Anatomy, Physiology, Dermatology, Hematology, Radiotherapy, Endocrinology, Ophthalmology, Oncology or any other clinical / paraclinical specialty/Superspecialty and **holding regular position in Government medical college/hospital.**
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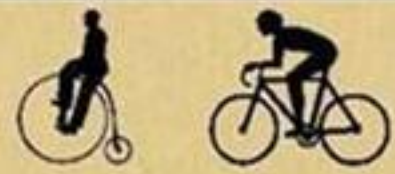

"Life is like riding a bicycle. To keep your balance you must keep moving."

Albert Einstein