M1 D2HP: TU4 Immunopathology and hematologic dysregulations

Inborn Errors of Immunity: Diagnosis Strategies and Recent advances in treatment

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Outline

1. Introduction to Inborn Errors of Immunity

2. How to investigate Inborn Errors of Immunity?
   A. Clinical context
   B. Immunological investigations
   C. Genetic investigations
   D. One example case

3. Treatments of Inborn Erros of Immunity
A. The first gene therapy : Hematopoeitic Stem Cells graft
B. Out of the “bulles” : Success and hardships of gene therapy
C. New advances, 2 examples
   I. New Immunoglobulins preparations
   II. JAK inhibitors: A targeted therapy for an IEI

This symbol means the slide or part of the slide is very detailed and if it is a lot for you, you should only remember the key message

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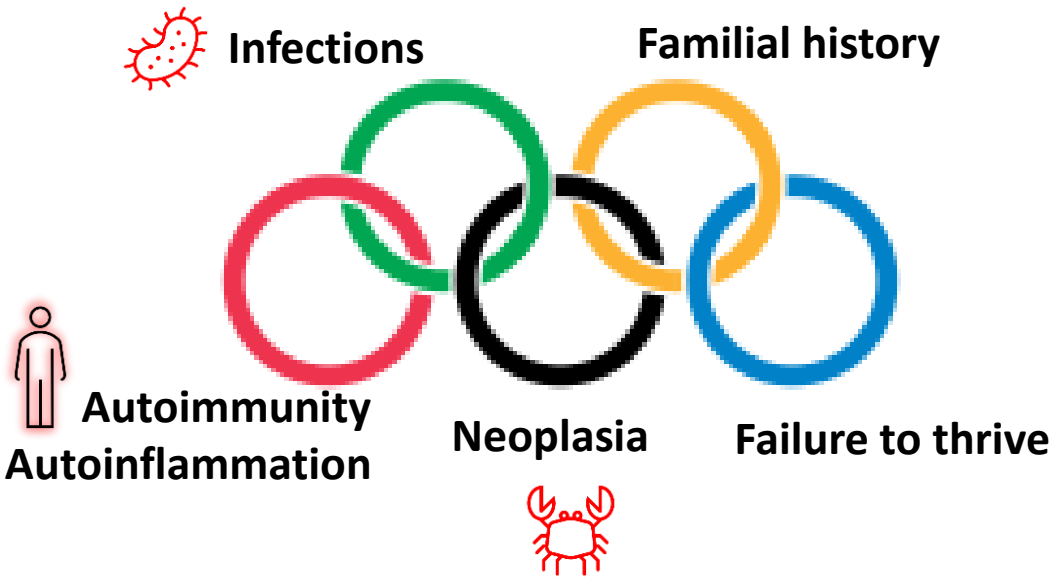
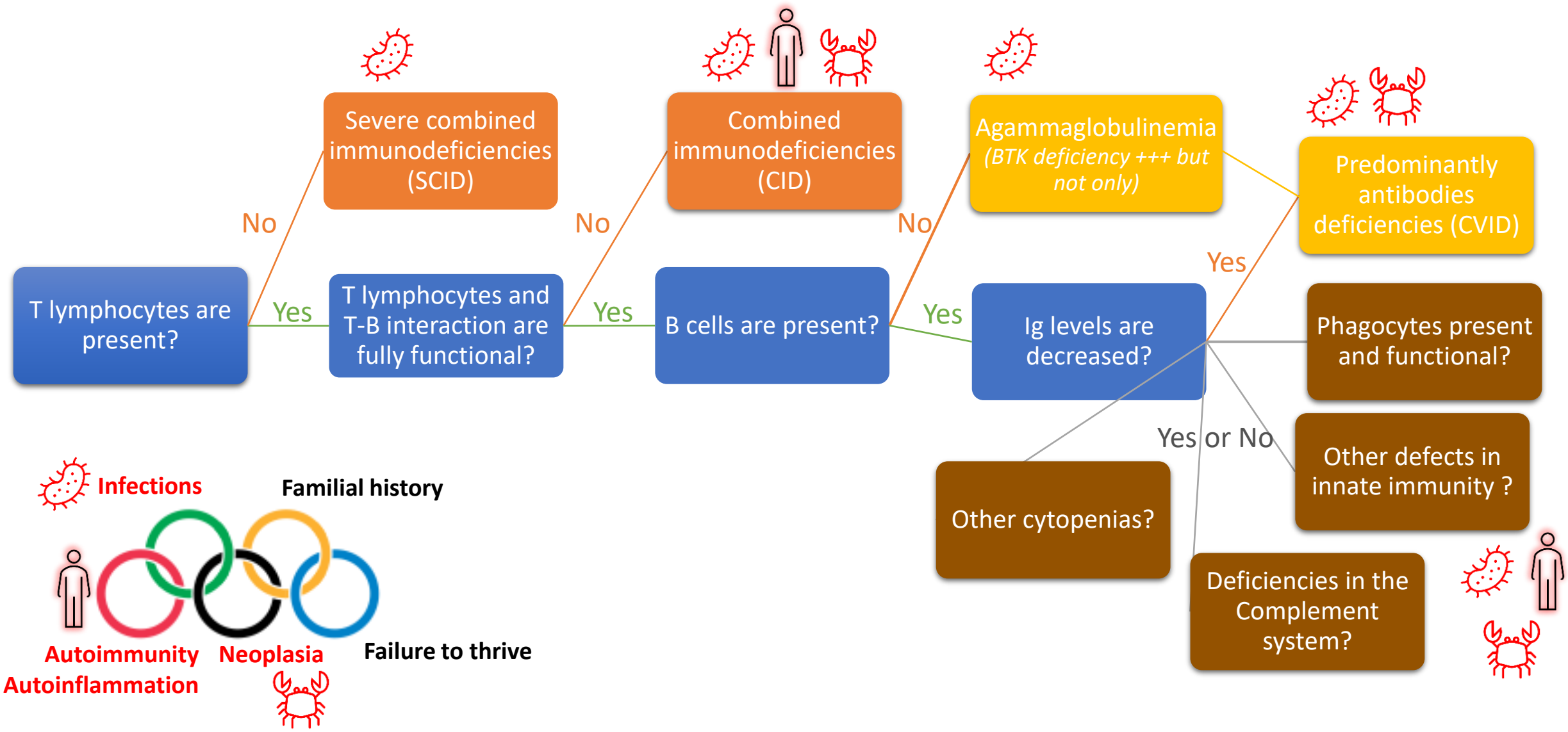
INBORN ERRORS OF IMMUNITY (IEIS)
= *PRIMARY IMMUNE DEFICIENCIES*

Inborn errors of immunity (IEI) comprise diseases arising from genetic defects that lead to abnormalities in immune cell development or function with a wide spectrum in severity and clinical manifestations

- Over 500 genetic diseases identified
- Rare disease = 1/4000 births
- Severe or repeated infections: Bacterial, viral, fungal...
- Many other clinical signs:
  - Autoimmunity and autoinflammation
  - Cancer
  - Alveolar proteinosis, granulomas
  - Hemophagocytosis, thrombotic microangiopathy, bradykinin angioedema



SIMPLIFIED CLASSIFICATION FOR HUMAN IEIS



Some defects are part of larger genetic syndroms, with manifestations outside the spectrum of immunity

CLASSIFICATION FOR HUMAN IEIS

Tangye *et al.*, J Clin Immunol, 2022 https://link.springer.com/article/10.1007/s10875-022-01289-3

A bit further

- **Combined immunodeficiency (T and B cells)** — Tables 1&2
  - Severe if < 300 T cells/mm^3
- **Predominantly antibody deficiencies** — Table 3
- **Diseases of immune dysregulation** — Table 4
- **Congenital defects of phagocytes** — Table 5
- **Defects in intrinsic and innate immunity** — Table 6
- **Autoinflammatory diseases** — Table 7
- **Complement deficiencies** — Table 8
- **Bone marrow failure** — Table 9
- **Phenocopies of inborn errors of immunity** — Table 10

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IEI DIAGNOSIS: GENERAL STRATEGY

Screening tests
Blood numeration and cytology
Ig levels and serology

Clinical phenotype suggestive of IEI

Strong candidate gene?

Advanced tests
Blood lymphocytes phenotype
Neutrophils oxidative function
T cells proliferation
Protein expression

Yes or No

High throughput gene sequencing
Panel, WES or WGS

Yes

Targeted gene sequencing
Sanger

CLINICAL INVESTIGATIONS : WARNING SIGNS

1) **A family history evocative of IEIs** *(or of known IEIs)*

2) **Recurrent respiratory tracts infections, *currently or during childhood***

3) **A single episode of invasive pyogenic infections**

4) Any unusual infection : chronic or severe

5) **Recurrent infection to the same pathogen**

6) **Failure of an infant to gain weight or grow normally, chronic diarrhoea**

7) **Others :**

Auto-immunity, chronique inflammation, persistent fever, allergy or severe eczema, adenopathy, lymphoproliferation, lymphoma, cancer, granuloma, cytopenias, macrophagic activation syndrom, malformations, cognitive disorders, …

RECURRENT, SEVERE OR UNUSAL INFECTIONS

1) **A family history evocative of IEIs** *(or of known IEIs)*

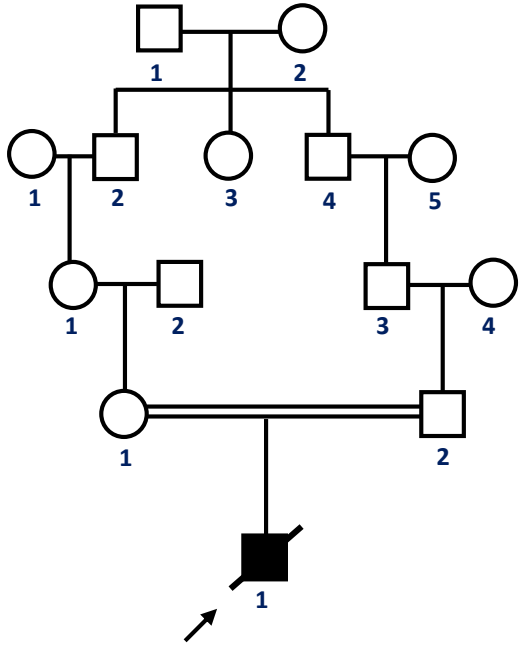
Mendelian mode of inheritance

Consanguinity?

Premature deaths in the family?

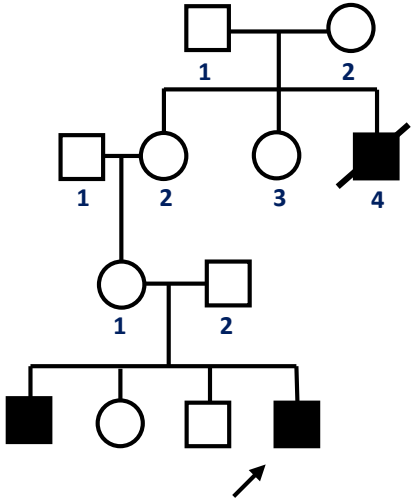
History of infections, of cancer, etc?

Are siblings healthy?



Autosomal recessive

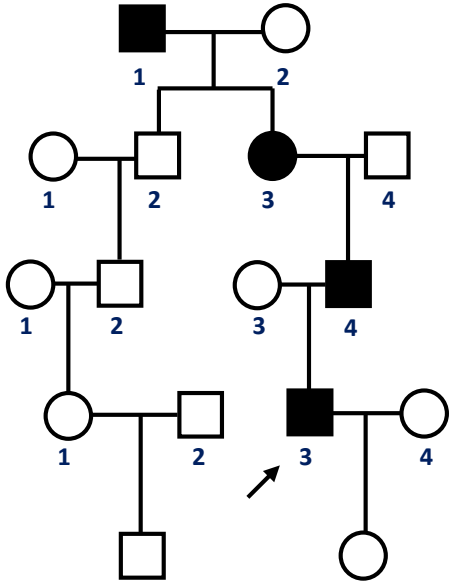
Biallelic variants



X-Linked recessive

Male are affected

Women are asymptomatic carriers



Autosomal dominant

Monoallelic variant

FAMILIAL HISTORY OF IEI OR CLINICAL SIGNS IN THE FAMILY

2) **Recurrent respiratory tracts infections, *currently or during childhood*:**

≥ 4 new ear infections within 1 year

≥ 2 serious sinus infections within 1 year A bit further

≥ 2 pneumonias within 1 year, or bronchiectasis

≥ 2 months on antibiotics with little effect

3) **A single episode of invasive pyogenic infections**

Ex: Meningitis, sepsis to encapsulated germs, …

4) **Any unusual infection : chronic or severe**

Ex: Ganglionar mycobacterial disease, chronic or severe EBV disease, severe herpes disease, pneumocystosis, deep skin or organ abscesses, persistent thrush in mouth or fungal infection on skin …

5) **Recurrent infection to the same pathogen**

The type of infections directs to different IEIs:

How early in life?

How severe?

Which germs?

Chronic?

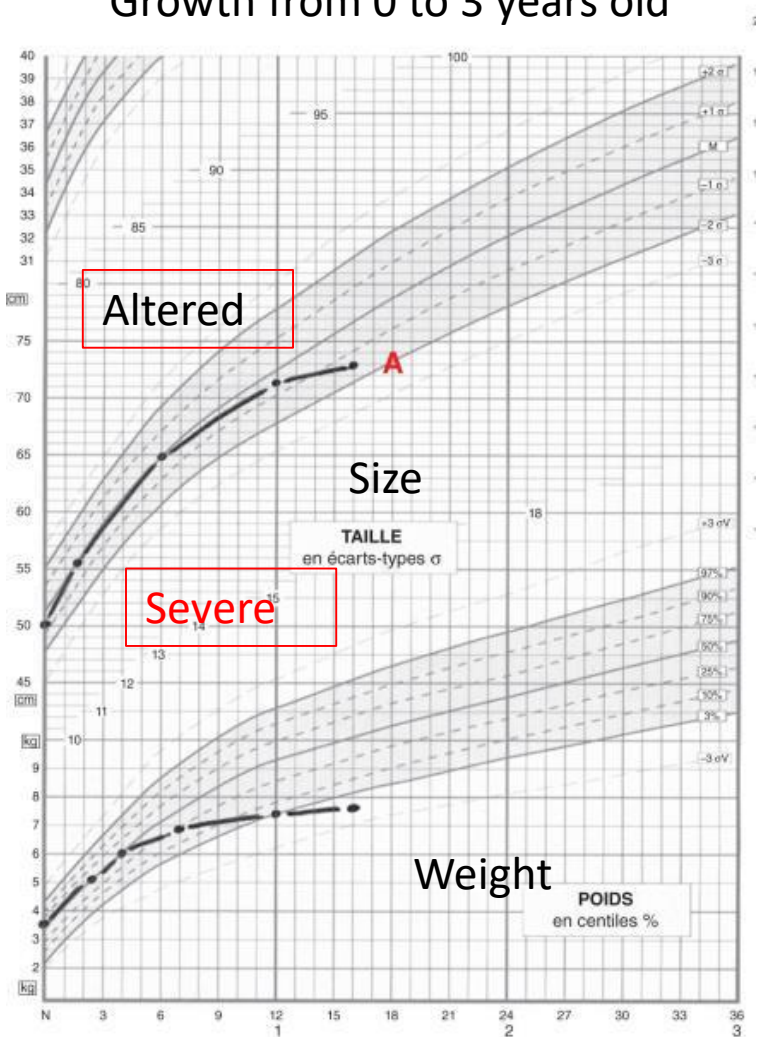
FAMILIAL HISTORY OF IEI OR CLINICAL SIGNS IN THE FAMILY

6) **Failure of an infant to gain weight or grow normally, chronic diarrhoea**

Crucial sign: can alert to a non symptomatic infections, to persistent inflammation, malabsorption, …

Necessitate a differential diagnosis to eliminate other disorders or simply malnutrition

Growth from 0 to 3 years old



+ Measure of the cranial perimeter during the first year of life

IEI DIAGNOSIS: FROM THE PHENOTYPE TO THE GENE

Screening tests
Blood numeration and cytology
Ig levels and serology

Advanced tests
Blood lymphocytes phenotype
Neutrophils oxidative function
T cells proliferation
Protein expression

Clinical phenotype suggestive of IEI

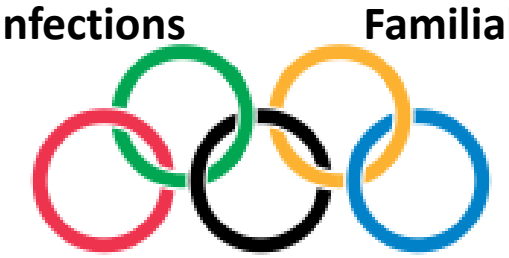
Strong candidate gene?

Yes or No

High throughput gene sequencing
Panel, WES or WGS

Yes

Gene sequencing
Sanger



The immune work-up is sequential from screening tests to more advanced explorations

SCREENING TESTS OF AN IEI

HIV-1/2 serology

1) Complete blood count + smear blood review

2) Quantitative immunoglobulins determination

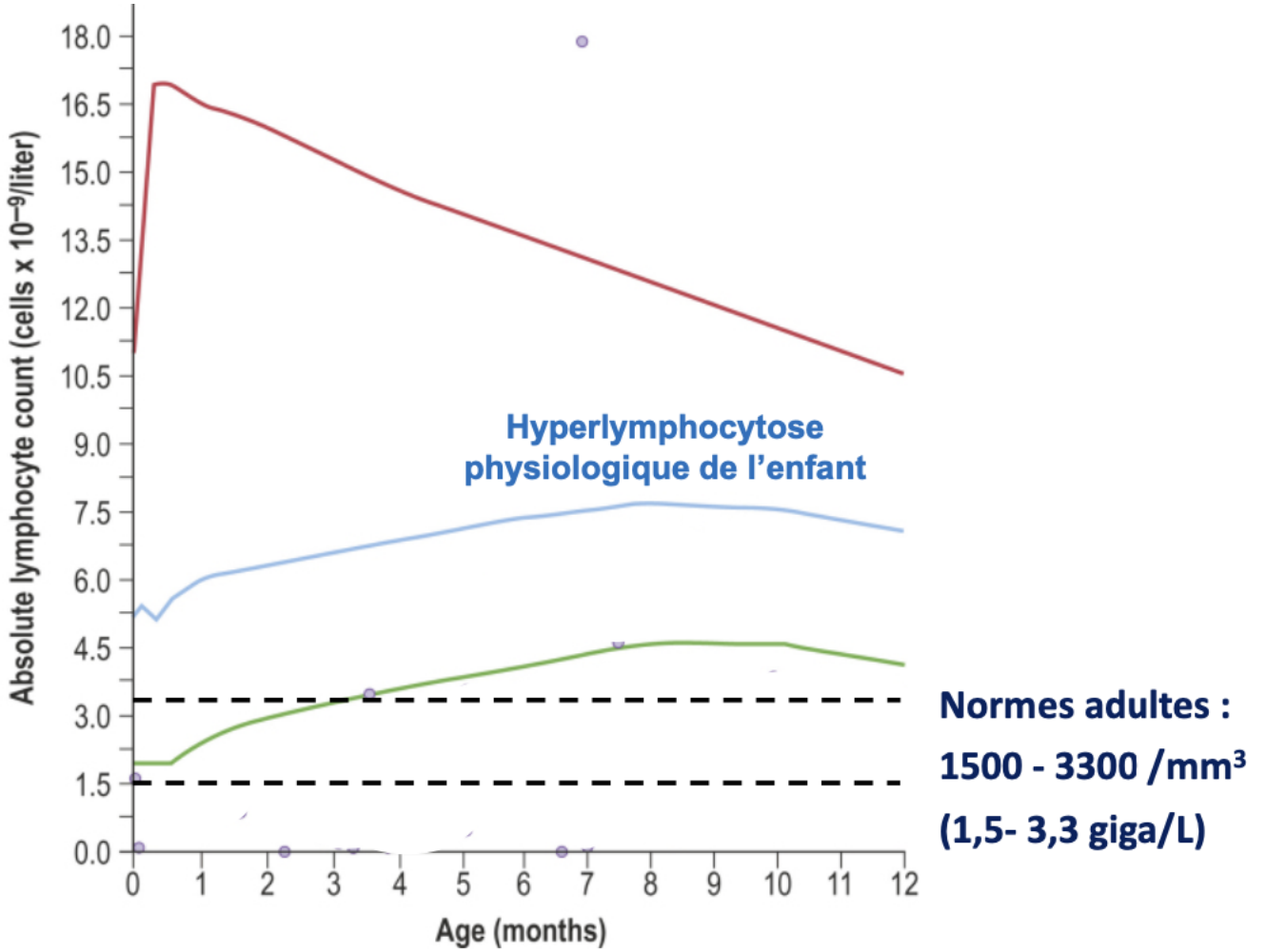
3) Serologies to pathogens the patient have been vaccinated against

SCREENING TESTS OF AN IEI: BLOOD COUNT

- Hb (anemia?)
- Platelet count
- Polynuclear neutrophils count
- Lymphocytes count (RANGES ADJUSTED FOR AGE GROUPS)

Do not forget that lymphocyte counts fluctuate, however severe lymphopenia should be investigated

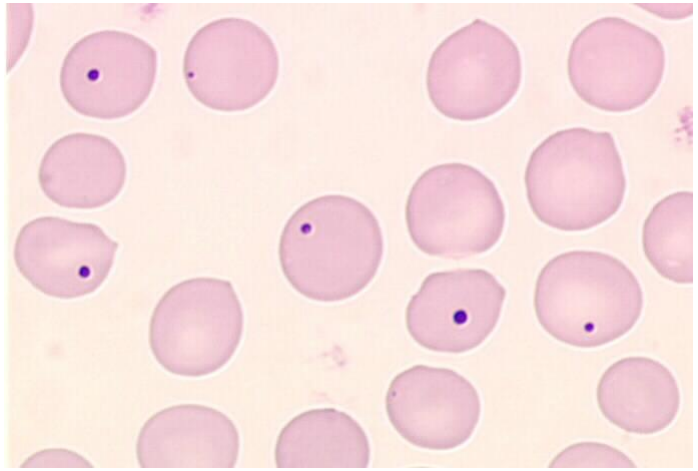
- Monocytes count



Lymphopenia is a crucial sign for IEIs but other cytopenias also direct to different IEIs (ex: monocytopenia and mendelian susceptibility to mycobacterial diseases)

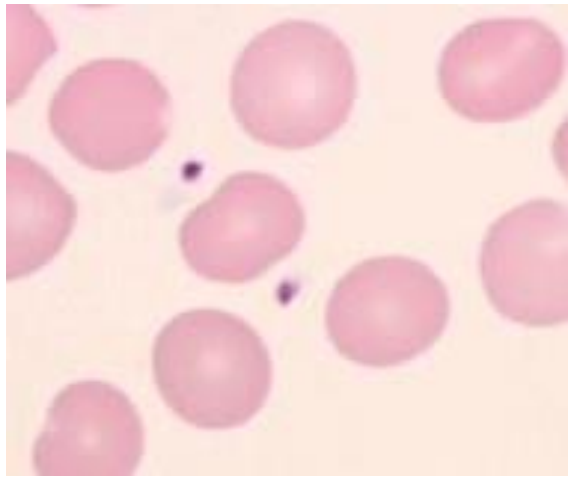
MANUAL BLOOD SMEAR REVIEW

A bit further



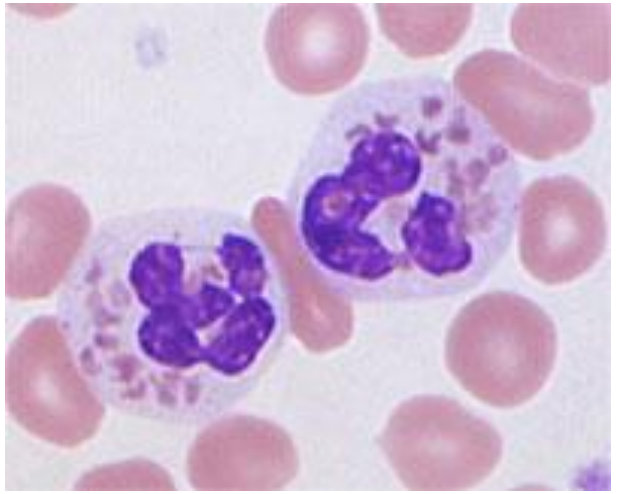
Howell-Jolly bodies

(Asplénia)



Microthrombocytopenia

(Wiskott-Aldrich syndrome and X-linked thrombopenia)

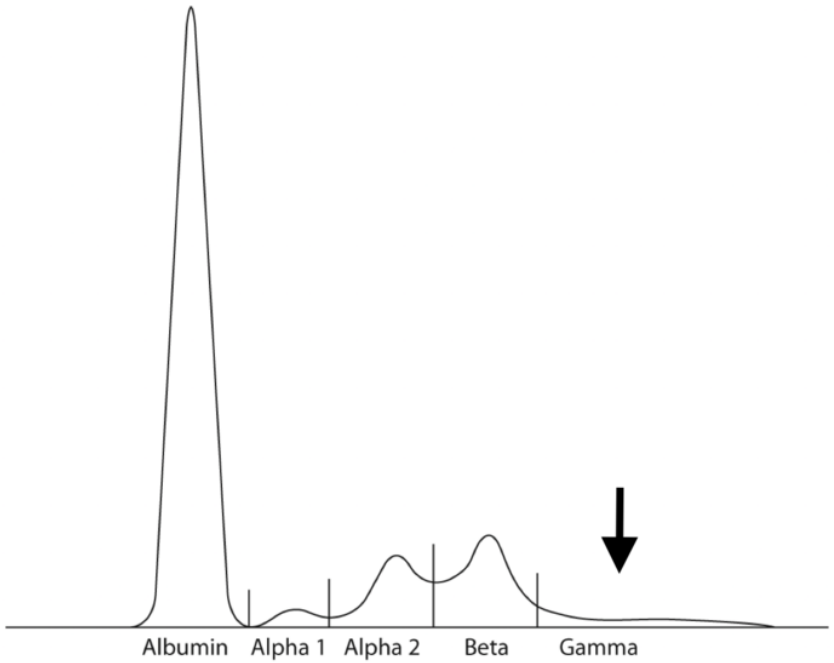


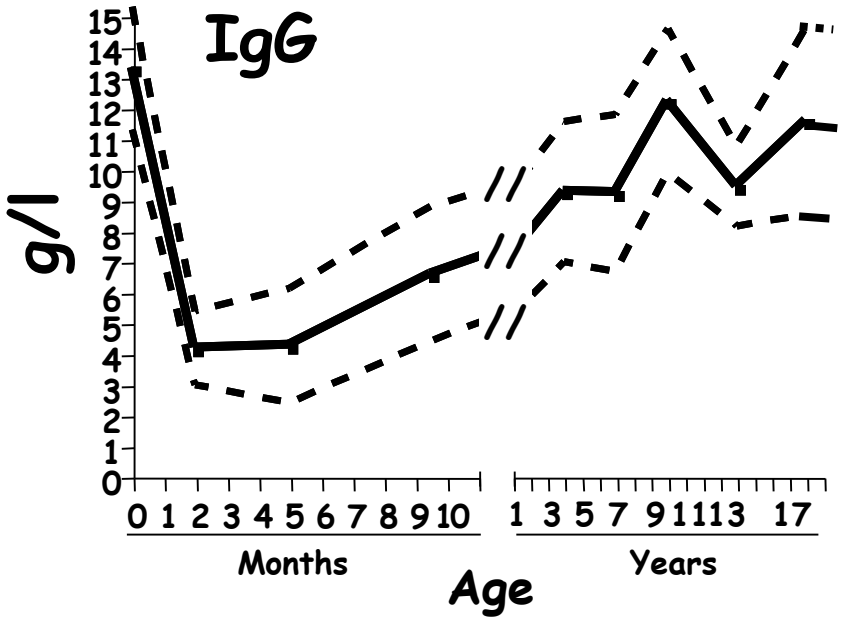
Granules in granulocytes

(Chediak-Higashi syndrome)

SCREENING TESTS OF AN IEI : QUANTITATIVE Ig DETERMINATION

- IgG, IgA and IgM titers





Essential to use age-adjusted normal ranges! (moderate hypogammaglobulinemia in old age)

- *Advanced tests: IgG1, IgG2, IgG3, IgG4 subclasses levels ; IgE titers*

Severe hypogammaglobulinemia directs to CVID and hypogammaglobulinemia is found in many IEIs

SCREENING TESTS OF AN IEI: SEROLOGY TO PATHOGENS

- Tetanus and diphtheria toxoids
- Polyribosyl ribitol phosphate (PRP) capsular polysaccharide of *Haemophilus influenzae* type B
- Any serology to infections that the patient experienced

Negative serologies directs to default in T and B lymphocytes cooperation or defaults in antibody production

ADVANCED TESTS

If abnormal screening tests results or depending on the context

- **Immune phenotyping of lymphocytes**

Evaluation of subpopulations of T cells are key for infants <1 year old

- ***In vitro* proliferative response to mitogens and antigen**

- **Complement**
  - Infection to encapsulated bacteria or auto-immune diseases

- **DHR reduction or nitroblue tetrazolium: Measure the functionality of phagocytes**
  - Tissue infections, aphtosis, colitis

A bit further

- **IgE levels**
  - Tissue infections, eczema

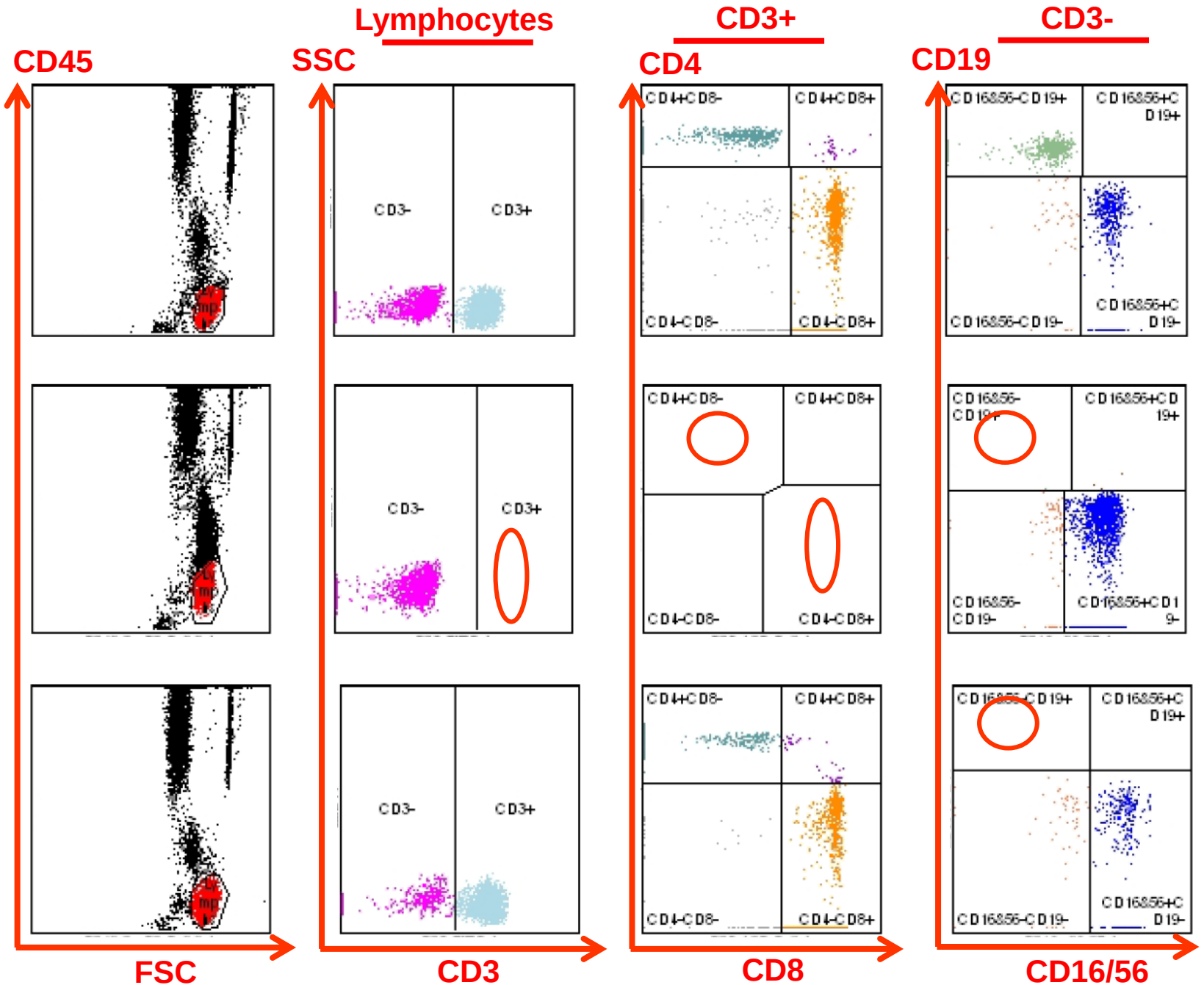
ADVANCED TESTS : IMMUNOPHENOTYPING OF LYMPHOCYTES

A bit further

Normal immunophenotyping in a 16 yo patient

Severe combined immunodeficiency (SCID) T-B-NK+

X-linked agammaglobulinemia

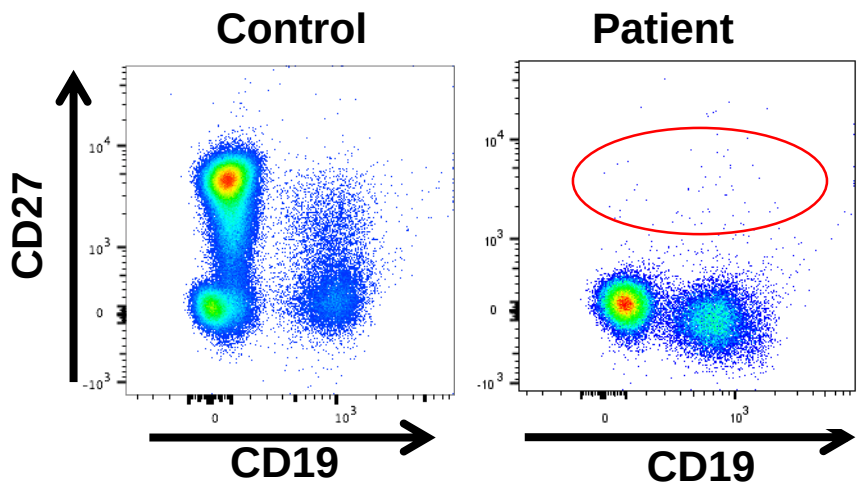


ADVANCED TESTS : IMMUNOPHENOTYPING OF LYMPHOCYTES

- 2 years old patient with EBV+ Hodgkin lymphoma

- Immunophenotyping

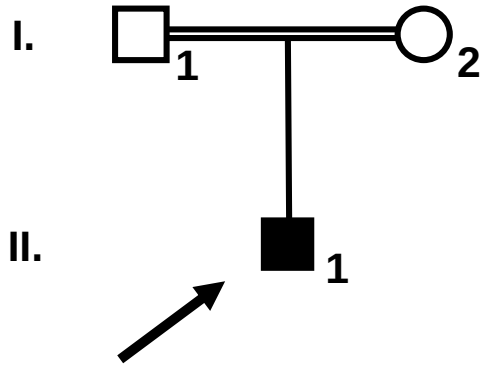
CD27 = Memory B cells



CD19 = B cells

A bit further

CD27 deficiency: poor production of immunoglobulines, no memory B cells



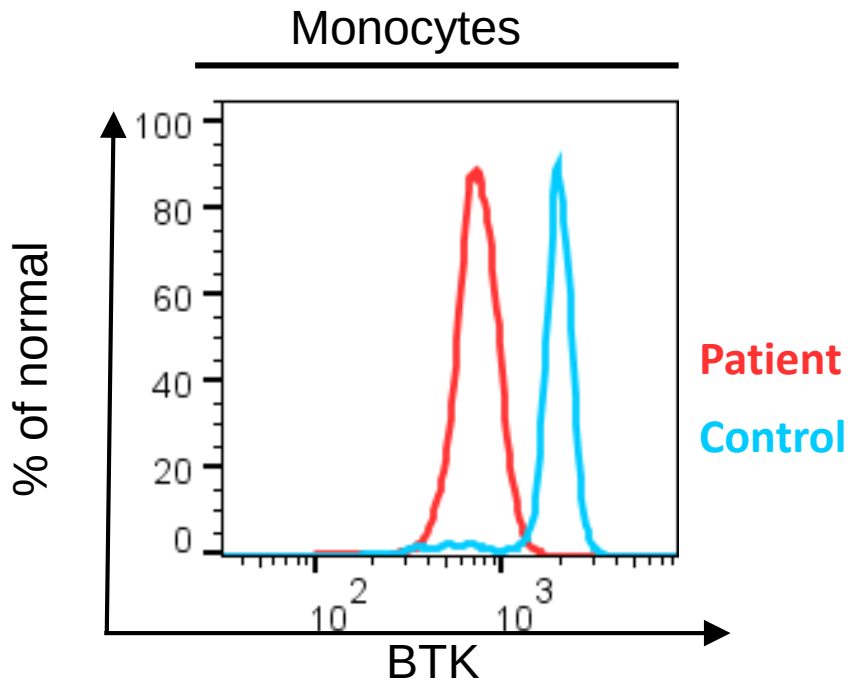
- Curative treatment for CD27 deficiency: Hematopoietic stem cell transplantation

If the deficiency had not been diagnosed, he would have received chemotherapy for lymphoma, likely inefficient

ADVANCED TESTS: SPECIFIC STAINING IN FLOW CYTOMETRY

In expert laboratories specific staining of membrane or intracellular proteins or transcription factors by flow cytometry can help the diagnosis

Ex: Btk deficiency in Bruton's disease (X-linked agammaglobulinemia)



Careful: Expression is not the same as function
A protein can be present and dysfunctional

IMMUNE WORK UP OF AN IEIS: DO NOT OVER ESTIMATE MINOR ABNORMALITIES

- Moderate lymphopenia:

  Transient due to viral infections such as RSV or VZ : To be performed again on a new sample away from the actue phase infection

- Low responses against vaccine antigens

Vaccines up to date? To be performed after (re)vaccination

- IgA deficiency = 1/600
- IgG4 deficiency = 10 % of population

- Impaired complement activity
- Impaired DHR

→ Preanalytical conditions: unstable at ambient temperature

To be performed again on a new sample appropriatley handeld

- Moderetely decreased native T cells, hypogammaglobulinemia: immunosenescence in old age

Look at the history of infections/neoplasia during life

IEI DIAGNOSIS : THE CLINICAL PHENOTYPE DEFINES THE PRESENCE OF AN IMMUNODEFICIENCY

Clinical phenotype suggestive of IEI

Screening tests
Blood numeration and cytology
Ig levels and serology

Advanced tests
Blood lymphocytes phenotype
Neutrophils oxidative function
T cells proliferation
Protein expression

Strong candidate gene?

Yes or No

High throughput gene sequencing
Panel, WES or WGS

Yes

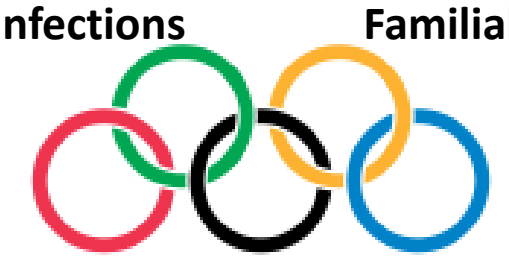
Targeted gene sequencing
Sanger

Under clinical suspicion, genetic analysis should be performed even if the first line immune work-up is normal

IEIs DIAGNOSIS: GENETIC ANALYSIS AND ITS CHALLENGES

Screening tests
Blood numeration and cytology
Ig levels and serology

Clinical phenotype suggestive of IEI



Strong candidate gene?

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Blood lymphocytes phenotype
Neutrophils oxidative function
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Protein expression

Yes or No

High throughput gene sequencing
Panel, WES or WGS

Yes

Gene sequencing
Sanger, MLPA

A bit further

SEQUENCING STRATEGY in IEIs, ADVANTAGES AND LIMITS

Targeted gene sequencing
Sanger, MLPA

Single candidate gene

- **Advantages of targeted gene sequencing**
  - **Fast to perform and analyze**
  - **Low cost**
- **Limits of targeted gene sequencing**
  - **May not be able to detect large duplications or deletions**
  - **If you are wrong on the candidate gene, you can loose precious time during an emergency situation**
  - **Harder to perfom for big geneswith many exons**
  - **Harder to analyze for genes with pseudogenes**
  - **May not be able to detect somatic mutations**

High throughput gene sequencing
Panel, WES or WGS

Single or several candidate genes:

- **Panel**
- **Whole exome sequencing (WES)**
- **Short read whole genome sequencing (WGS)**
- **Long read whole genome sequencing**

- **Advantages of high-througput sequencing**
  - **Simultaneous analysis of many genes**
  - **Higher diagnosis yield**
- **Limits of high-througput sequencing**
  - **More costly**
  - **Harder to analyze (bioinformatics skills++)**
  - **Secondary Finding: incidental**
  - **Identification of variant of unknown significance**

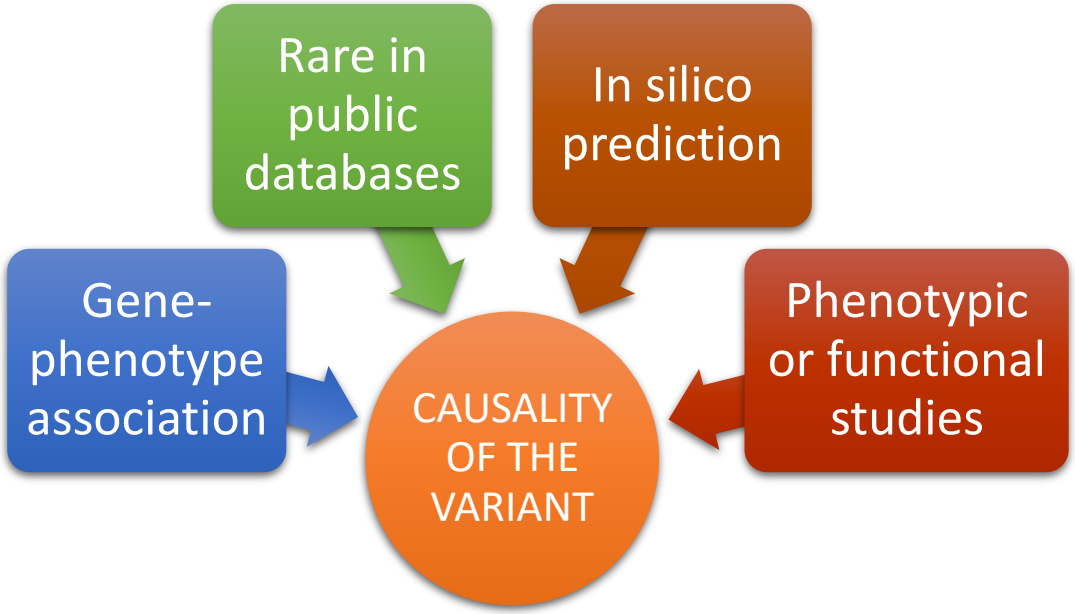
INTERPRETATION OF A GENETIC TESTING

- Three kinds of variants
  - Nucleotid variants: **SNV** (*single nucleotide variant*) et **delins** (deletions or insertions from 1 to 49 nucleotides)
  - Non-balanced structural variant s≥ 50 nucleotids: **CNV** (*copy number variant*: **deletions**, **duplications**)
  - Non-balanced structural variant : **BSV** (*balanced structure variant*: **inversions**, **insertions**, **translocations**)

A bit further

- 5 classes of variant (ACMG)
  - Class 5: **pathogenic variant**
  - Class 4: **likely pathogenic variant**
  - Class 3: **variant of unknown significance**
  - Class 2: **likely benign variat**
  - Class 1: **benign variant**

A bit further



Richards S* et al., *Genet Med, 2015

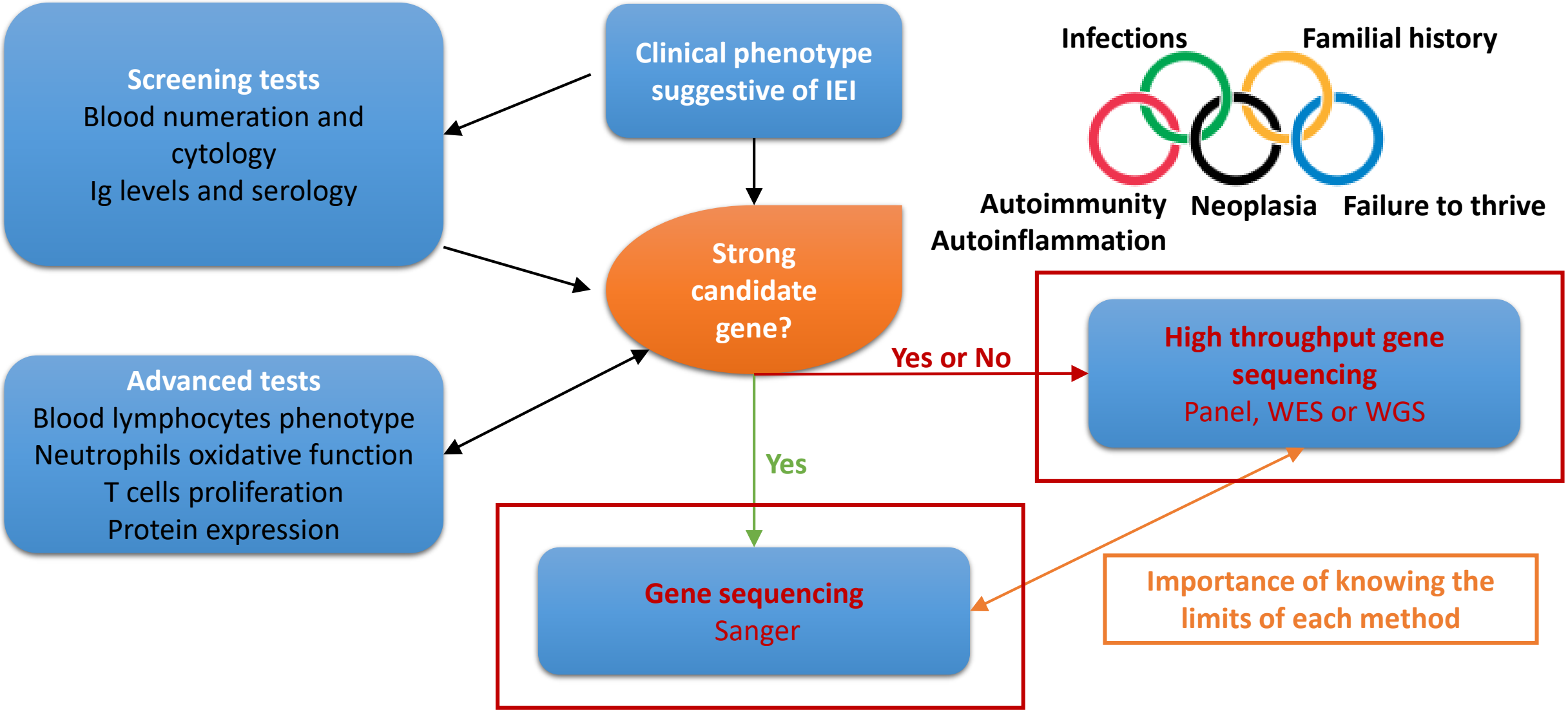
A bit further

USEFUL TOOLS FOR GENETIC TESTING

- *In silico* pathogenicity score
  - PolyPhen-2
  - CADD
  - Alpha-missense
  - Phast (non exonic variant)
  - Spice AI (splicing variants)
- *Other population genetics based score*
  - pLI
  - CoNeS: https://pubmed.ncbi.nlm.nih.gov/33408250/
  - Missense tolerance ratio
  - Gene damage index
- *Public database*
  - https://gnomad.broadinstitute.org/
  - https://decaf.decode.com/
  - https://www.rgc-research.regeneron.com/me/license-and-terms-of-use
  - Specific database: Iranome, TurkishVariome, GreatMiddleEast database, 100KAsia etc.

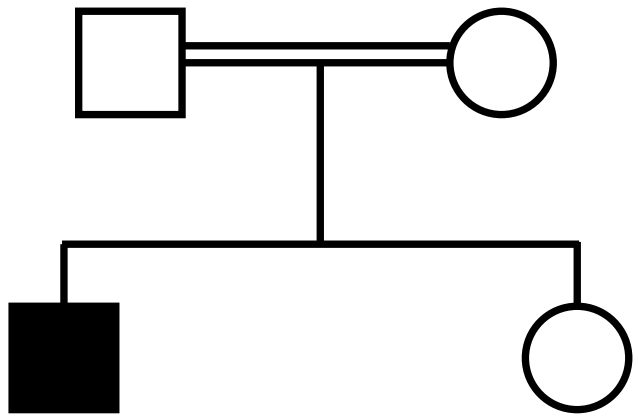
https://www.hgid.org/computational-tools/

IEIs DIAGNOSIS: GENETIC ANALYSIS AND ITS CHALLENGES

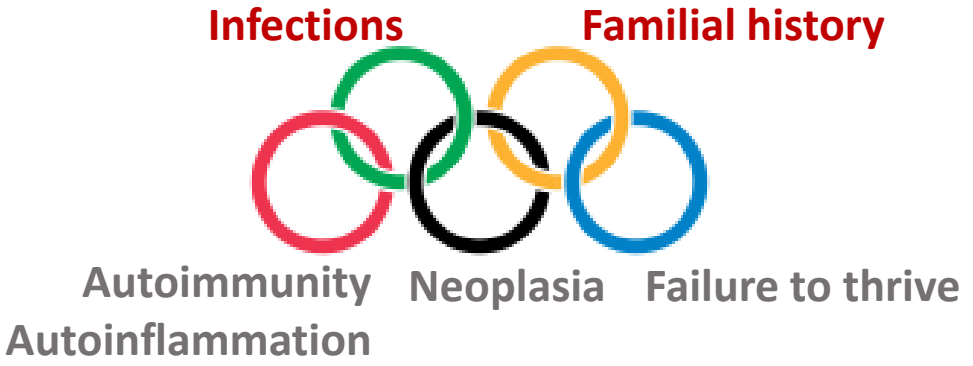


EXEMPLE CASE: CLINICAL PRESENTATION

- 10 yo male patient born to Turkish consanguineous parents



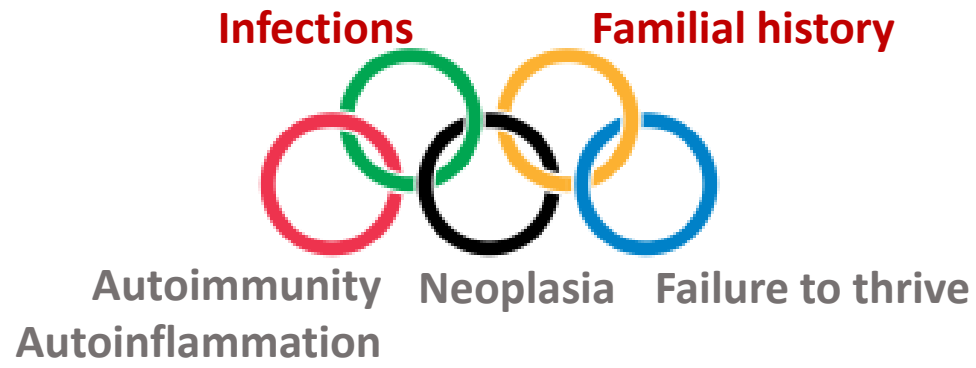
- History of repeated infections
  - Hospitalized for RSV bronchiolitis at 2 months old
  - Hospitalized for an O_2 dependant non documented pneumonia at $4^{1/2}$ months old
  - Hospitalized in the ICU for severe respiratory distress and sepsis at 2 yo. Germs identified: *H. influenza* and RSV



EXEMPLE CASE: CLINICAL PRESENTATION AND IMMUNE SCREENING

- 10 yo male patient lineage born to Turkish unrelated parents

- History of repeated infections
  - Hospitalized for RSV bronchiolitis at 2 months old
  - Hospitalized for an O_2 dependant non documented pneumonia at $4^{1/2}$ months old
  - Hospitalized in the ICU for severe respiratory distress and sepsis at 2 yo. Germs identified: *H. influenza* and SRV

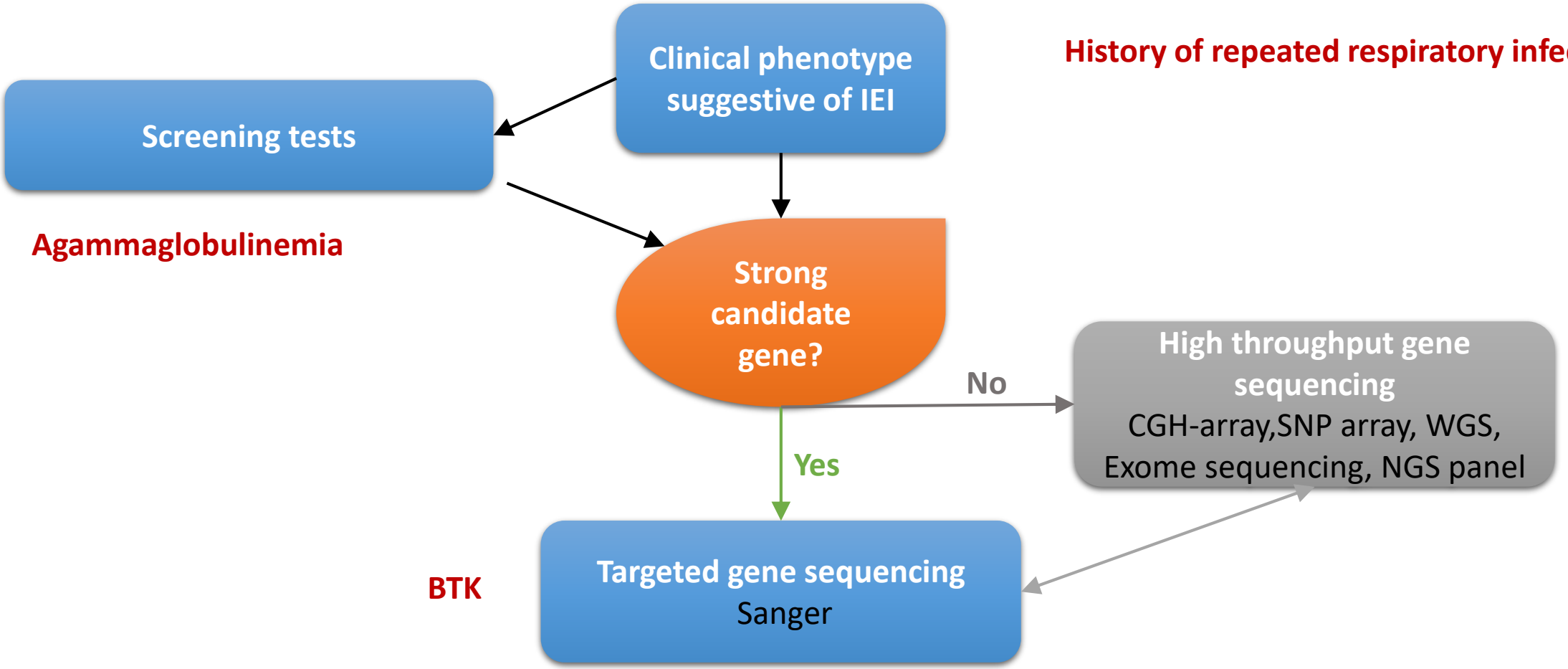


LAB WORKUP

- Blood count: Low neutrophil (670/mm^3)
- Hypogammaglobulinemia (<detection limits)
- Profound B lymphopenia (19/mm^3)

= Agammaglobulinemia

EXEMPLE CASE: DIAGNOSIS STRATEGY AND GENETIC ANALYSIS



Sanger sequencing of BTK: **No pathogenic variants**

EXEMPLE CASE: PHENOTYPIC ANALYSIS

Clinical phenotype suggestive of IEI

History of repeated respiratory infections

Screening tests

Agammaglobulinemia

Strong candidate gene?

Specific tests:
Protein expression : BTK

Absence of BTK expression in monocytes

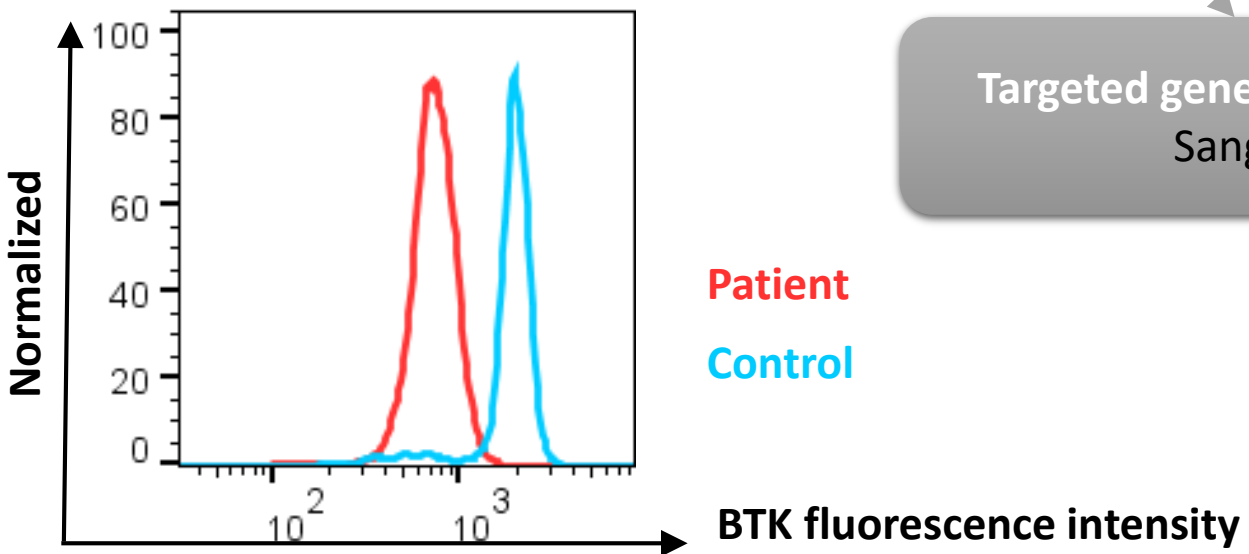
No

High throughput gene sequencing
NGS panel

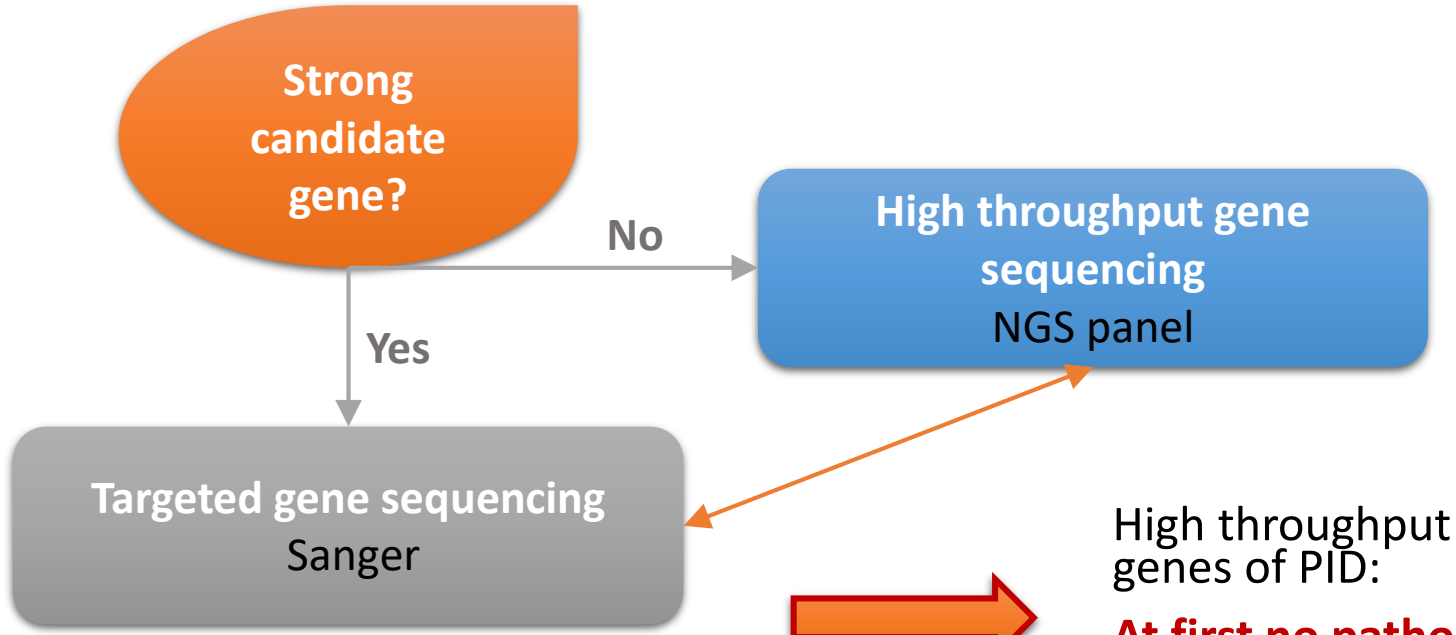
Yes

Targeted gene sequencing
Sanger

BTK



EXEMPLE CASE: GENETIC ANALYSIS



BTK

High throughput sequencing of a panel of >500 genes of PID:

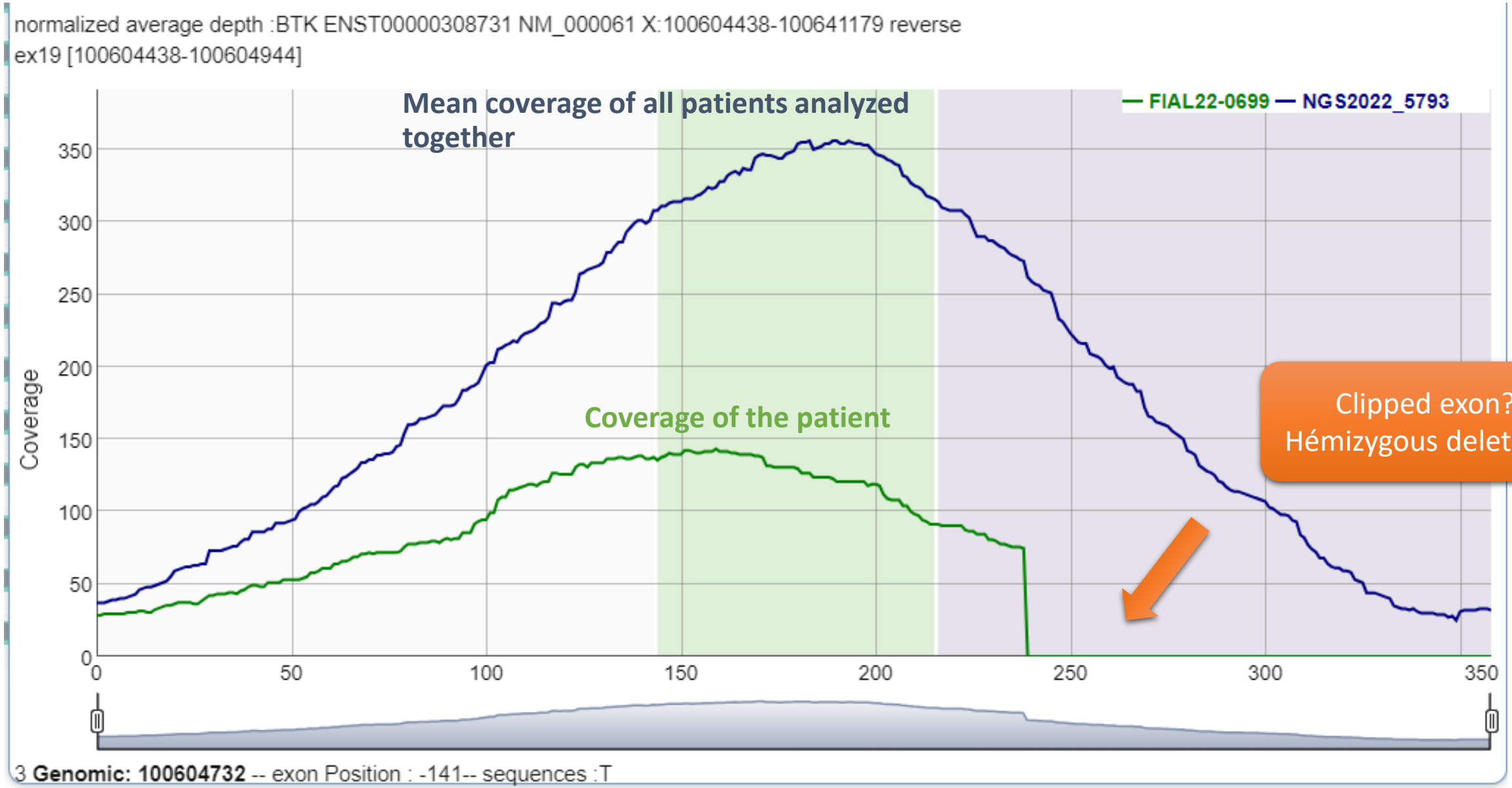
At first no pathogenic variants or CNV were identified

Specific tests:
Protein expression : BTK

Absence of BTK expression in monocytes

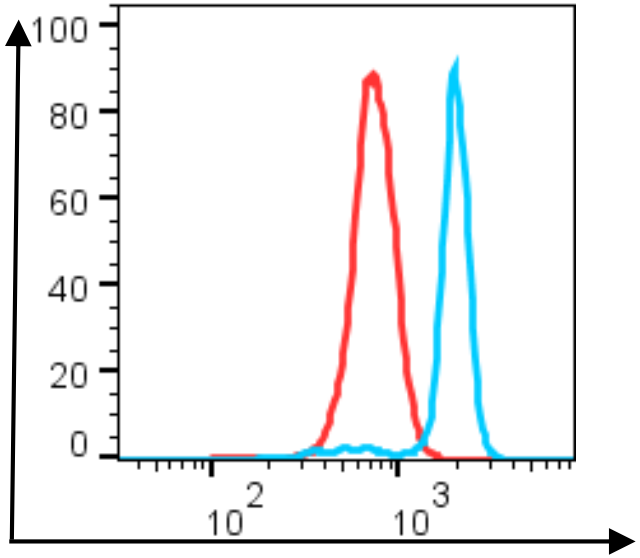
BTK was reanalyzed thoroughly

EXEMPLE CASE: GENETIC ANALYSIS



ALWAYS COME BACK TO THE CLINICAL AND IMMUNOLOGICAL PHENOTYPE

Agammaglobulinemia in a boy



Patient

Control

New analyse of the BTK gene

GENETICITS AND BIOINFORMATICIAN COME HAND IN HAND

Since then a caller for *Alu* insertion has been added to the analyse pipeline of our panel of PID genes

S I F				BTK	X-100608510-GGTCGTACTAGACTATTA-G	hap he 11/3 21%	-	X:100608511	ENST00000308731	-172_ex18	c.1751-172delTAATAGTCTAGTACGAC	intronic	TAATAGTCTAGTACGAC/-		-	-0.0000	-	-				0:0
									ENST00000621635	-172_ex18	c.1853-172delTAATAGTCTAGTACGAC	intronic	TAATAGTCTAGTACGAC/-		-	-0.0000	-	-				0:0
S I F				BTK	X-100604968ins-ALU	mel he 15/17 53%	-	X:100604968	ENST00000308731	-24_ex19	ins-ALU	intronic	A/ANT		-	-0.0000	-	-				0:0
									ENST00000621635	-24_ex19	ins-ALU	intronic	A/ANT		-	-0.0000	-	-				0:0

OUTLINE

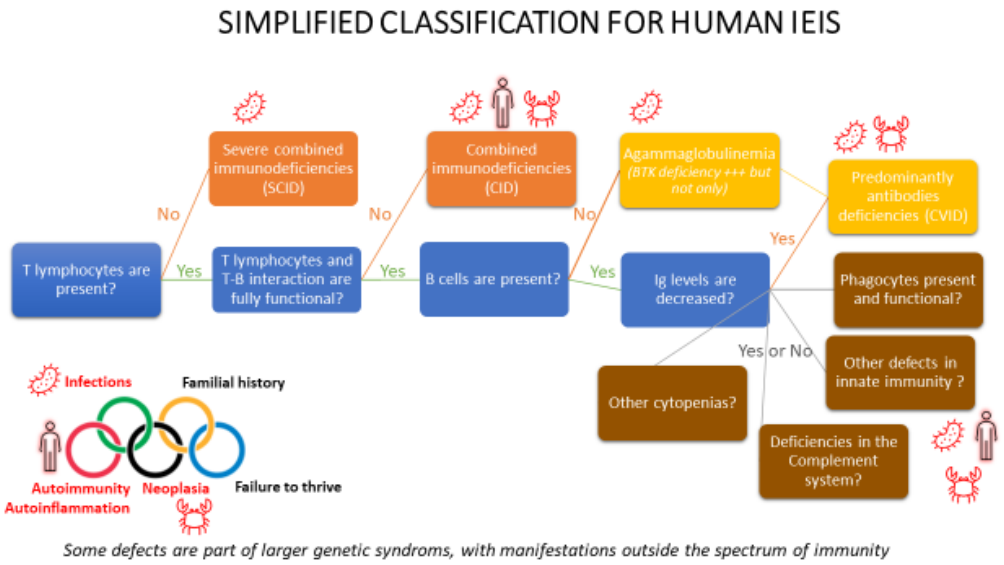
1. Introduction to Inborn Errors of Immunity

2. How to investigate Inborn Errors of Immunity?
   A. Clinical context
   B. Immunological investigations
   C. Genetic investigations
   D. One example case

3. Treatments of Inborn Errors of Immunity
A. The first gene therapy : Hematopoietic Stem Cells graft
B. Out of the “bulles” : Success and hardships of gene therapy
C. New advances, 2 examples
   I. New Immunoglobulins preparations
   II. JAK inhibitors: A targeted therapy for an IEI

TREATMENTS OF INBORN ERRORS OF IMMUNITY

Before gene therapy or targeted therapies : symptomatic and preventive care



Isolation, chimioprophylaxy (antibiotherapy, antifungal and antiviral therapy,), immunoglobulins substitution

?

Anti inflammatory therapies (mainly unsuccessful)

Immunoglobulins substitution (unsuccessful in preventing cancer), chemotherapy

Largely insufficient

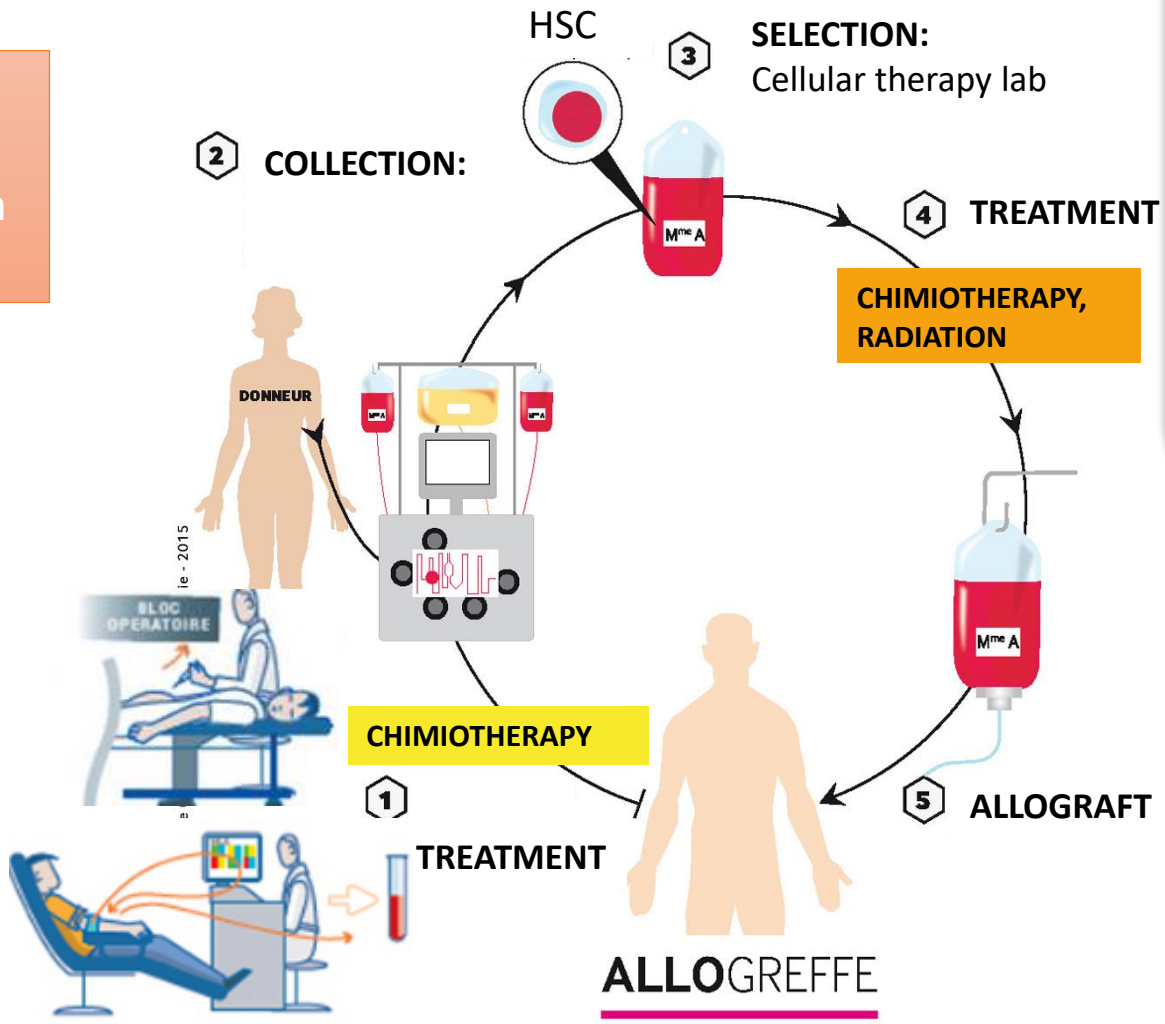
Poor quality of life in some pathologies

However, some of these therapies are sometimes sufficient (ex: Immunoglobulins substitution in CIVD)

THE FIRST GENE THERAPY : HEMATOPOIETIC STEM CELLS (HSCs) GRAFT

Replacing the deficient immune system with a functional one, from a the hematopoeitic stem cells of a donor

See HSCs graft and GvHD in V. Esteban-Martin course



Iliac crest bone marrow aspiration

Cytapheresis

Cord blood stem cells

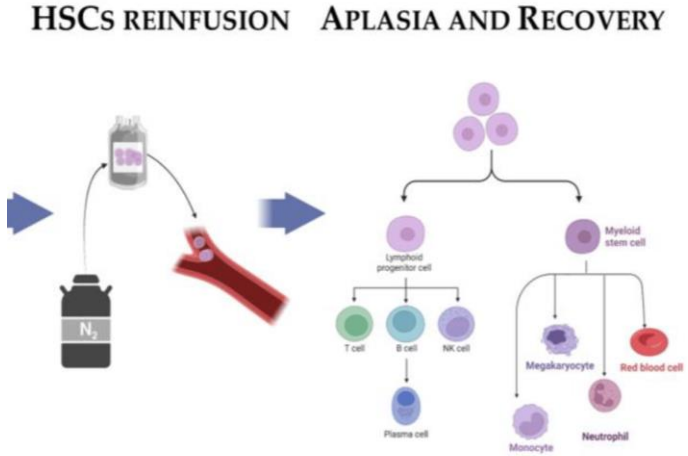
Factors associated with positive outcome:

Absence of infections before graft

Young age at transplant

Type of conditioning treatment

Sufficient recovery of naive CD4 T lymphocytes +1 year after graft



Supportive treatments

THE FIRST GENE THERAPY : HEMATOPOIETIC STEM CELLS (HSCs) GRAFT

Main risk: graft versus host disease (GvHD)
Can be fatal or lead to the loss of the graft
Can be treated if detected early

More likely with haploidentical donors

Importance of appropriate selection of HSC in the lab

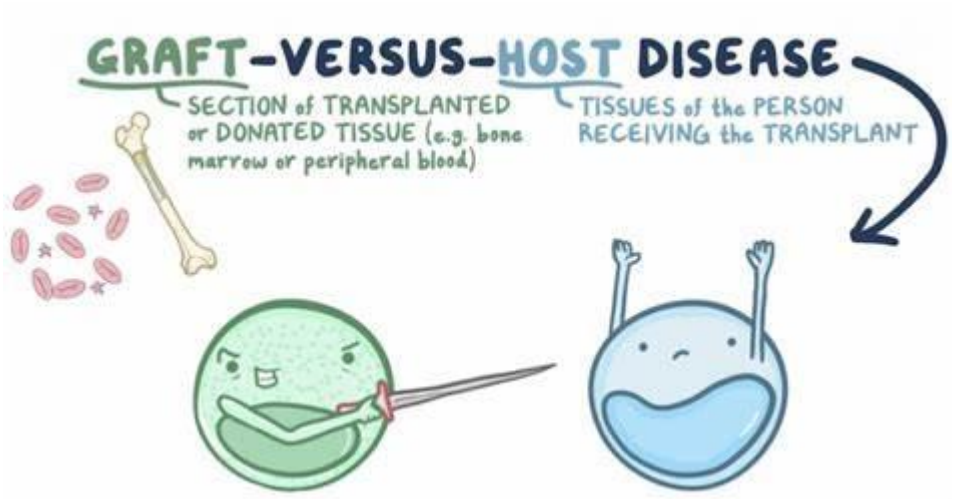
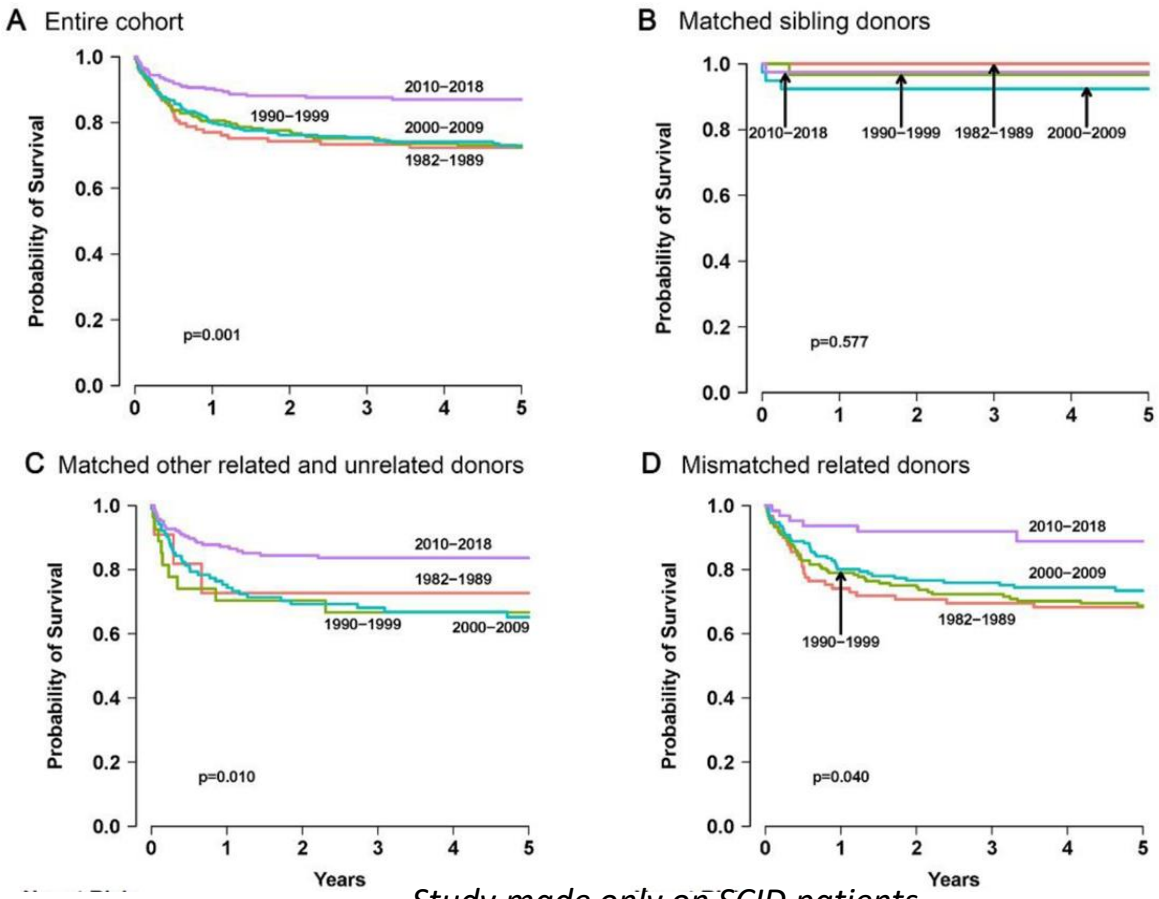


Image Credit: Osmosis.org

Due to constant improves in the process the overall survival in patients IEI patients with HSCs graft is now high



Study made only on SCID patients
Thakar MS, et al. Lancet. 2023

Theoretically, it seemed most patients with SCID or severe IEIs can now be treated with HSCs graft, however biology is never simple

THE FIRST GENE THERAPY : HEMATOPOIETIC STEM CELLS (HSCs) GRAFT

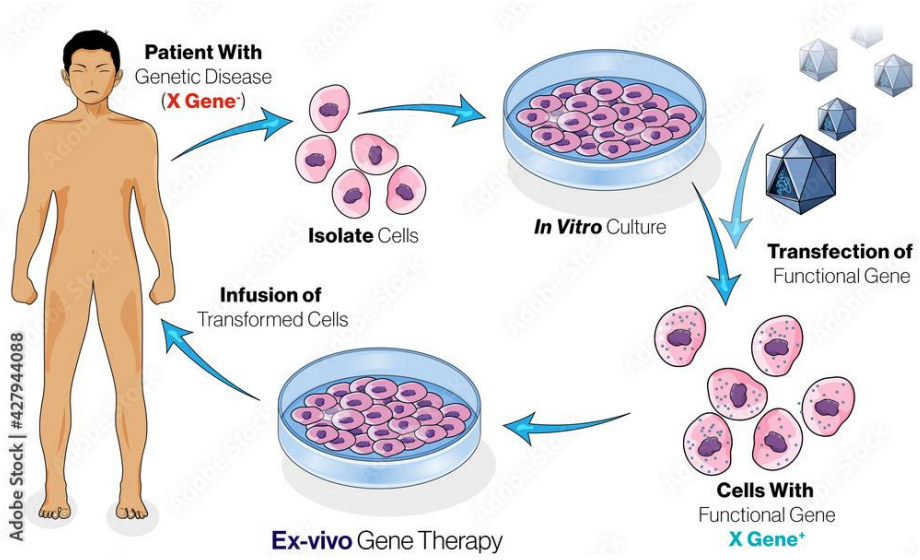
HSCs graft cannot always be performed:

- Lack of donor
- Late diagnosis (non-SCID)
- IEI caused by non immune cells (ex: many autoinflammatory IEIs)
- *Many other situations to be evaluated for each patients by a multidisciplinary team*

HSCs grafts are also sometimes not pertinent and benefice/risk balance should always be considered

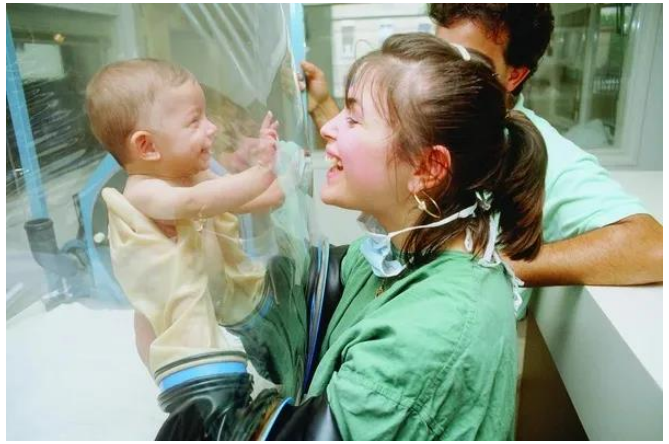
OUT OF THE “BULLES” : SUCCESS AND HARDSHIPS OF GENE THERAPY

Autologous graft of HSCs genetically modified: Fixing the patient immune system by modifiying its own stem cells so they can reconstitute a functionnal immune system



March 1999: **The « bébé bulles » are out of their bubble** with the first success of gene therapy in IEI (A. Fischer, S. Hacein-Bey, M. Cavazzana)

Hacein-Bey-Abina S, *et al*. Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med. 2002

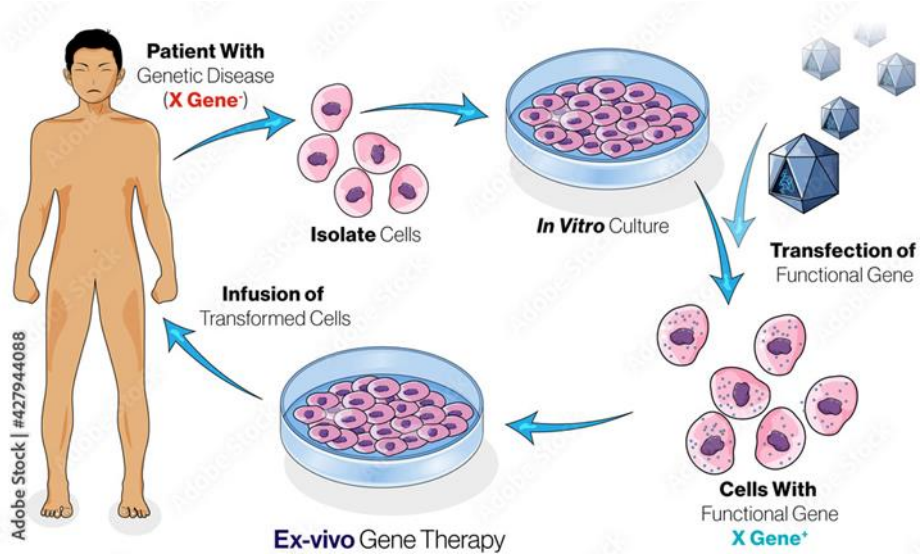


However a high rate of mutations due to the insertion of the gene was observed and many patients developped leukemia in the following years

Braun CJ, et al. Gene therapy for Wiskott–Aldrich syndrome—long-term efficacy and genotoxicity. Sci Transl Med. 2014 9 out of 10 patients with successful gene therapy but 7 of them developped leukemia

OUT OF THE “BULLES” : SUCCESS AND HARDSHIPS OF GENE THERAPY

New self inactivating lentiviral vectors (opposed to the first ones which were gamma-retroviral vectors) **are now being used in new gene therapy trial**



First generation: Strong enhancer element on the promoter region of the virus was able to activate nearby gene after integration in human genome

Third generation: The strong enhancer element was deleted and a less activating internal element activate the integrated gene but the the adjacent

Kohn D, et al. N Engl J Med. 2021.

Several cohort for different IEIs are being held across the world and first results are promising (diseases: ADA, WAS, SCID X1) Kohn et al. N Eng J Med,2021; Cicalese et al. Blood, 2016 ; Ferrua et al. Lancet Haematol, 2019 ; Mamcarz et al. N Eng J Med, 2019

Gene editing as opposed to gene addition may also be a new tool for gene therapy in IEI patients

IMPROVING ON EXISTING CARE: NEW IMMUNOGLOBULINS PREPARATIONS

Patients with IEIs classified as predominently antibodies deficiency are usually treatd by immunoglobulin substitution
However the infusion are usually 99% IgG

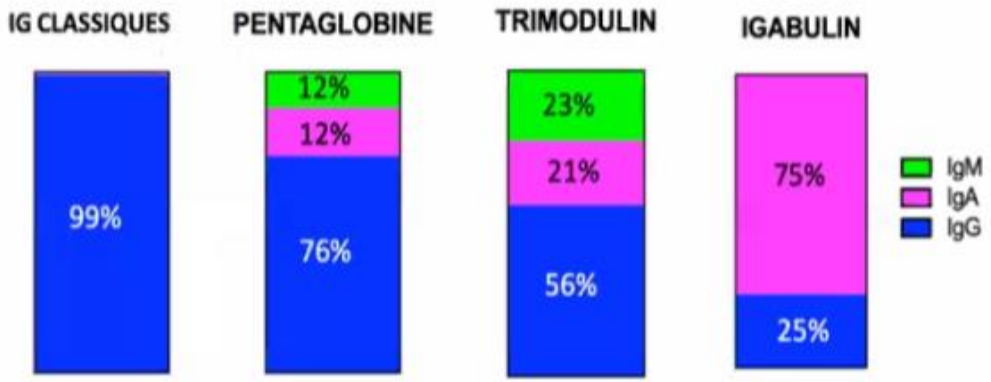
New preparations enriched in IgA and IgM are currently under trial in IEIs
They already have other indications (ex: sepsis in premature neonates)

Aim:

- Reducing infections rate and hospitalization length in patients with repeated infections under proper Ig subsitution

- Reducing gastro intestinal infections

Risks:
IgA allergies? The existence of IgA allergies is currently discussed



First results are promising with a reduce number in infections rate and hospitalization length but groups are too small to conclude on gastrointestinal disorders yet (Results shown in conferences)

JAK INHIBITORS: A TARGETED THERAPY FOR AN IEI

Interferonopathies are IEIs classified as autoinflammatory diseases. They are caused by constitutive activation if the interferon (IFN) type I pathway = Detection of danger

Main interferonopathies:

A bit further

- **AGS :** Mutations in the metabolism of nucleic acids, the ownnucleic acids form the patient as recognized as danger
- **SAVI and COPA:** Constitutive activation of the STING pathway (supposed to detect cytoplasmic DNA) which activates the IFN pathway
- **PRAAS/Candle:** Proteasome dysfunction
- **Interferon induced lupus/neuroinflammation:** Activation of the danger pathway (TLR pathway)

Main symptoms: Recurrent fever, severe arthralgias (can impede the walking development), myositis, skin ulcerations, neurological lesions (inflammation, neurological regressions or encephalitis), pulmonary fibrosis (can lead to transplantation), lupus glomerulonephritis

HSCs graft would not be useful as many different cells are involved, not only immune cells

Plus the mechanisms of some interferonopathies are still being elucidated

JAK INHIBITORS: A TARGETED THERAPY FOR AN IEI

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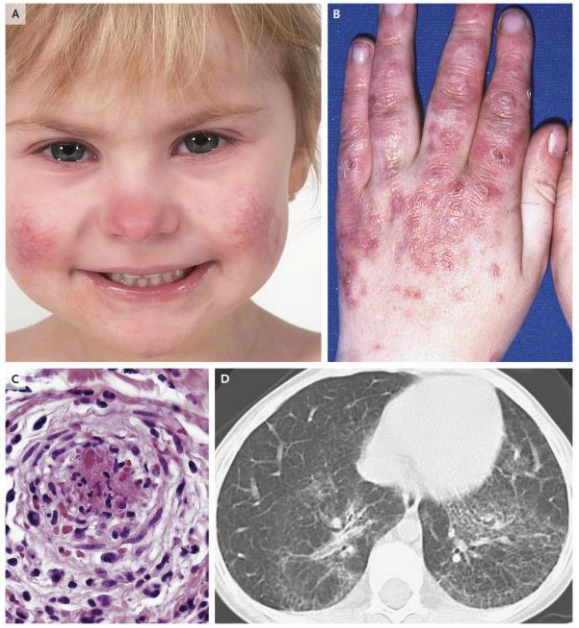
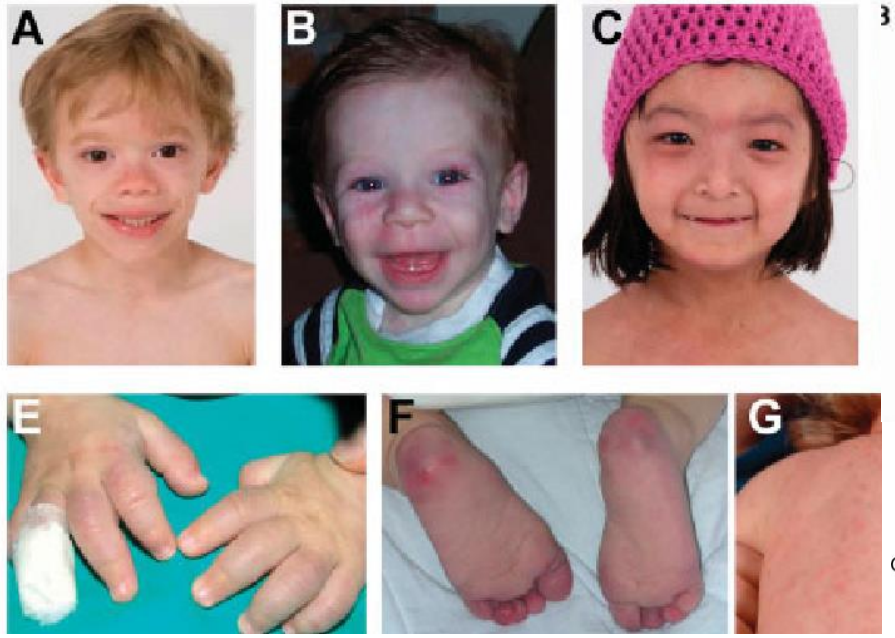
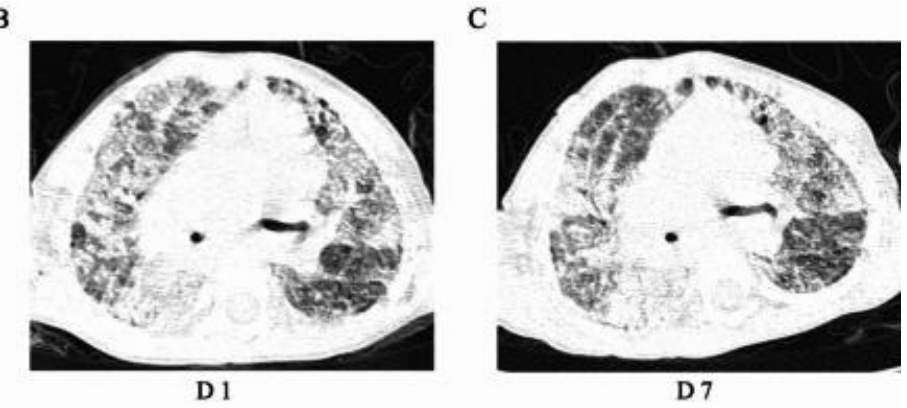


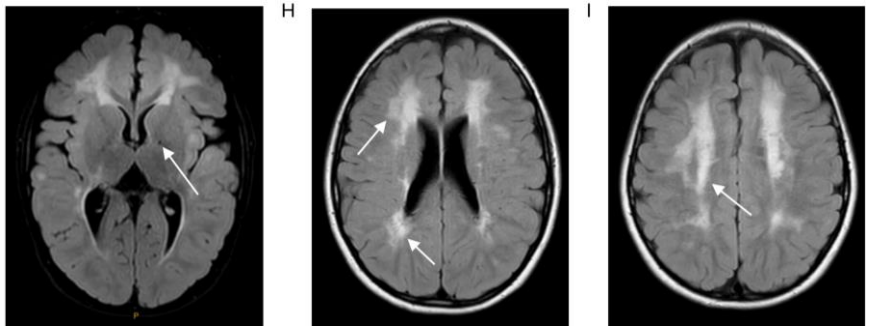
STING mutations



CANDLE syndrom



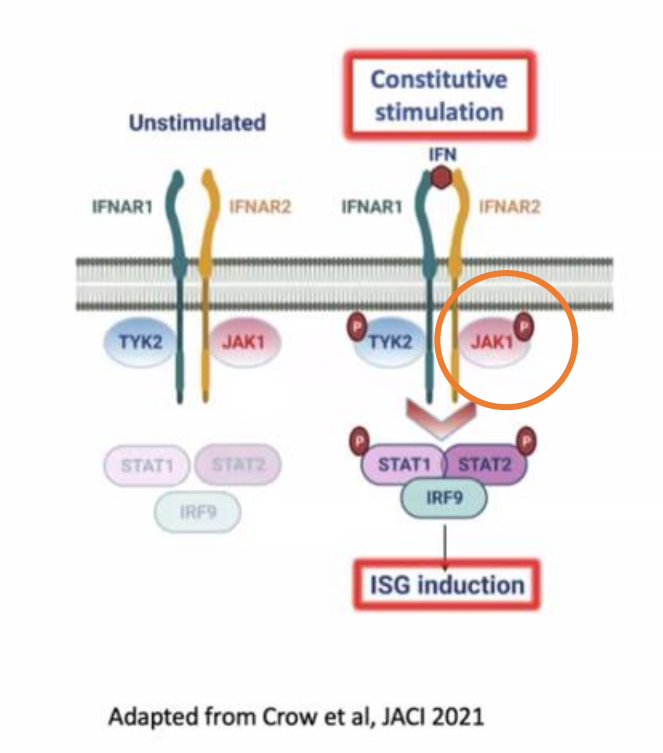
Severe interstitial lung disease in STING syndrom



White matter signal alterations in brain MRI (with FLAIR imaging) on a patient with AGS

JAK INHIBITORS: A TARGETED THERAPY FOR AN IEI

The activation of the production of the IFN type I cannot currently be blocked but we can block the pathway activated by the type I IFN



Adapted from Crow et al, JACI 2021

JAK inhibitors: Developped for autoinflammatory diseases such as rhumatoid arthritis, they inhibit different JAKs depending on the molecule
Ruxolitinib, Tofacitinib, Filgotinib,…

Anifrolumab: Blocker of IFNAR1, developped for LES

Deucravacitinib: *TYK2 inhibitor in clinical trials in LES, is considered*

Impressive results on arthritis and skin lesions, efficient on pulmonary lesions with reduction of O2 ventilation
Does not pass the BHE barrier well and has litttle impact and neurological complications

JAK INHIBITORS: A TARGETED THERAPY FOR AN IEI

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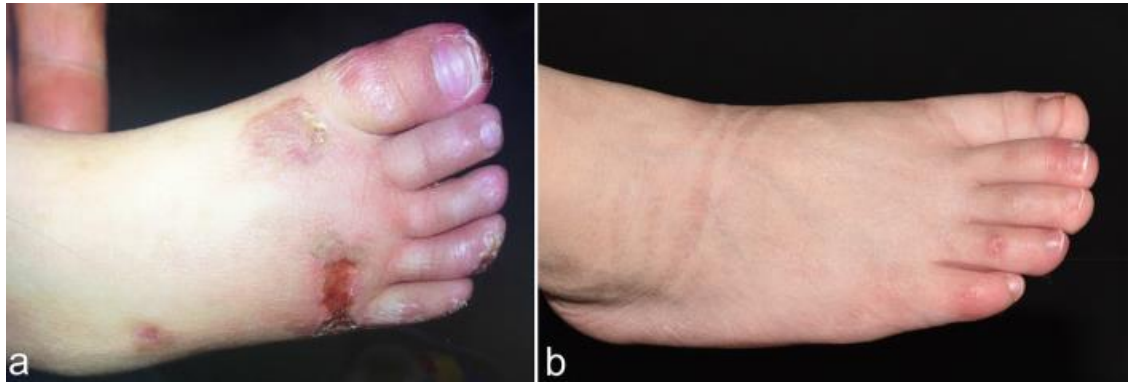
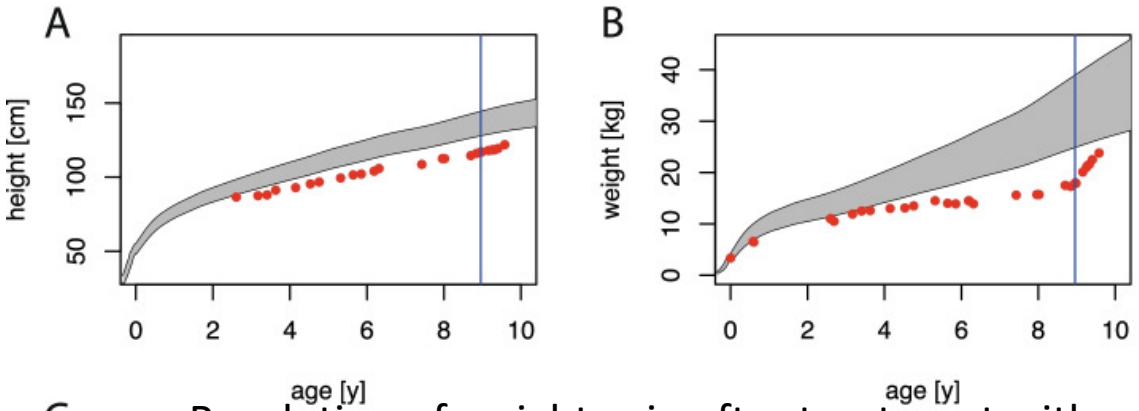
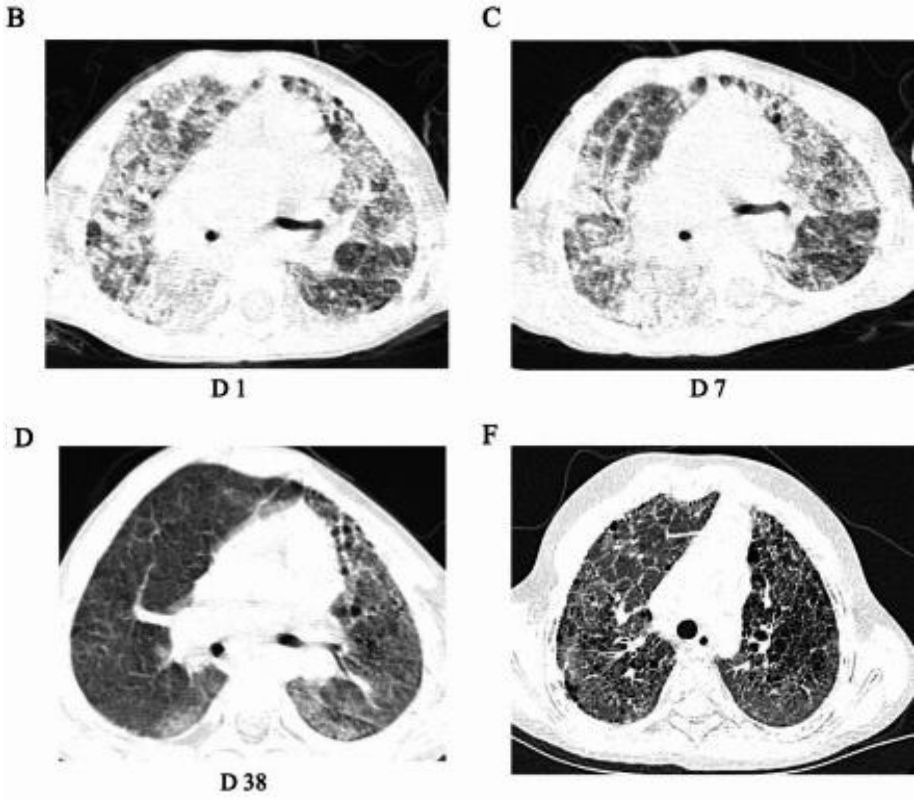


Resolution of chilblains after treatment with tofacitinib



C Resolution of weight gain after treatment with ruxolitinib

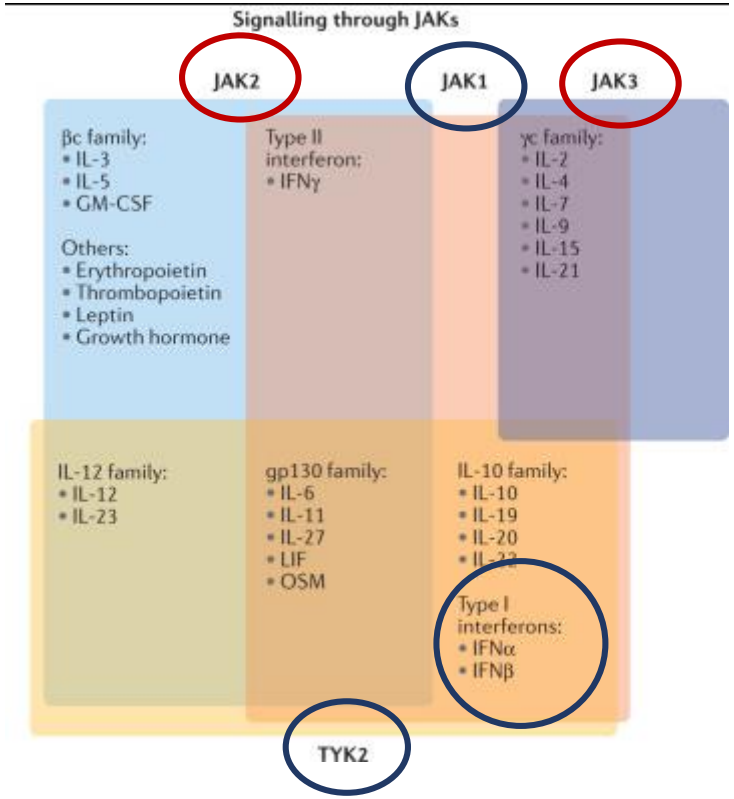


Resolution of severe interstitial lung disease after treatment with baracitinib

B: At diagnosis, C: After conventionnal immunosuppression, D : 1 week after baracitinib, F: 14 months after initiation of treatment: Persistance of lesions on CT scan but improvment of symptoms

JAK INHIBITORS: A TARGETED THERAPY FOR AN IEI

JAK inhibitors in interferonopathies are used at massive doses: around 4 times an adult dose for a child: it causes a pan-JAK inhibition



Ideally only JAK1 or TYK2 should be inhibited

JAK2 and JAK3 are also inhibited causing side effects:

- Severe infections: aspergillosis, mycobacterium infections, VZV infections, BK virus nephropathy
- Stunted growth, dyslipidemia, weight gain
- Rare vascular events
- Increased inflammatory episodes if the treatment is abruptly stopped

What about the long terms effects?

What about treatments efficient on the neurological symptoms?

TAKE HOME MESSAGES

IEIs are mainly associated with infections but also neoplasia and autoinflammatory diseases
They are rare but should be always be investigated facing alerting clinical signs
Minor immune abnormalities should not be overinterpreted

The clinical and immunological phenotype of the patient are key and should lead the diagnosis
Genetic analyses should always be performed when facing a strong clinical suspicion even if the immune work up is normal
Clinicans and geneticists should work closely with their bioinformaticians

HSCs graft is highly sucessuful in IEIs care, especially when performed earlier for patients with less infections: early diagnosis is then key for success of teatment and survival
In less severe IEIs, preventive or substituitive care is sometime enough

Advances in care for IEIs focuse on targeting the specific actors or pathways of the mmune systtems that are dysfunctionnal and there are more innovative therapies currently developping than the one presented in this class