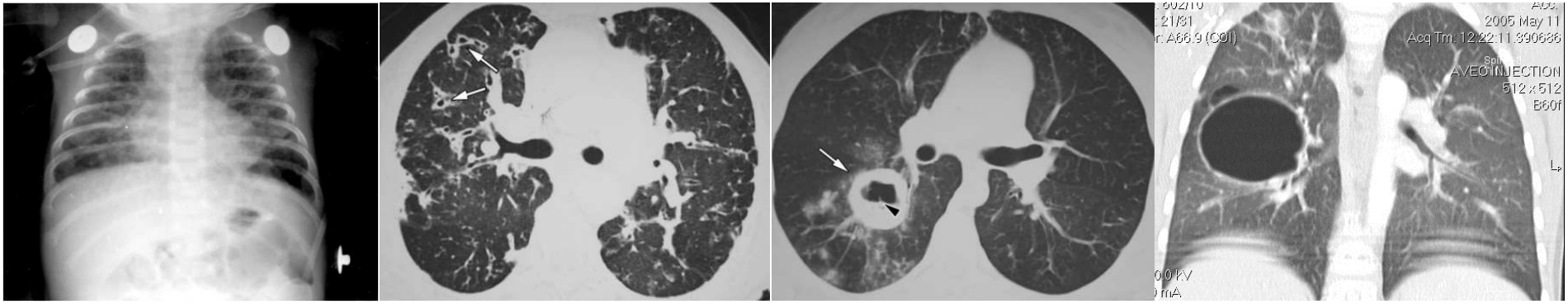
Susceptibilité génétique aux infections



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INSERM U980, Faculté Necker

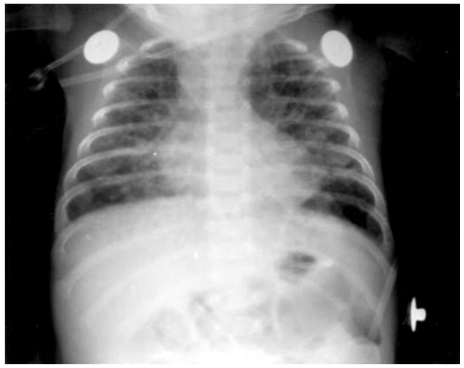
Classification PIDs

1. Combined T and B cell immunodeficiencies
2. Antibody immunodeficiencies (B cell immunity)
3. Phagocytes deficiencies (PN, mono, Macro, DC)
4. Opsonisation deficiencies (complement)
5. Defects in innate immunity
6. Diseases of immune dysregulation
7. Auto-inflammatory disorders

(Notarangelo et al. JACI 2009)

Defects of Cell-Mediated Immunity
clinical signs

- Recurrent severe infections (bacteria, viruses, fungi, parasite)
  - Often caused by opportunistic pathogens *(P.jirovici, BCGitis…)*
- Failure to thrive – particularly prominent
- Chronic diarrhea
- Graft versus Host Disease (materno-foetal or after blood transfusion).

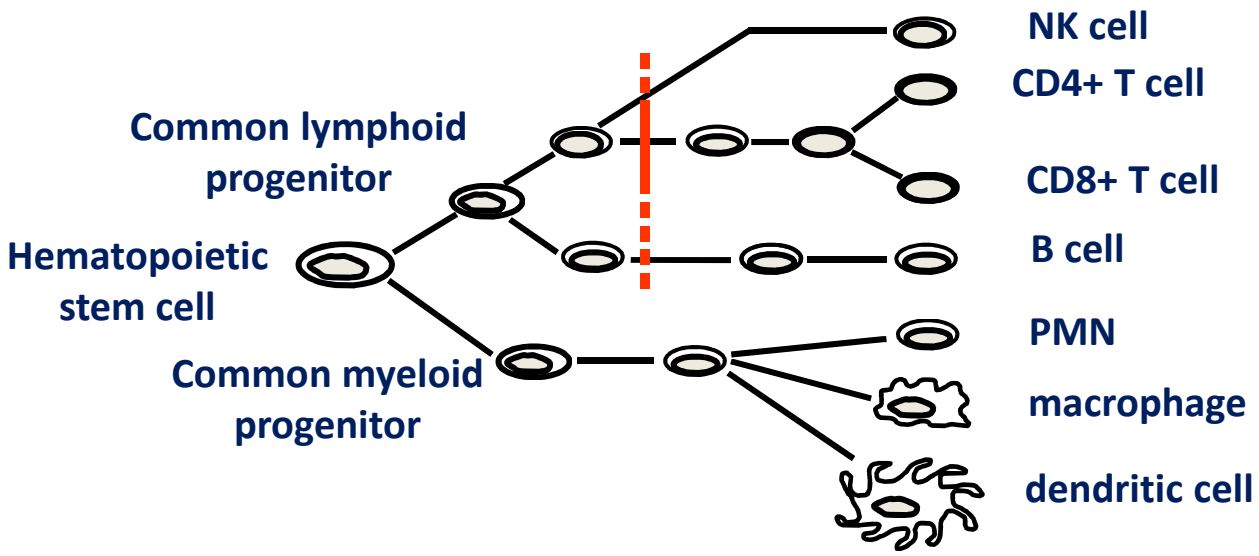


(T. Niehues et al Clin Imm 2010)

Combined immunodeficiency

T lymphopenia cell deficiency with or without B and/or NK cells

- **If T cells < 500 cells/mm3 : Severe combined immunodeficiency**
- **Usually, diagnostic during chilhood**



CID and genetic defects

Up 60 (25 for SCID) genes to be studied (expanding year after year):

1. **Enzymatic disorders:** ***ADA, AK2, PNP***
2. **Cytokine signaling pathway defects:** ***IL2RG, JAK3,IL7RA, IL2RA,***
3. **VDJ disorders:** ***RAG1, RAG2, DCLRE1C, DNAPKC, DNA ligase IV, NHEJ1***
4. **TCR signaling pathway disorders:** ***CD45, CD3D, CD3E, CD3Z,CD3G, CD8A, ZAP70, LCK, ORAI1, STIM1, MAGT1, TRAC, UNC119***
5. **Thymus differentiation defects:** ***CORO1A, TBX1, FOXN1***
6. **Switch defects:** ***TNFSF5, TNFRSF5***
7. **Class II and I deficiencies:** ***C2TA, RFXANK, RFX5, RFXAP, TAP1, TAP2, TAPBP***
8. **Others:** ***STAT5B, ITK, CD27, DOCK8, MST1/STK4, WASP, FOXP3, IKBA, RHOH, CARD11***
9. **DNA repair defects:** ***ATM, MRE11, NBS1, BLM, DNMT3B, ZBTB24, PMS2, RNF168, RMRP, SMARCAL1***
10. **Dyskeratosis:** ***DKC1, TERC, TERT, NOP10, NHP2, TIN2, C16orf57, TCAB1***

Humoral Defects

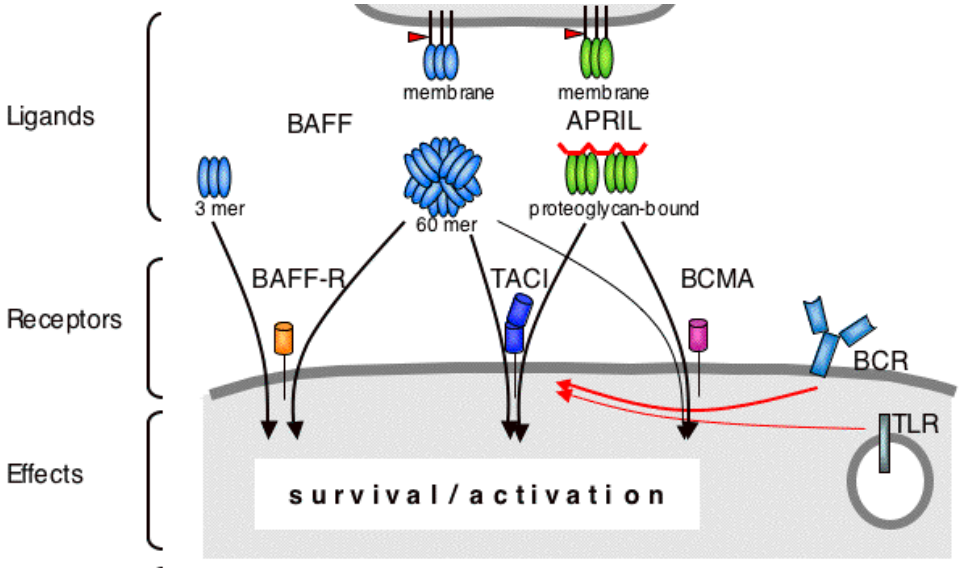
- **X-linked agammaglobulinemia (XLA) = Bruton**
- **AR agammaglobulinemia *(μ heavy chain, l5, Iga, Igb, BLNK)***
- **Switch deficiency syndromes (AID and UNG)**
- **Common variable immunodeficiency (CVID)**
- **Selective IgG subclass deficiency**
- **Specific polysaccharide antibody deficiency (SPAD)**

Clinical signs

Bacterial infections (lung and ENT).
Bronchiectasis, sinusitis
Chronic Gastroenteritis
+/-Autoimmune Disease

Commun Variable Immunodeficiency (DICV)

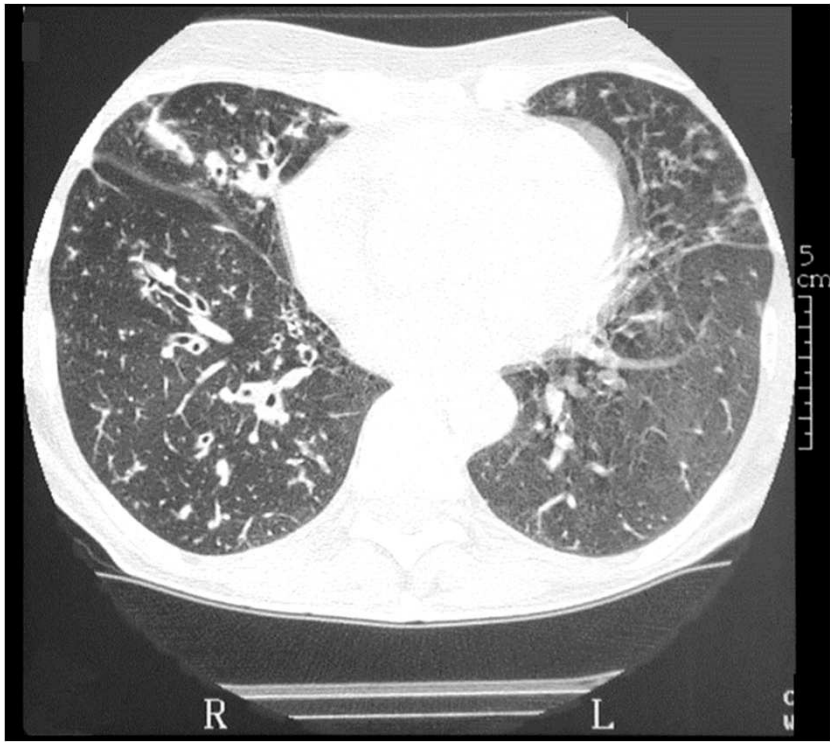
- **Frequency 1/30-50 000, M = F, 15 to 30 years, family forms: 20%**
- **Heterogeneous syndrome with lack of Ig production :**
  - **Failure to produce Ig: IgG + another IgA or M)**
  - **Presence of B cells > 1%**
  - **Exclusion of other known genetic defects: XLA (Bruton), Thymoma (Good)**
    Hyper-IgM (CD40L, CD40, AID, UNG)
    XLP (Purtilo)
- **Genetic etiologies: rare, ICOS, TACI, BAFF-R, CD19, CD20, CD81**



Commun Variable Immunodeficiency (DICV)

- **Infections:**
  - **ENT and lung (bronchiectasia)** ***(H. influenzae , S. pneumoniae, S. aureus)***
  - **Sepsis (*Pseudomonas , S. pneumoniae, H. influenzae)***
  - **Chronic diarrhea (*Giardia lamblia*, Salmonelles, *Campylobacter)***

- **Proliferation**
  - **lymphoid proliferations**
  - **granulomatosis**
  - **cancer**
- **Autoimmunity**
  - **cytopenia**
  - **rheumatoid**



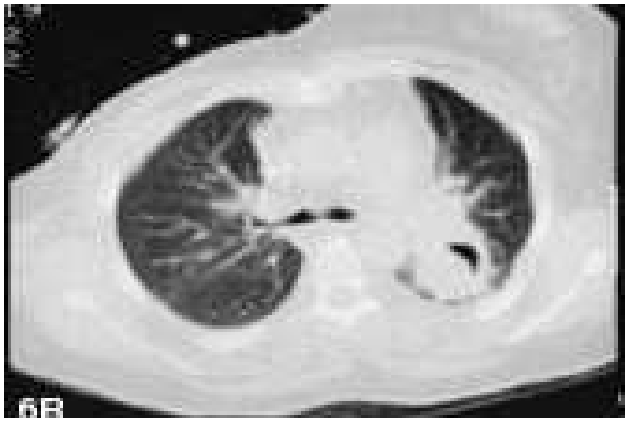
DICV et manifestations cliniques

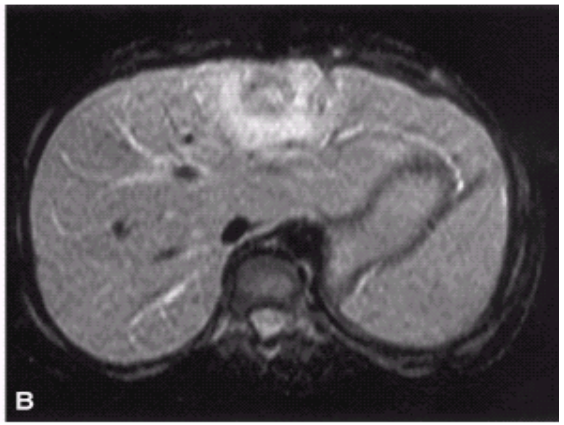
(Chapel et al. Blood 2008, n= 389 ESID)

Chronic granulomatous disease (CGD)

- Inherited disorder of phagocytic cells
- Frequence: 1/220 000
- Recurrent tissular bacterial (*S.aureus,* enterobacteria..)

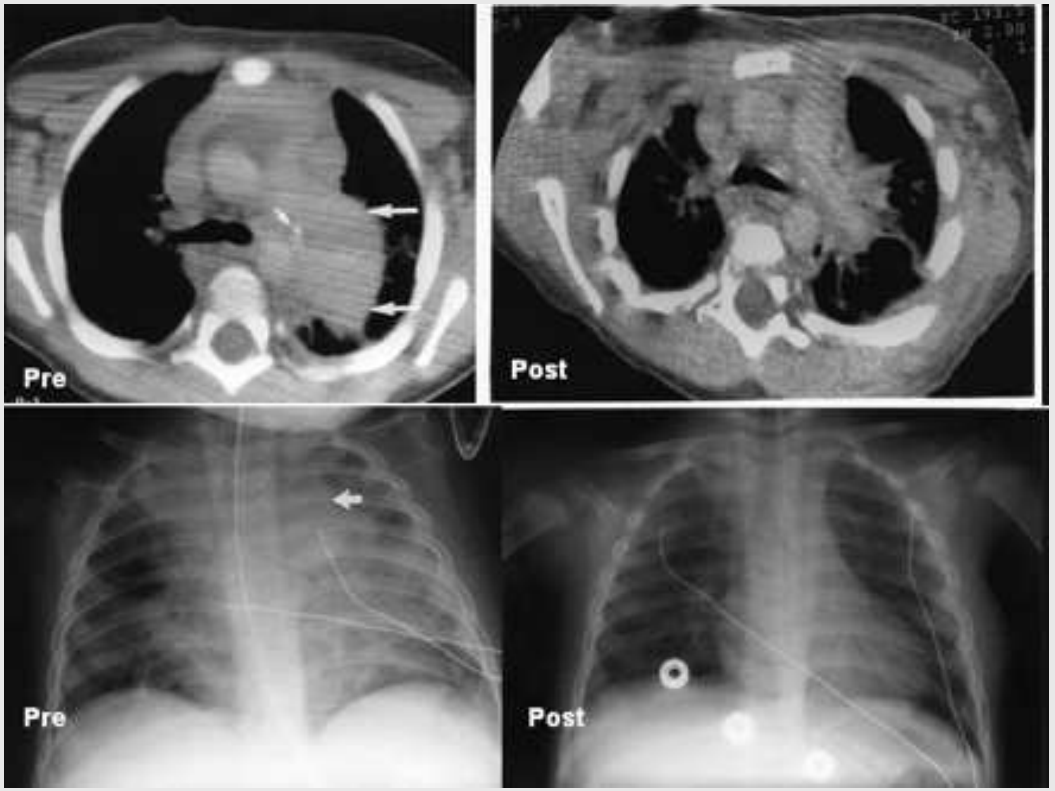
  and fungal (Aspergillosis+++, *C. albicans*+) infections
- Associated Symptoms
  - Excessive Granulomata – often in GI tract (IBD like diseases)
  - Chorioretinitis
- Treatment (Antibacterial and antifungal prophylaxis) +/- HSCT





Chronic granulomatous disease (CGD)

- **Pneumonia: *Aspergillus* (41%), bacteria**
- **Abscess: - Subcutaneous: *Staphylococcus spp* (27%)**
  - **Hepatic: *Staphylococcus spp* (50%)**
  - **Lung: *Aspergillus* (23%)**
  - **Brain: *Aspergillus (*58%)**
- **Adenitis: *Staphylococcus spp* (26%), *Salmonella*, *Actinomyces*, *BCG***
- **Osteomyelitis: *Serratia* (29%), *Aspergillus* (22%)**
- **Septicaemia: *Salmonella* (18%), *Burkholderia* (12%), *Candida* (11%)**
- **Meningitis: *Candida* (20%)**
- **Aspergillus is responsible for 1/3 of death**


Pre
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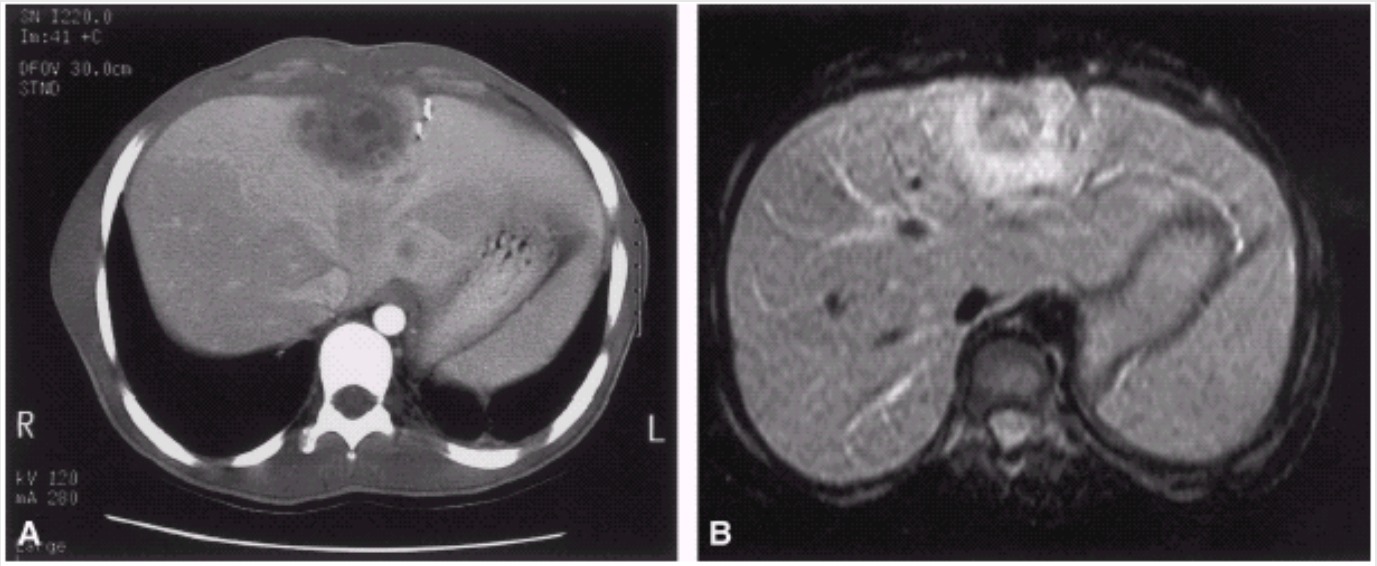
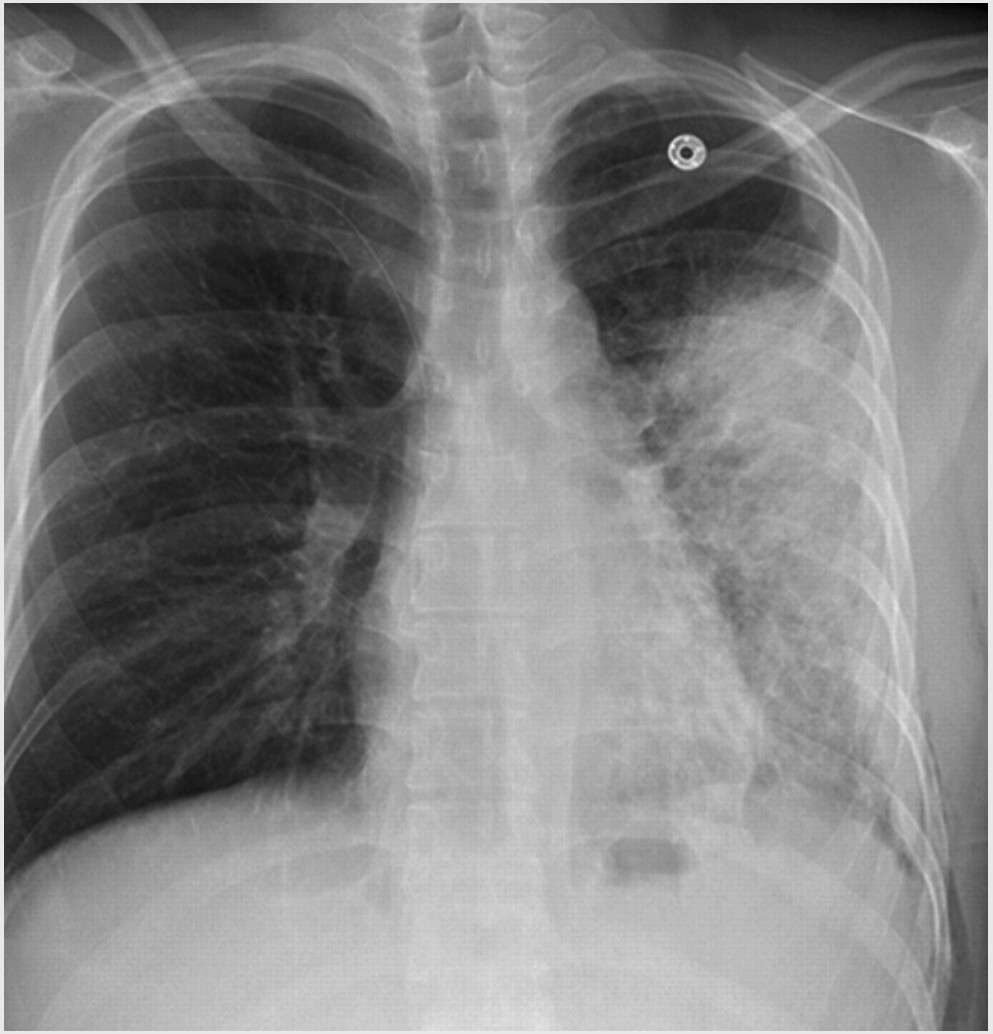

R
L
A
B

—22-year-old man with history of chronic granulomatous disease presenting with fever and productive cough for 10 days.



Godoy M C B et al. AJR 2008;191:1570-1575

5 genes: XR (*CYBB*, gp91phox) = 67%

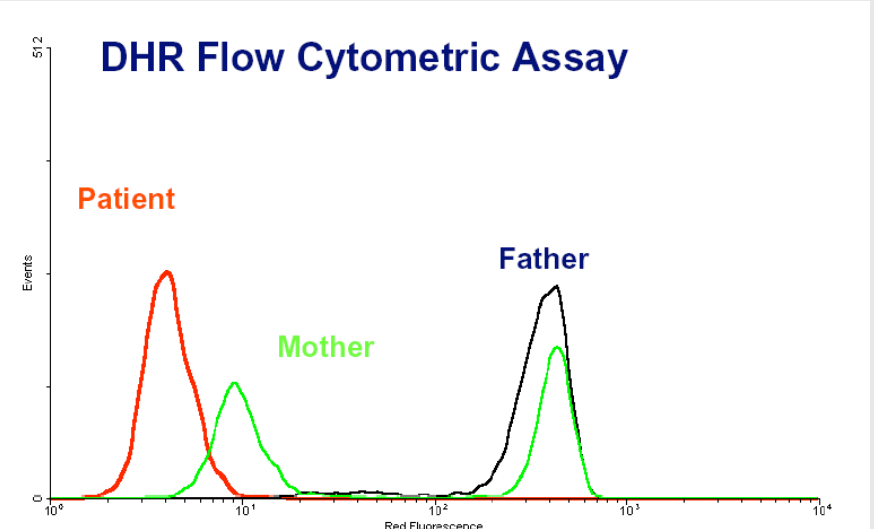
AR (*NCF1*, p47phox) = 33%

AR (*CYBA*, p22phox) = 5%

AR (*NCF2*, p67phox) = 5%

AR (*NCF4*, p40phox)= 1 pt

Nitroblue tetrazolium reduction (NBT)



NEJM

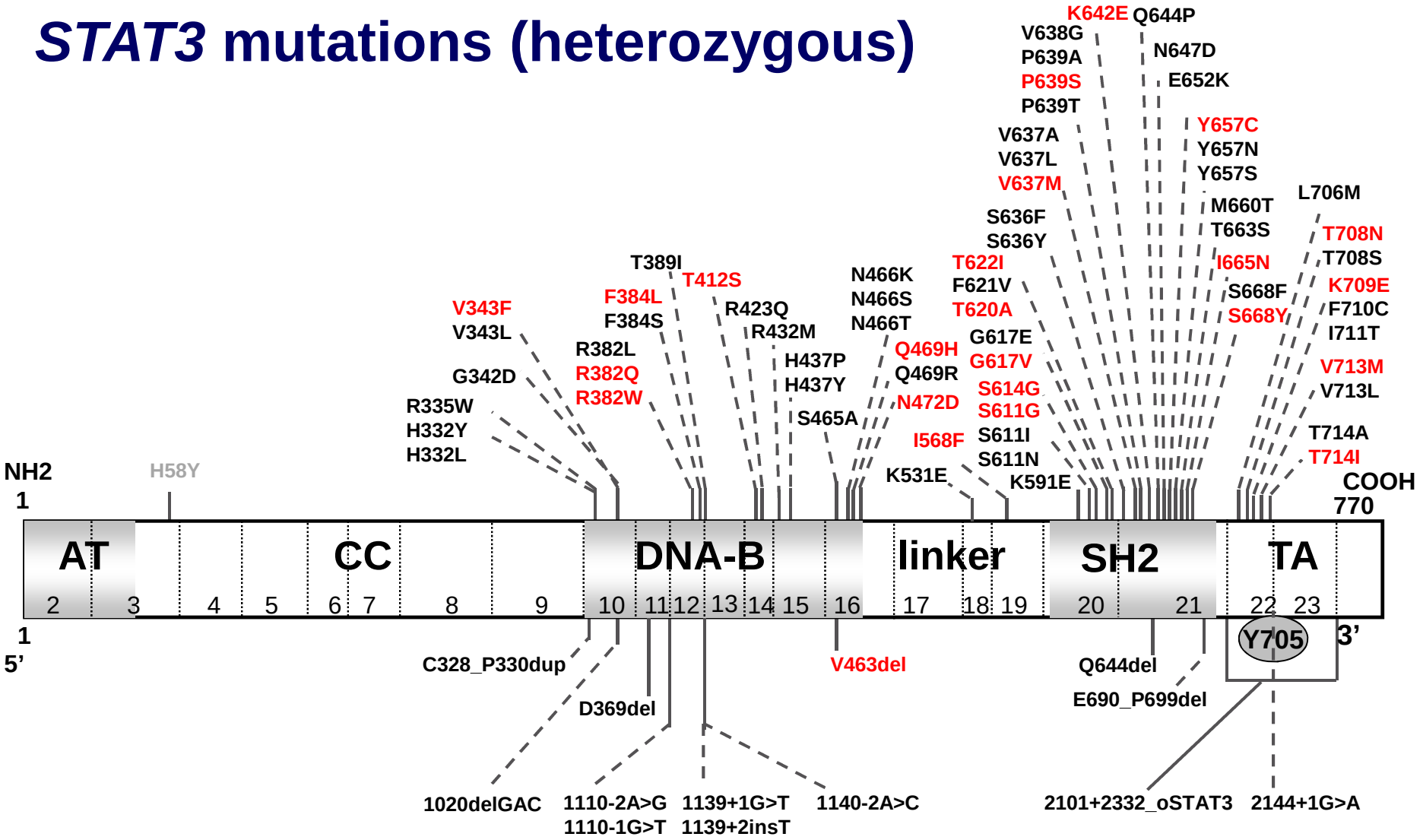
HyperIgE syndromes - introduction

- **HyperIgE (>2000IU/ml in adult) and recurrent infections**

- **Genetic heterogeneity:**
  - **Autosomal dominant form**
    - **AD-HIES or Job (Davis et al Lancet 1966) or Buckley syndrome (Buckley et al. 1972 Pediatrics)**
  - **Autosomal recessive forms**
    - **TyK2 genetic defect (one patient) (Minegishi et al. 2006, Immunity)**
    - **AR-HIES + T cellular immunodeficiency (Renner et al. 2004, J Ped)**

    ⇒ DOCK8 deficiency (Zhang et al. 2009, NEJM)

STAT3 mutations (heterozygous)



n=60 French patients, 24 mutations, 13 news

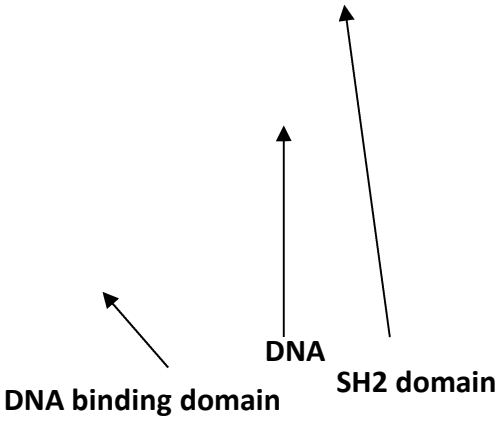
55% mutation located in the DNA binding domain (DBD),

32% in the SH2 domain,

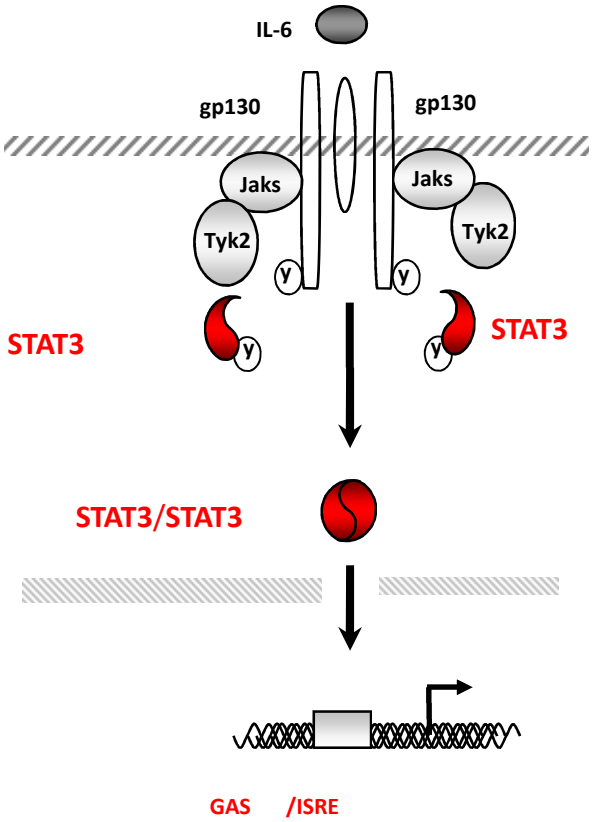
2% in the linker domain and 10% in the TA domain (Chandesris et al. 2012 Medicine)

STAT3 (transcriptional factor)

- **STAT3 is involved in responses to multiple cytokines:**
  - IL-6 receptor superfamily (gp-130) :
    IL-6, IL-11, IL-27, IL-31,
    OSM, CNTF, LIF and CT-1
  - IL-10
  - IL-2 family cytokines: IL-2, 7, 9, 15 and 21
- **STAT3 nuclear translocation**
  Acute-phase protein genes (APP genes)



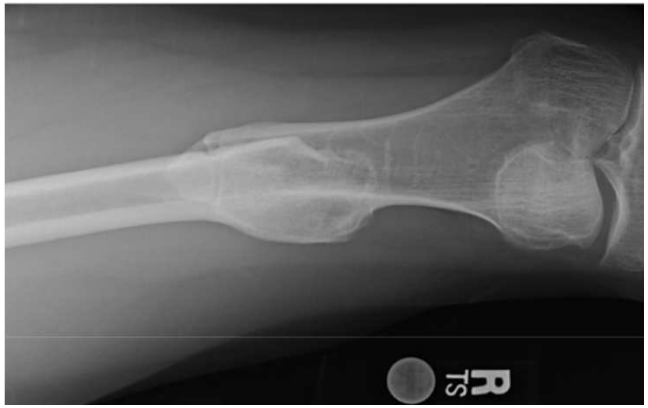
(Becker et al. 1998, Nature)



STAT3 deficiency-clinical phenotype

(B.Grimbacher, NEJM 1999)

Dysmorphia variable



Hyperextensibility

Retained primary teeth

Fractures
+ Osteoporosis

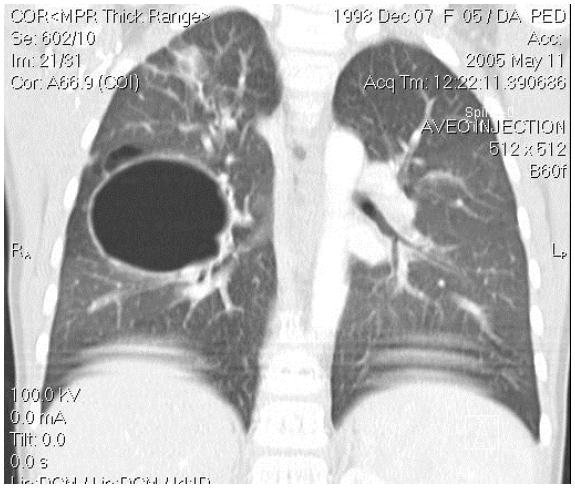
(JL Stefan, C. Thomas)

STAT3 deficiency-clinical phenotype

eosinophilic spongiotic dermatitis

recurrent cold skin abscess

(C. Bodemer)



Candidiasis (80%)

Recurrent bacterial Pneumonia and II cyst Formation (Asperillosis)

(Eberting, et al. Arch dermato, 2004)

Bacterial pneumonia 92% of patients

Mean age of first pneumonia = 39.5 months (range 0 to 192 months)

3 episodes per patient (range 1 to 30 episodes)

1 SDRA woman 20 yo

1 child of 14 months died (*S.pneumoniae*)

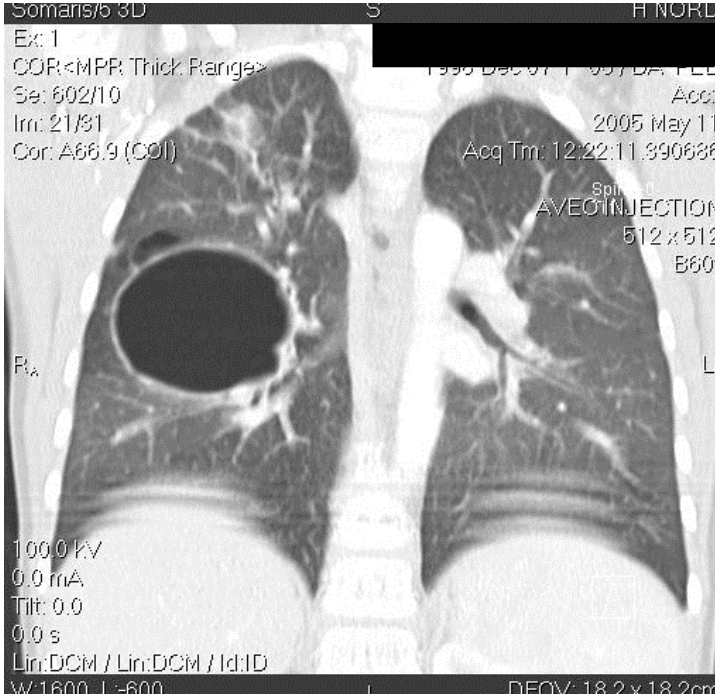
Acute pneumonia Germs :

***S. pneumoniae* 30%**

***S. aureus* 29%**

***Haemophilus influenzae* 13%,**

Lung-complications



Sequellae secondary to previous bacterial infections = 68% of patients:

mean = 21 years (range 1 to 45 years)

- Bronchiectasis in 66% of patients

- Pneumatoceles in 53% of patients

- Broncho-pleural fistulas, Hemoptysis, pneumothorax, Tracheal stenosis .

Lobectomies (range 1 to 3) in 22% of patients

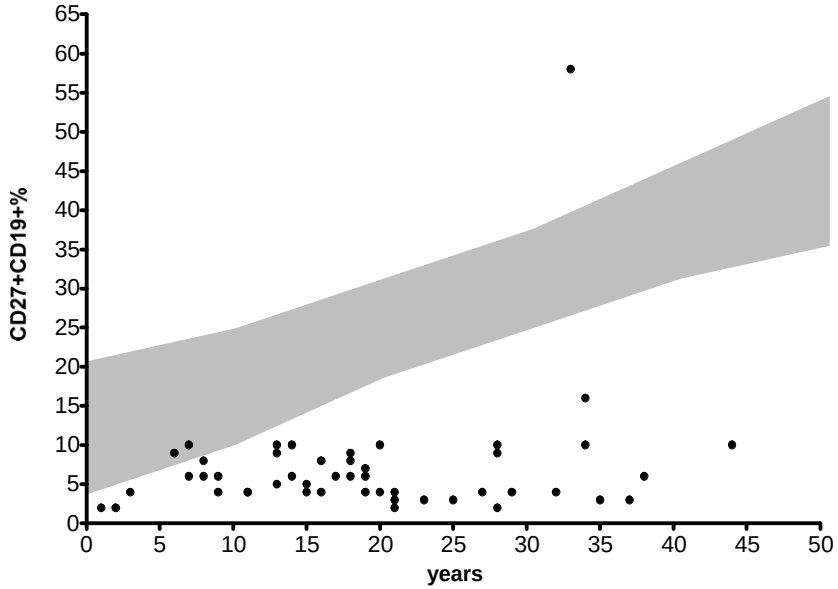
median age of 10 years (range 1 to 17 years)

***Aspergillus spp.*-related diseases were observed in 22% patients : Aspergilloma : 4 patients**

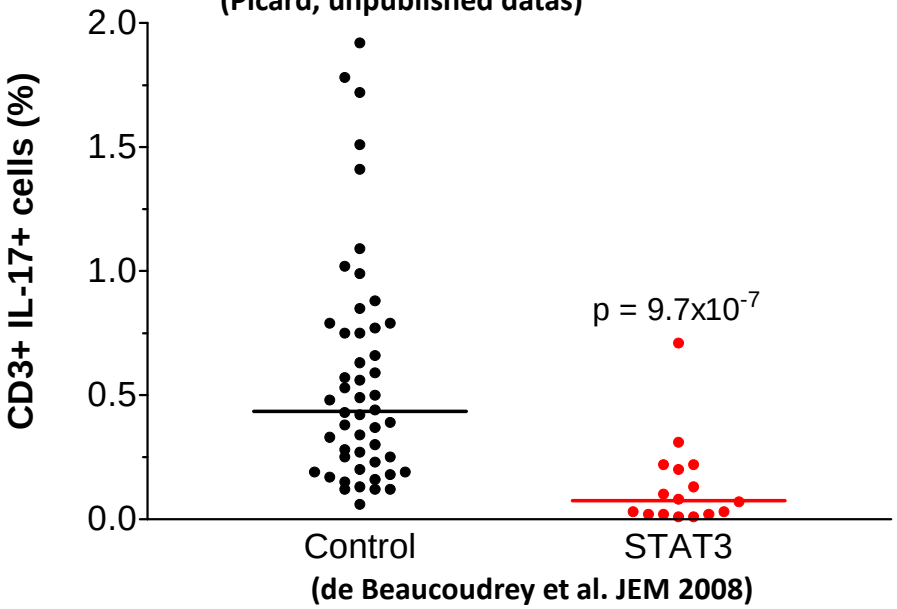
12.7 years (range 10 to 16 years)

STAT3 deficiency-Immunology

- Normal phagocytic explorations
- PEo > 600 cell/µl : 75% patients
- B immunity :
  - B memory cell lymphopenia
  - IgE : Increased in all patients
  - Normal or ↑ of IgG, A and M
- T immunity:
  - Th17 lymphopenia
  - TTL : normal



(Picard, unpublished datas)



(de Beaucoudrey et al. JEM 2008)

Summary immunology-STAT3+/-deficiency

- **Bacterial susceptibility of STAT3+/- deficient patients:**
  - **B cell memory deficiency (impairment of IL-21 signalling pathway)**
  - **Defect in differentiation of naive B cells in plasma cells (IL-21 sig. pathway)**
  - **Defect in inflammatory response (impairment of IL-6 signalling pathway)**
  - **TH17 lymphopenia**

- **Skin & mucosal immunity to *C. albicans* is controlled by IL-17-producing T cells and cytokines IL-17A, IL-17F, IL-22.**

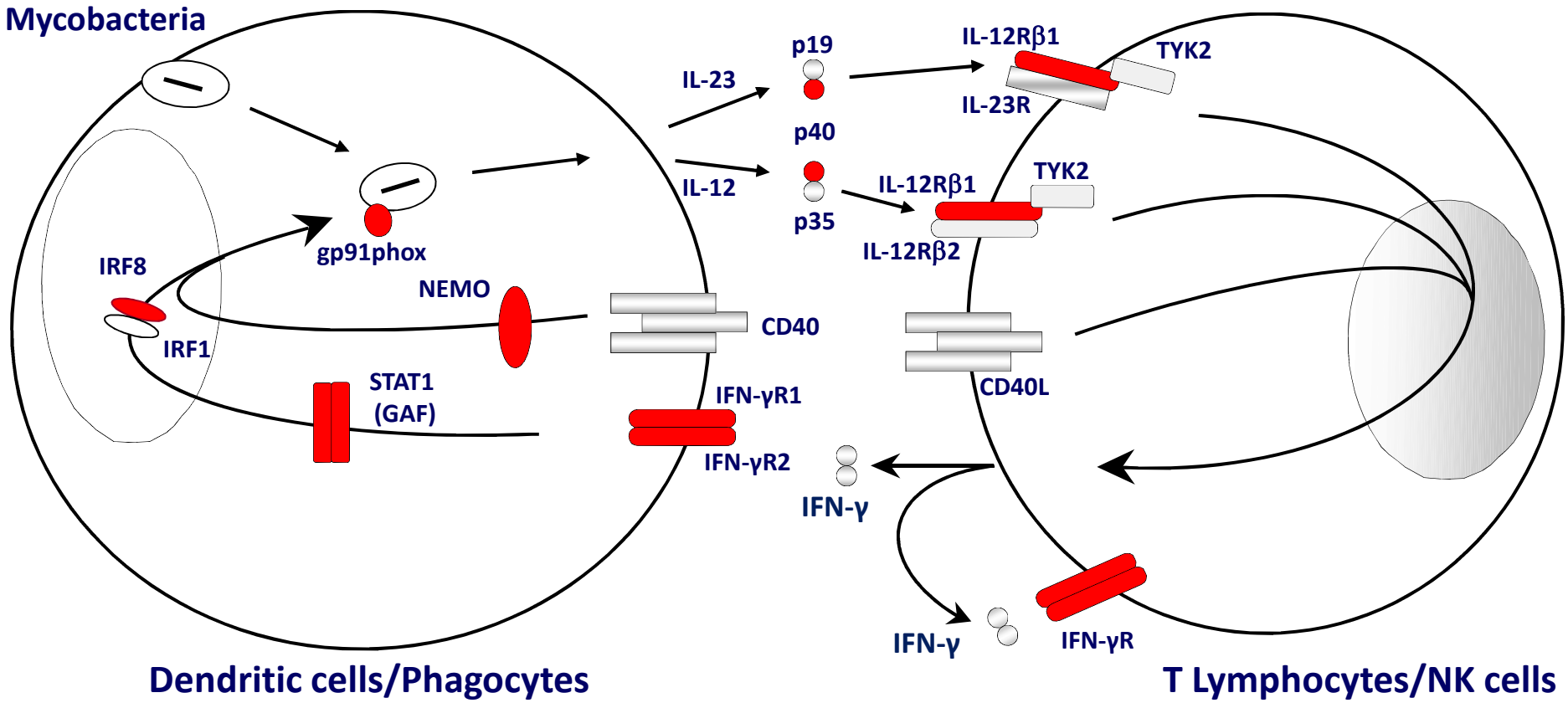
- **Pneumocyst formation ⇒ Role of IL-6-dependent gp130/STAT3 pathway in repair of the brochiolar epithelium**

(mice specific deletion of Stat3 in lung epithelial cells, Kida et al. Am J Physiol Lung Cell Mol Physio 2005)

Conclusions

- **Infections are the main clinical signs of primary immunodeficiency**
- **Several PIDs developped pneumonia :**
  - **Interstial pneumonia →CID**
  - **Reccurent bacterial infection →B cell deficiency**
  - **Fungal or bacterial abscess → CGD**
  - **lung complications such asbronchiectasia or pneumatoceles**

Mendelian susceptibility to mycobacterial disease:
8 genes so far



First genetic etiology discovered in 1996: Newport et al. *N Engl J Med* 1996.

Jouanguy E, et al. *N Engl J Med* 1996.

Courtesy of S.Boisson-Dupuis

Inherited disorders of the IL-12/23-IFNγ loop

Gene	Cellular exp.	Deficiency	Inheritance	Frequence
IFNGR1	- + + +++	Complete Complete Partial Partial	AR AR AR AD	~30%
IFNGR2	- + +	Complete Complete Partial	AR AR AR	< 5%
STAT1	- + +	Complete Partial Partial	AR AD ADomissive	< 5%
IL12RB1	- +	Complete Complete	AR AR	~40%
IL12B	+	Complete	AR	~14%
NEMO	+	Partial	XR	<3%
CYBB	+	Partial	XR	< 2%
IRF8	- +	Complete Partial	AR AD	< 2%

Inherited disorders of the IL-12/23-IFNγ loop: IFN-γR1 deficiency

IFN-γR1 deficiency	AR Complete deficiency (n=22)	AD Partial deficiency (n=38)
IFN-γ signalization	none	residual
Asymptomatic pts	no	yes, 8%
BCG infection	100% of vaccinated	73% of vaccinated
EM infection	77%	82% (mostly, *M. avium*)
Salmonella infection	14%	5%
Infection localization	Mostly disseminated	Bones (80%)
Mortality	64%	5%

(Dorman et al. Lancet 2004)

Inherited disorders of the IL-12/23-IFNγ loop: IL-12Rβ1 and IL-12p40 deficiencies

	AR IL-12Rβ1 deficiency (n=141)	AR IL-12p40 deficiency (n=49)
Cellular phenotype	No response to IL-12	No IL-12 production
Asymptomatic pts	Yes, 6%	Yes, 10%
BCG infection	78% of vaccinated	97.5% of vaccinated
EM infection	16%	4%
Salmonella infection	40%	22%
Infection localization	Lymph nodes +/- skin (vasculitis)	Lymph nodes
Mortality	29.7%	28.6%

(de Beaucoudrey et al. Medicine 2010)

(Prando et al. Medicine in press)

Mendelian susceptibility to mycobacterial diseases

- ✓ Importance of IL-12/23-IFNγ signaling pathway in anti-mycobacterial immunity
- ✓ Correlation signaling by IFNγ and disease severity

AR IL-12Rβ1 deficiency is also a genetic etiology of severe TB