Déterminants et causes du Lupus systémique

Pr. Laurent ARNAUD

Service de rhumatologie, Hôpitaux Universitaires de Strasbourg
Centre National de Référence des Maladies Systémiques Autoimmunes Rares

Mes liens d’intérêt…

Laurent ARNAUD a réalisé des activités de consulting pour : Alexion, Amgen, Astra-Zeneca, GSK, Janssen-Cilag, LFB, Lilly, Menarini France, Novartis, Pfizer, Roche-Chugaï, UCB.

Un peu d’histoire…

Pourquoi “lupus” ?

855

Herbernus

de Tours

(Eracle)

Hildric, dit-il, étoit affligé d'une de
ces ulceres qu'on nomme des loups, à

Première trace écrite de l'utilisation du mot "lupus"

855

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Hildric, dit-il, étoit affligé d'une de ces ulceres qu'on nomme des loups, à cauſe qu'elles mangent les chairs; & celui-

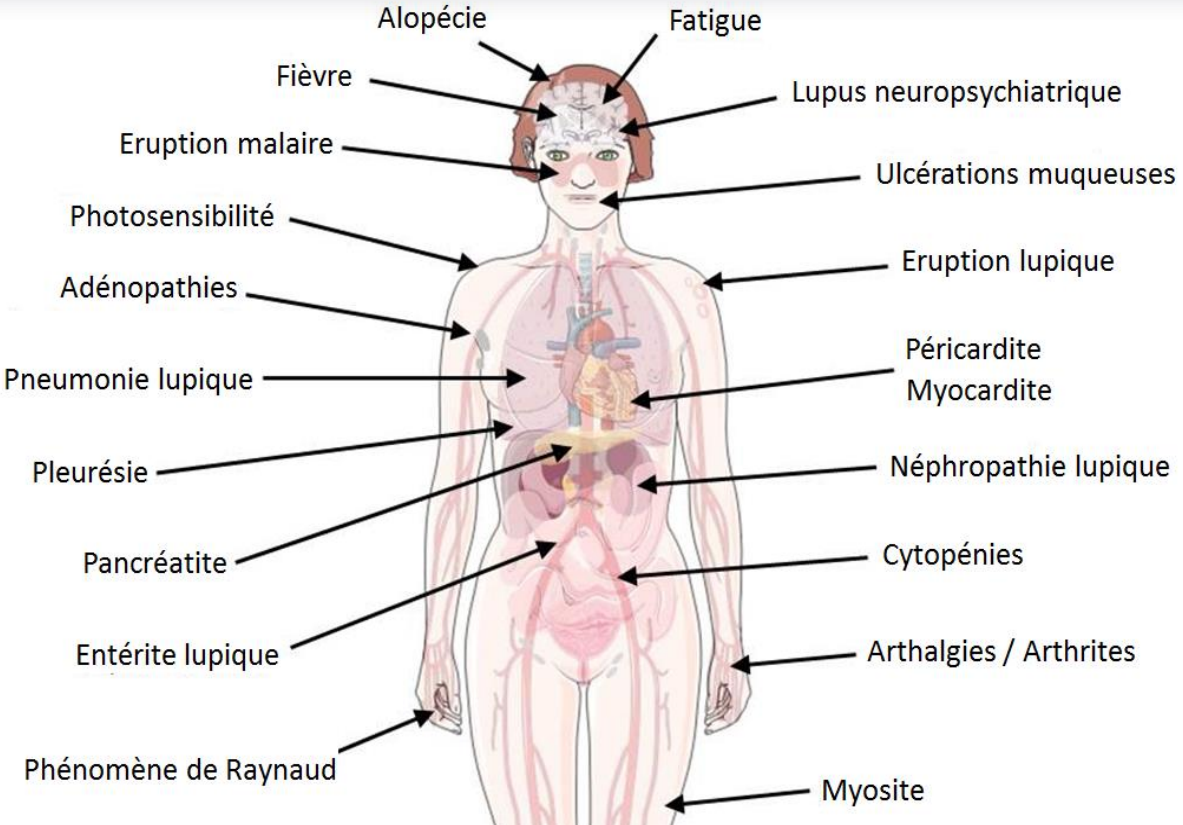
Le lupus systémique

Maladie autoimmune non spécifique d'organe

Caractérisée par:

- Manifestations cliniques polymorphes
- Présence d'anticorps anti-nucléaires (99%)
  - *anti-ADN natif (60-80%)*

Une maladie très polymorphe



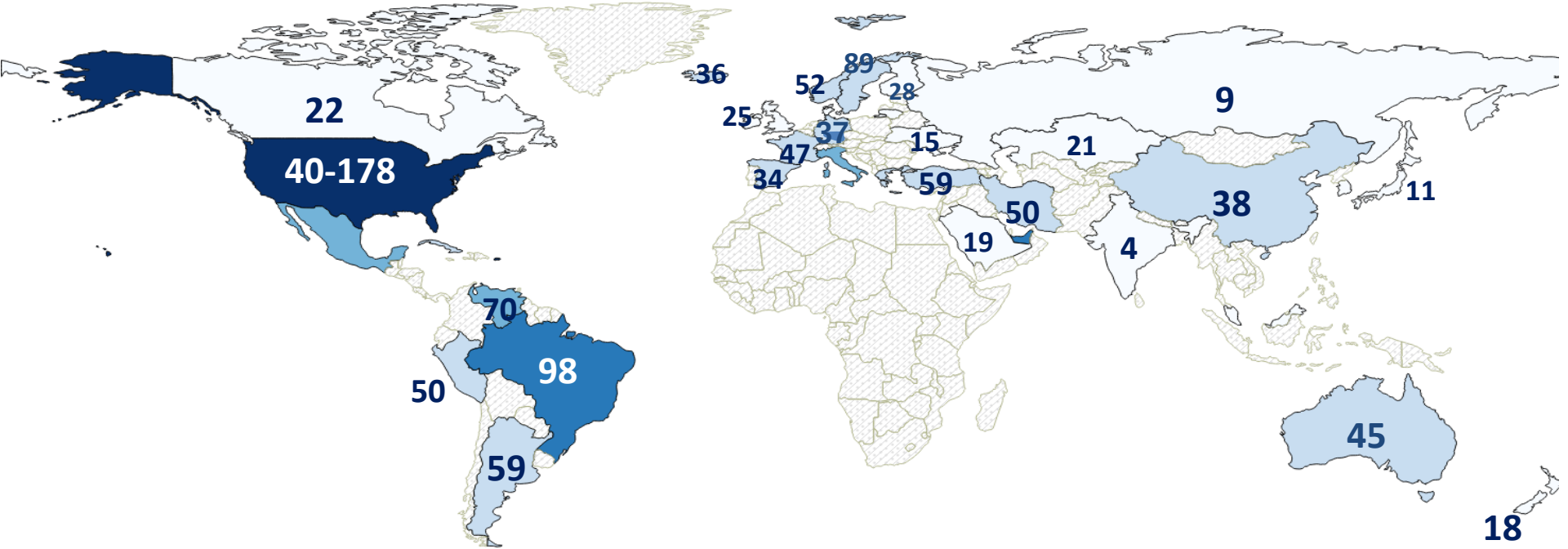
Arnaud & van Vollenhoven. **Advanced Handbook of SLE**. Edition Springer

Une maladie très polymorphe

Clinical manifestations	At first visit (%)	During follow-up (%)
Arthritis	69	84
Malar rash	40	58
Fever	36	52
Photosensitivity	29	45
Nephropathy	16	39
Serositis	17	36
Neuro involvement	12	27
Oral ulcers	11	24
Thrombocytopenia	9	22
Adenomegaly	7	12
Discoid lupus	6	10
Myositis	4	9
Hemolytic anemia	4	8
Pulmonary involvement	3	3

Cervera et al. Medicine 1993

Prévalence du lupus en Europe



Prevalence / 100 000

Arnaud et al. Autoimmun Rev 2014

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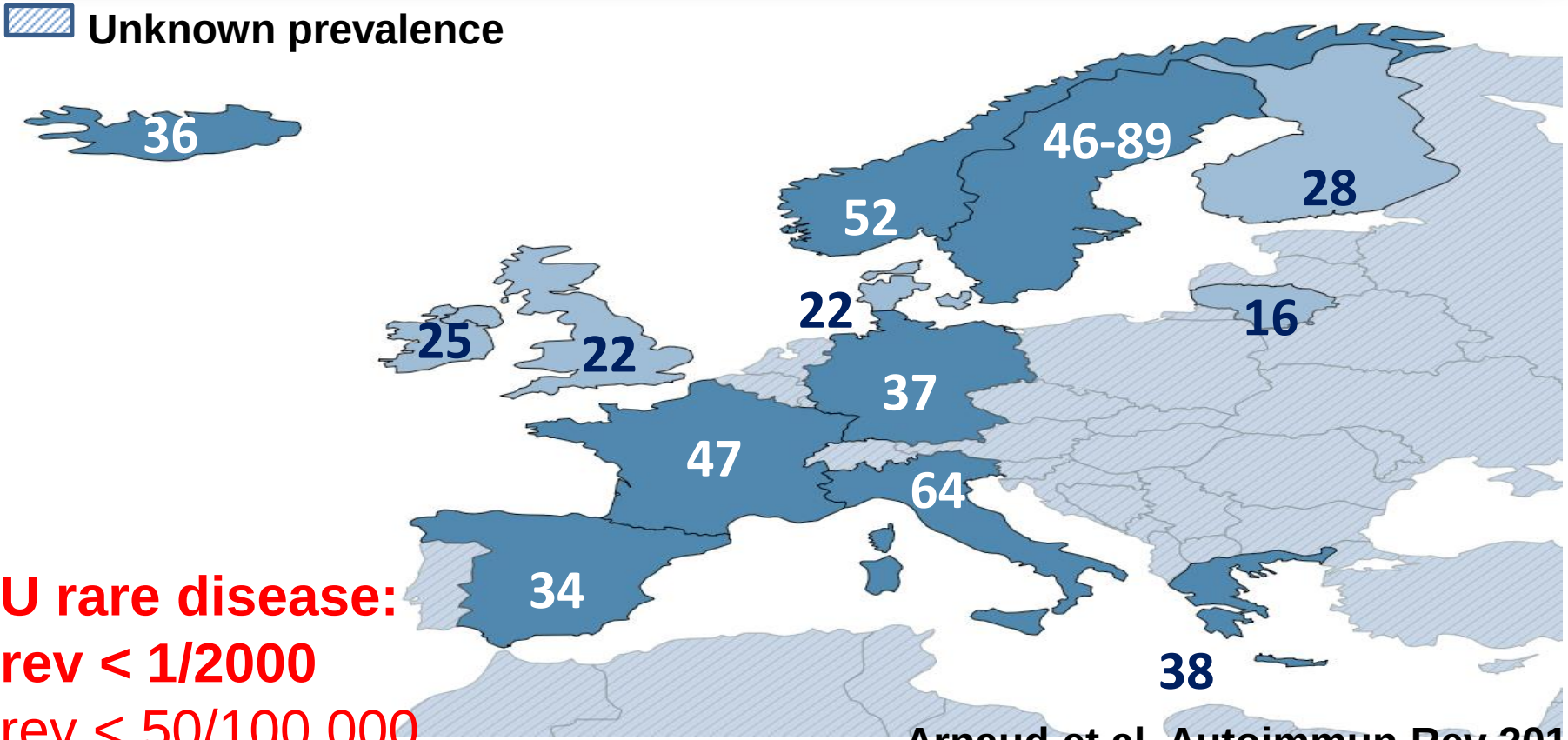
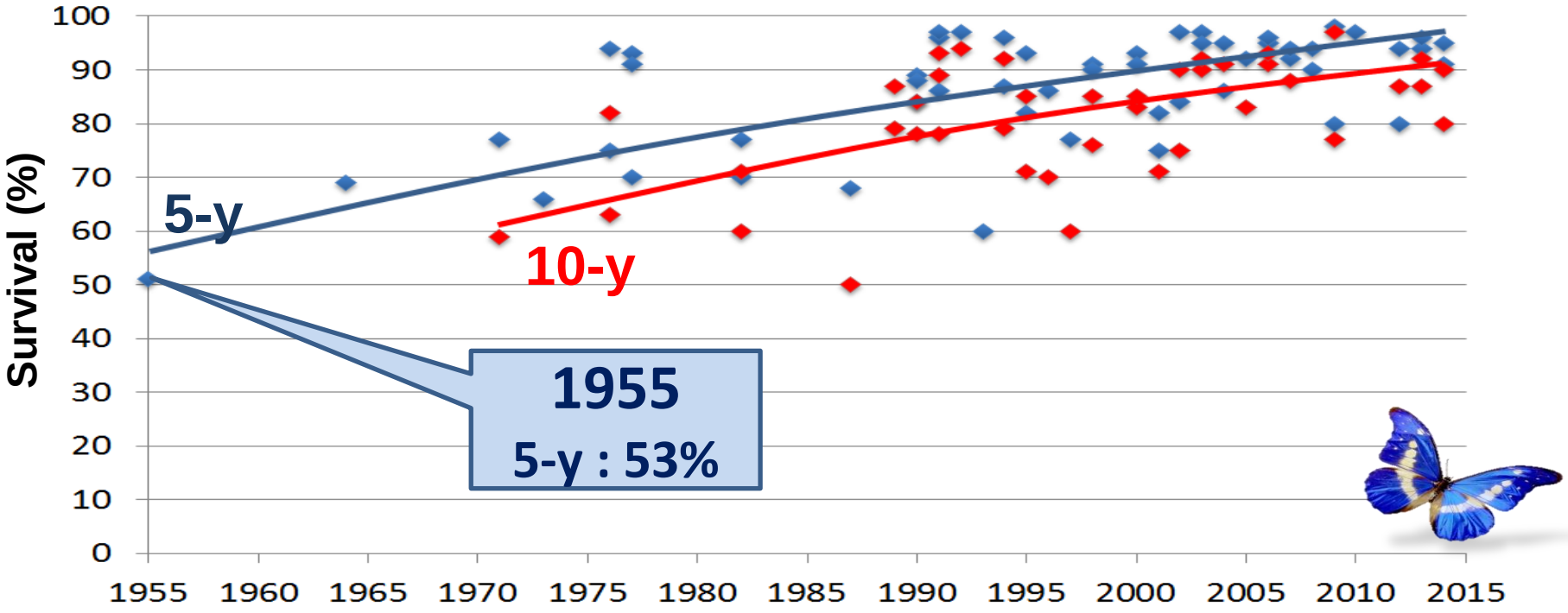


EU rare disease:
Prev < 1/2000
Prev < 50/100 000

Arnaud et al. Autoimmun Rev 2014

Survie et lupus

Amélioration+++ de la survie à 5 ans et 10 ans



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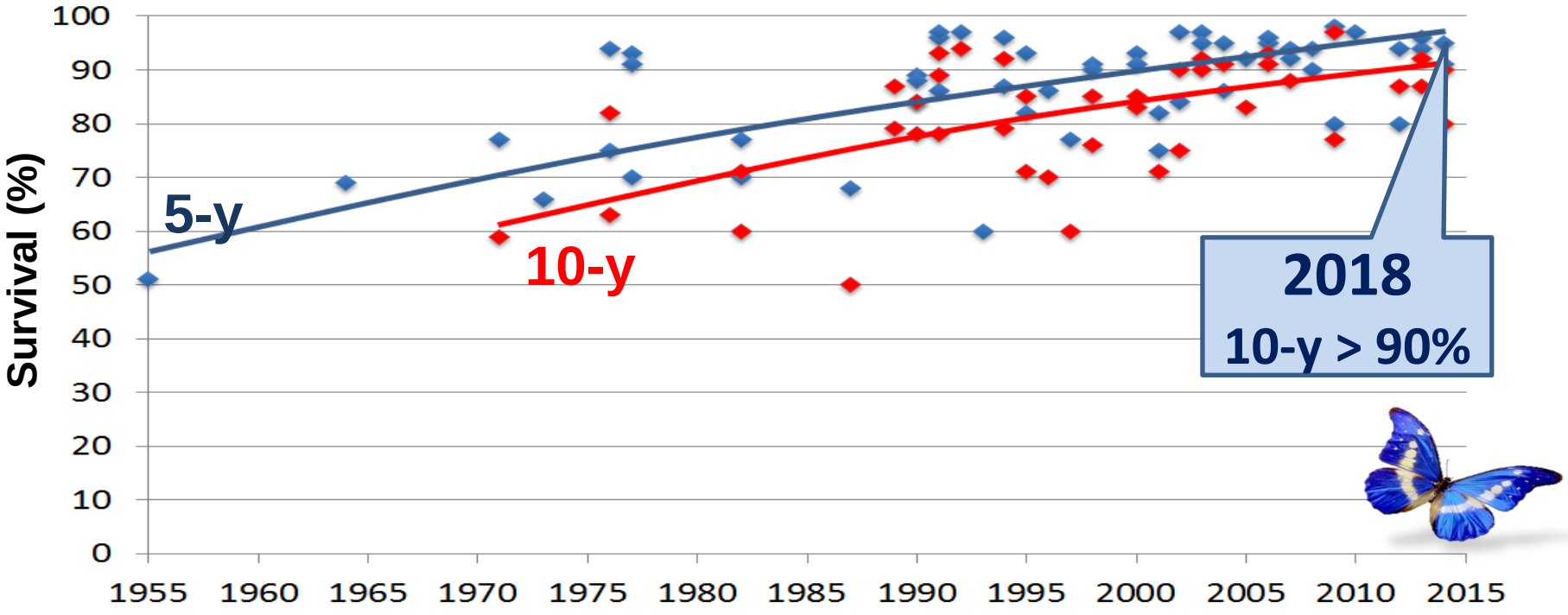


Les « causes » du lupus

Génétique

(>110 gènes impliqués*)

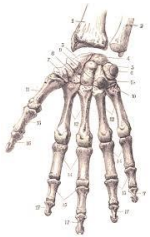
Hormones

(oestrogènes)

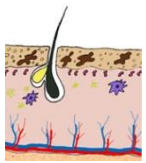
Environnement

(ex : UV, médicaments)

Système immunitaire

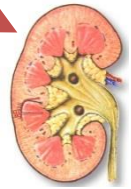


Articulations



Peau

Séreuses



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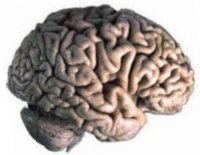
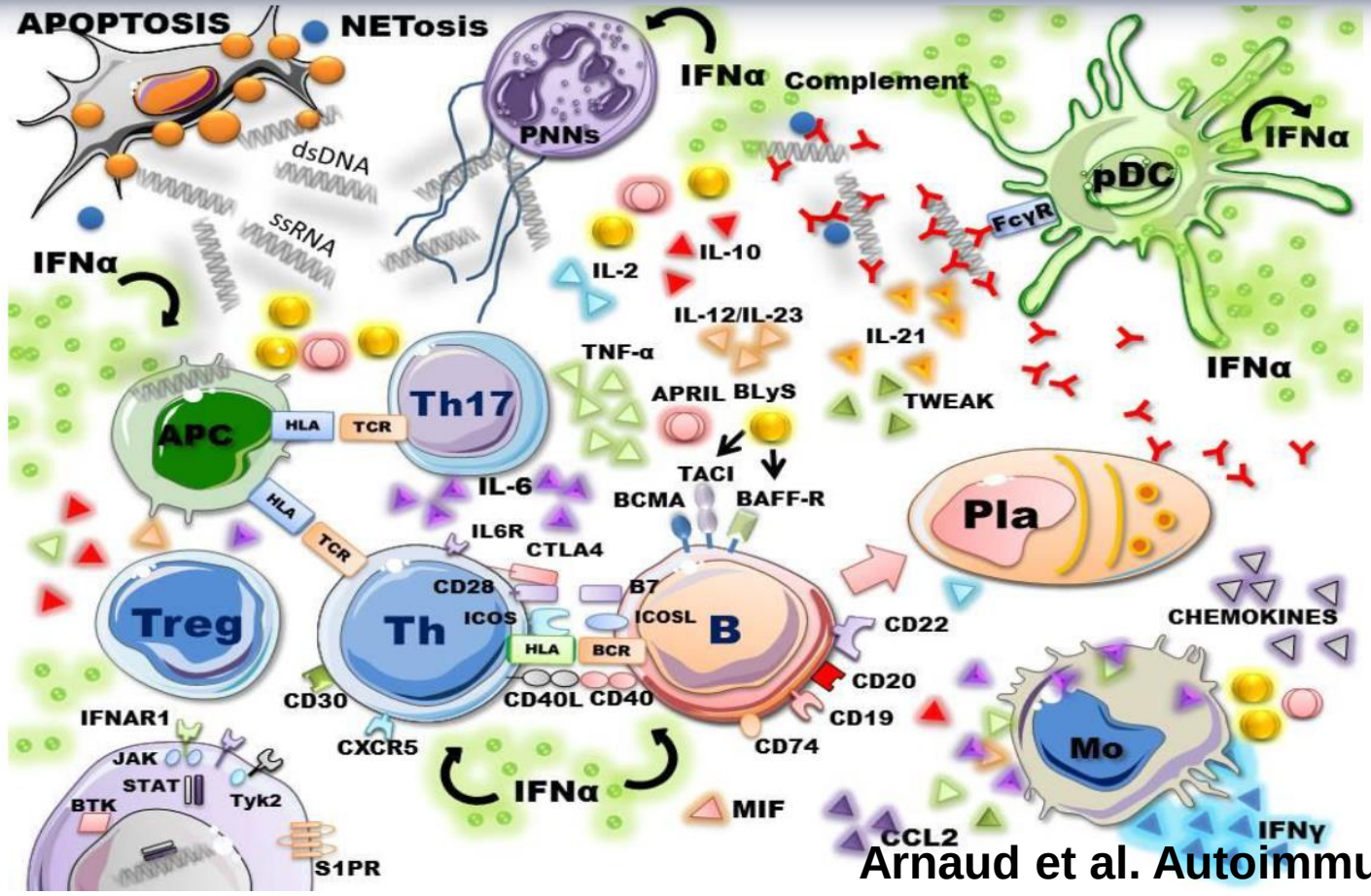


SNC

*Rares formes monogéniques

Une maladie auto-immune



Arnaud et al. Autoimmun Rev 2018

Les « causes » du lupus

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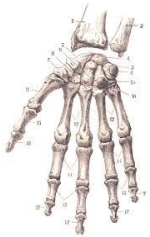
Système immunitaire



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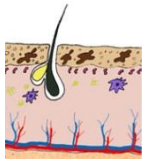

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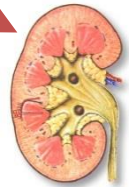

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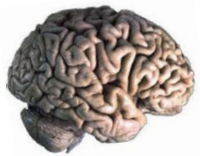

SNC

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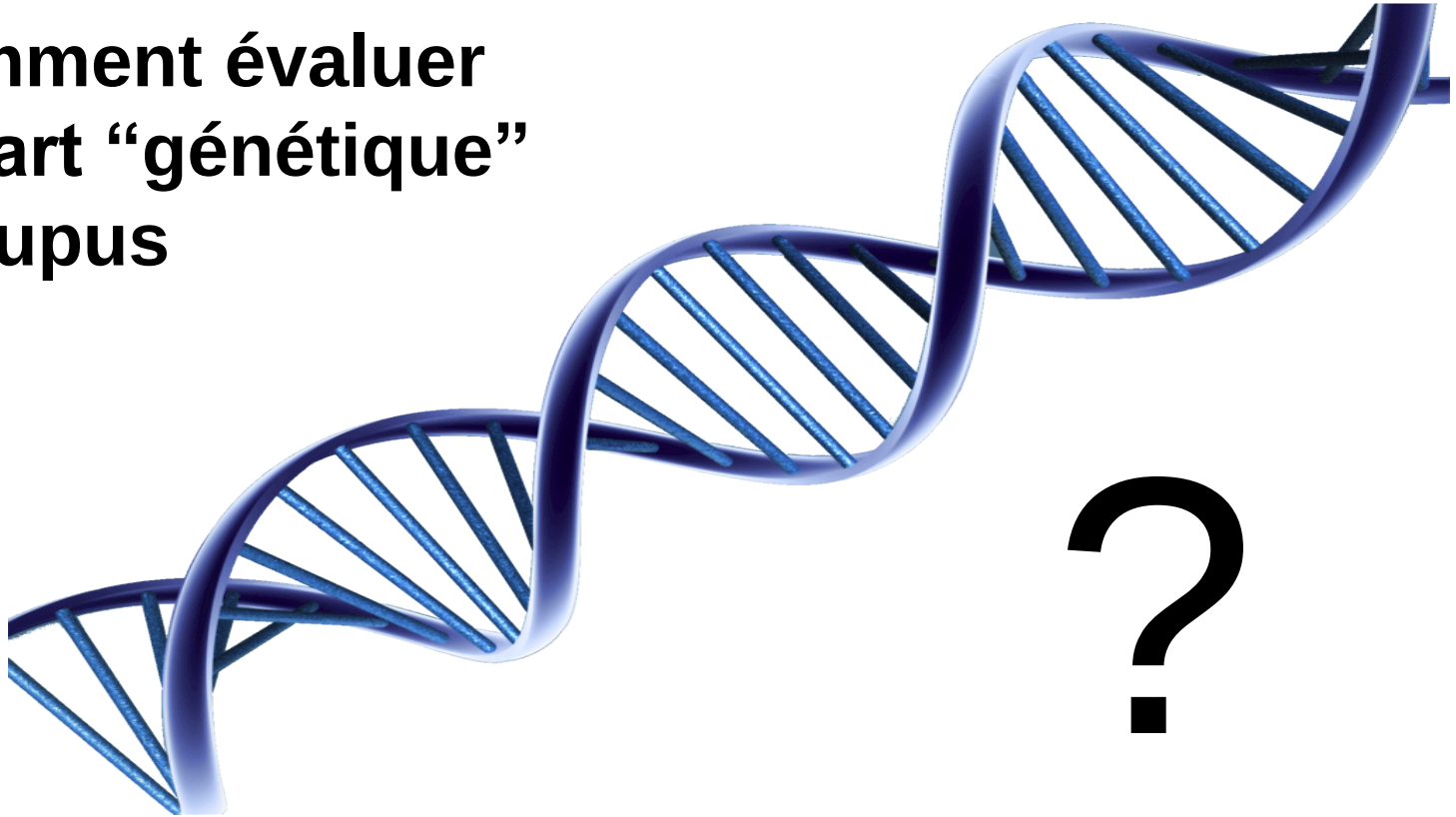
Les « causes » du lupus

Comment évaluer la part “génétique” du lupus



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Concordance entre jumeaux

Jumeaux homozygotes versus dizygotes

VS

Concordance in monozygotic twins: 14 - 57%

Block et al. Am J Med 1975
Deapen et al. Arthritis Rheum 1992

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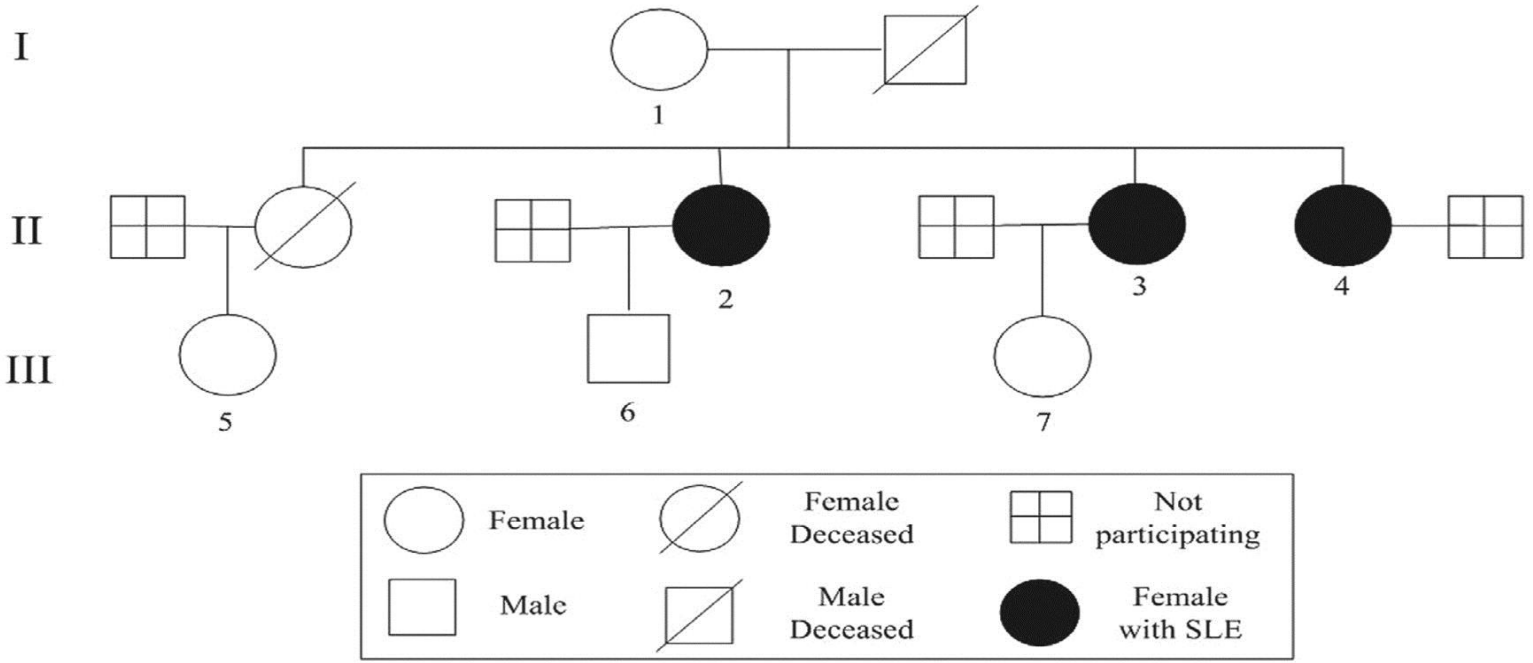
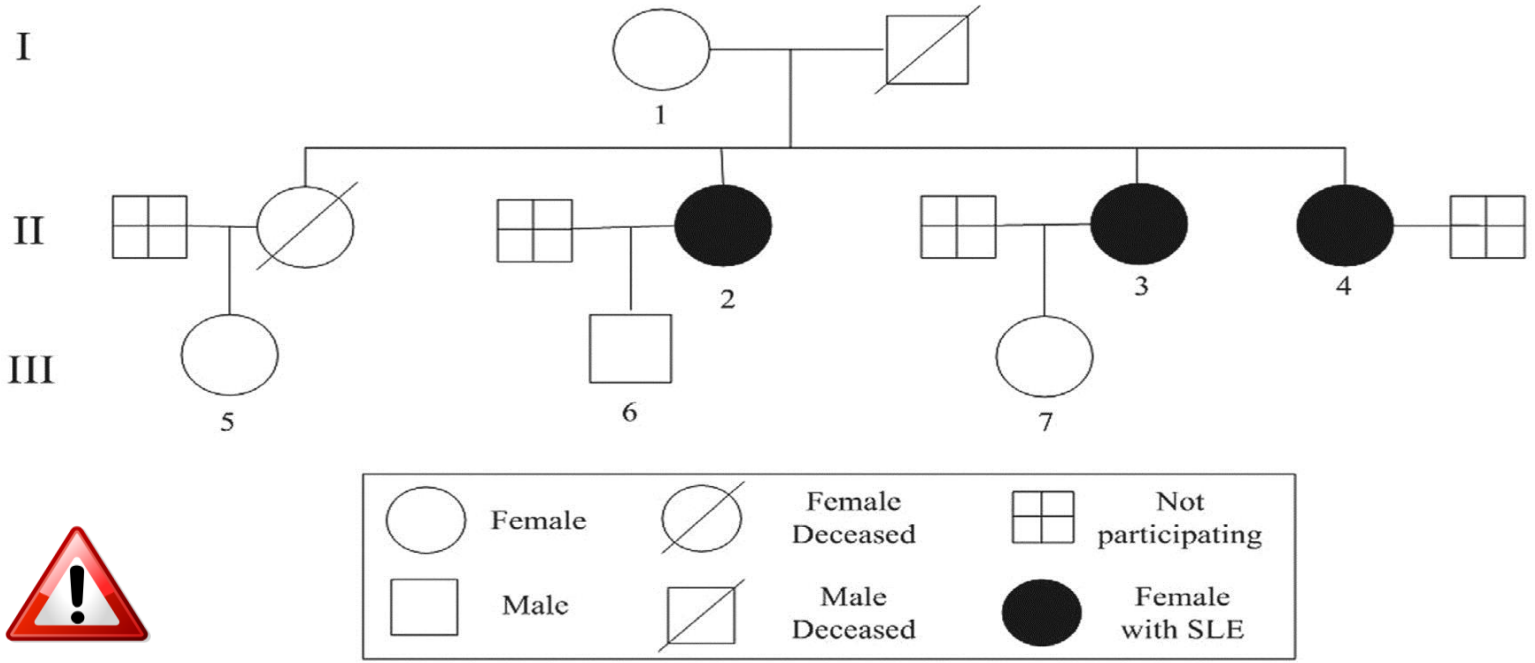
Pourrait-être environnemental

Formes familliales



Wu et al. Lab Medicine 2009

Formes familliales



Pourrait-être environnemental

Wu et al. Lab Medicine 2009

Formes familliales

Familial Aggregation of Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Other Autoimmune Diseases in 1,177 Lupus Patients From the GLADEL Cohort

$$\lambda = \frac{\text{Prevalence in relatives}}{\text{Prevalence in general population}}$$

Table 4. Familial aggregation (λ) of systemic lupus erythematosus as calculated using 3 different putative prevalences in the general population (K)

	K		
Relationship	0.0005	0.001	0.005
Parents/offspring	54	27	5.4
Siblings	58	29	5.8
Aunts/uncles/ nieces/nephews	39	19.5	3.9
Cousins	22	11	2.2

Alarcon-Segovia et al. Arthritis Rheum 2005

Formes familliales

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Table 3. Prevalence of SLE in first-, second-, and third-degree relatives of SLE patients in the GLADEL cohort, and comparison with recorded prevalence of SLE in populations*

	Prevalence, %
SLE relatives	
First-degree	
Parents/offspring	2.7
Siblings	2.9
Second-degree (aunts/uncles/nieces/nephews)	1.95
Third-degree (cousins)	1.1
Populations	
European	0.010–0.081
African Caribbean	0.11–0.25
African American	0.375

* See Table 2 for definitions.

≈10%

Alarcon-Segovia et al. Arthritis Rheum 2005

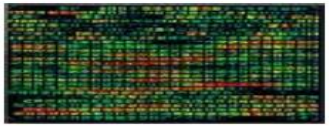
Genome Wide Association studies (GWAS)

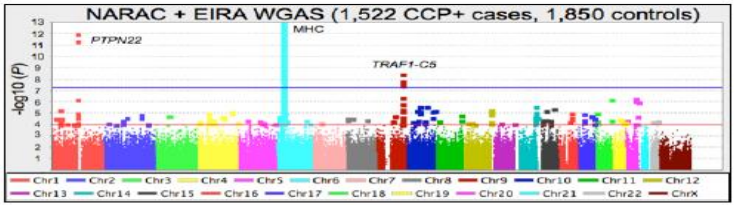
>700 cases
> 700 controls

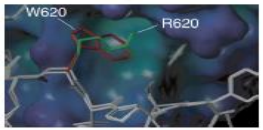
DNA-chip
> 1 000 000 SNPs

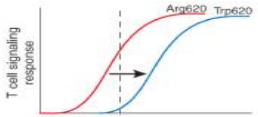
Analysis for differences in SNPs

Further genetic studies



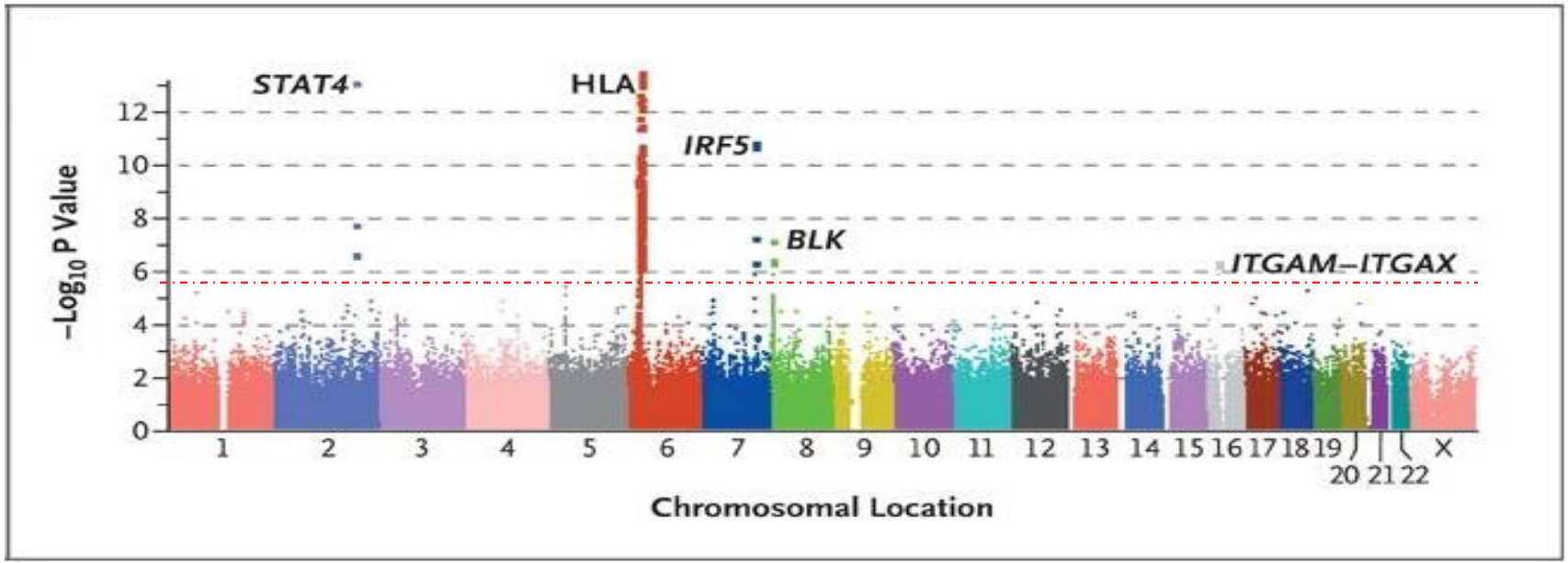






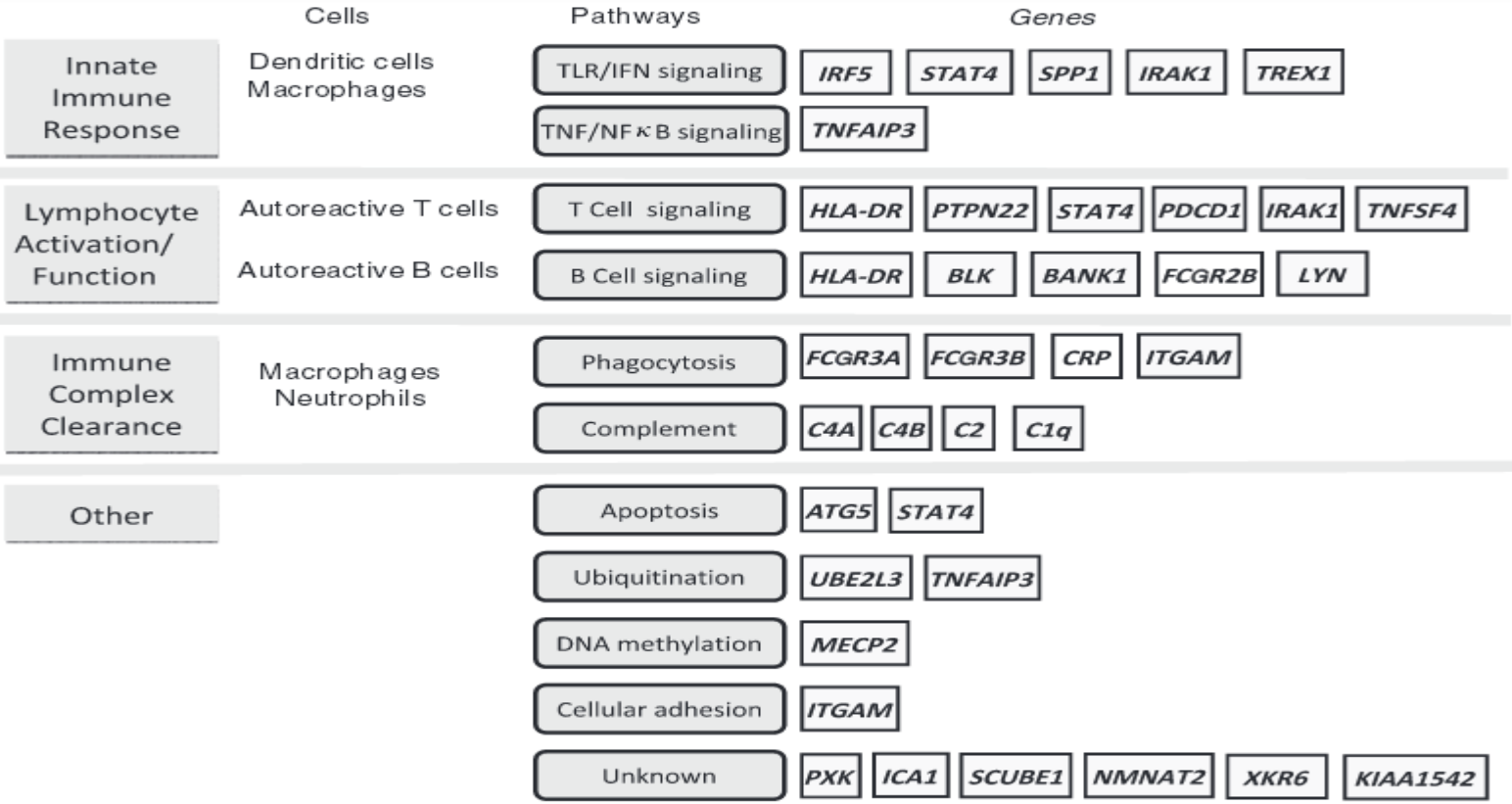
GWAS et lupus

Association of Systemic Lupus Erythematosus with *C8orf13–BLK* and *ITGAM–ITGAX*



Hom et al. NEJM 2008

GWAS et lupus

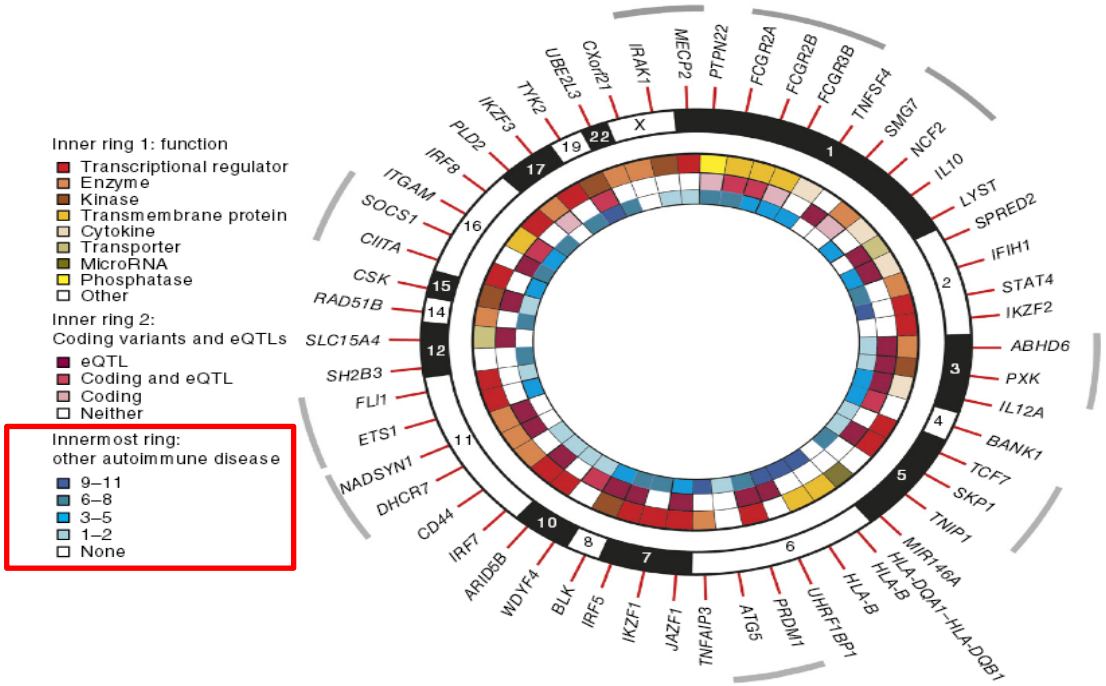


Moser et al. Genes Immun. 2009

GWAS et lupus

Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus

Figure 2 Summary of the functional roles of likely causal genes in SLE and other autoimmune diseases. The concentric rings in the figure show several layers of evidence to support functional annotation of the likely causal genes for SLE listed in **Table 2**. The genes are illustrated clockwise in chromosomal order, with gray arcs delineating loci at which several genes are implicated. Inner ring 1 shows each gene's functional category, taken from Ingenuity Pathway Analysis; inner ring 2 shows the presence of a *cis*-acting eQTL (**Fig. 1**) and/or coding variant; and innermost ring 3 shows the number of autoimmune diseases (excluding SLE) in ImmunoBase—type 1 diabetes, celiac disease, multiple sclerosis, Crohn's disease, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, autoimmune thyroid disease, juvenile idiopathic arthritis, alopecia areata, inflammatory bowel disease, narcolepsy, primary sclerosing cholangitis, Sjögren's syndrome, systemic scleroderma and vitiligo—previously reported to be associated with the gene.



Bentham et al. Nature Genet 2015

GWAS et lupus

Odd ratio

TREX1	25	Rare, found in 12 of 417 cases and 2 of 1712 controls
Complement C1q	~10	Rare, >90% −/− affected
Complement C4A	6.5	Rare, >70% −/− and −/+
and C4B		affected, CNV
Complement C2	~5	<10% −/− affected
HLA	2.36	Multiple effects
TNFAIP3	2.28	Rare haplotype (minor allele frequencies ~0.03 to 0.07)
FCGR3B	2.21	CNV
ITGAM	1.62	H77R
FcGR3A	1.6	F176V
IRF5	1.54	Three functional variants
STAT4	1.5	
IRAK1	1.5	Chromosome X, adjacent to *MECP2*
BANK1	1.4	
FCGR2A	1.35	H131R
ICA1	1.32	
PTPN22	1.3	N European; familial lupus
CRP	1.3	−707 mutation
TNFSF4/OX40	1.3	
LYN	1.30	
SCUBE1	1.28	
KIAA1542	1.28	rs49663128, SLEGEN GWAS, marker for *IRF7*
PXK	1.25	
XKR6	1.23	
Chromosome 5q33.3	1.23	rs2431697, SLEGEN GWAS
Chromosome 1q25.1	1.22	rs10798269, SLEGEN GWAS
BLK/FAM167A (C8orf13)	1.22	
UBE2L3	1.22	
MECP2	1.2	Chromosome X, adjacent to *IRAK1*
PDCD1	1.2	
ATG5	1.19	
NMNAT2	1.18	
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Lupus « polygénique »

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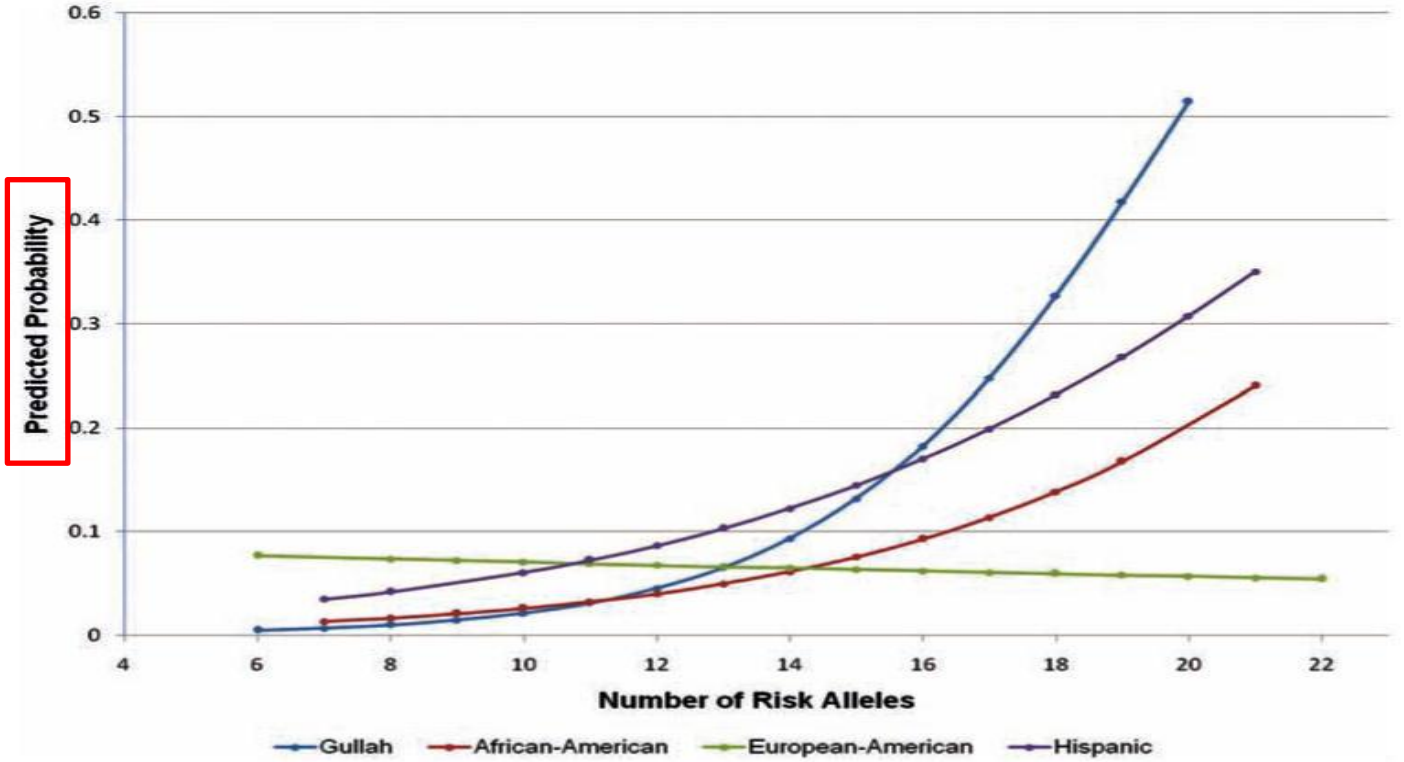
Moser et al. Genes Immun. 2009

Graham et al. J Intern Med 2009

Lupus polygénique

Influence du nombre d'allèles de susceptibilité

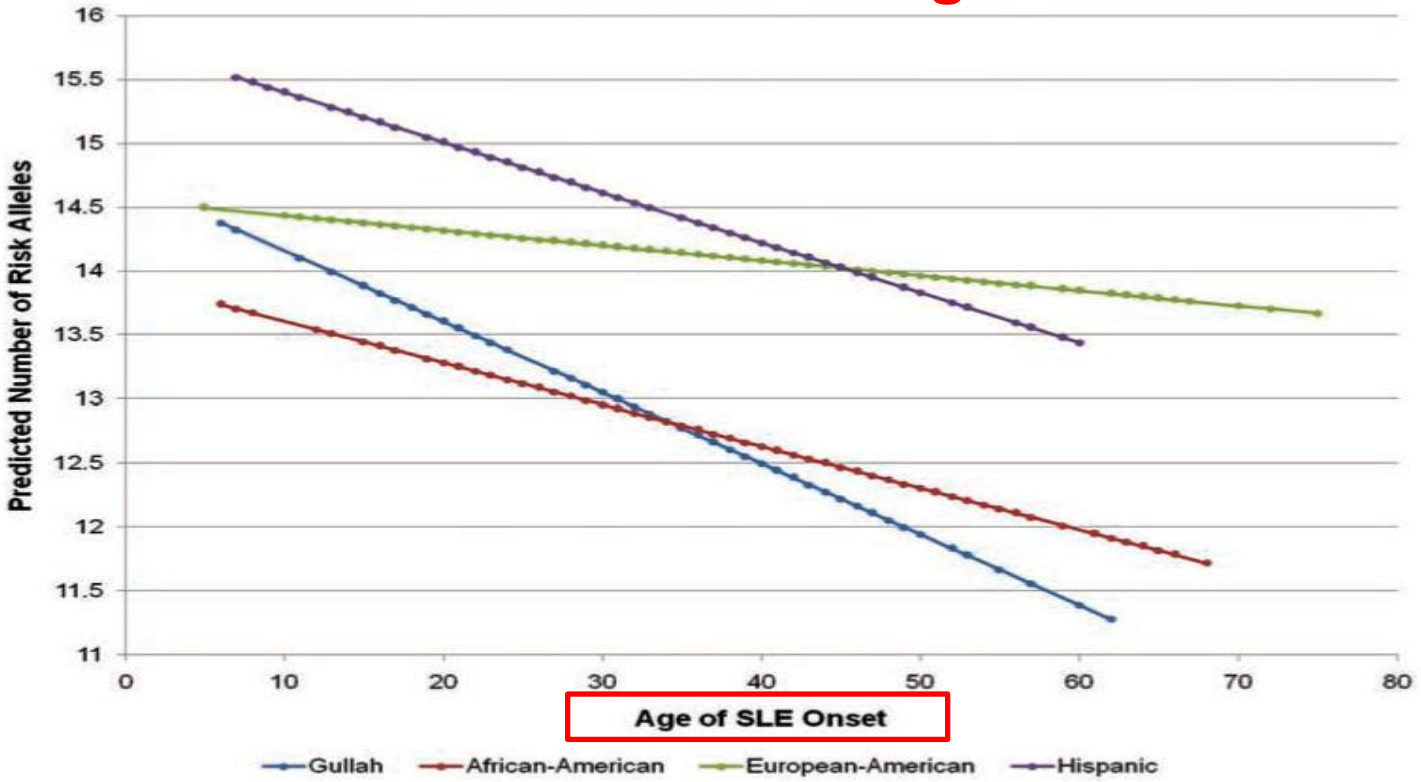


19 susceptibility SLE alleles were tested

Webb et al. ARD 2011

Lupus polygénique

Influence de l'âge



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Lupus monogénique (très rare)

Moser et al. Genes Immun. 2009
Graham et al. J Intern Med 2009

Lupus monogéniques

Interferonopathies

Interféronopathies de type I associées au LES.

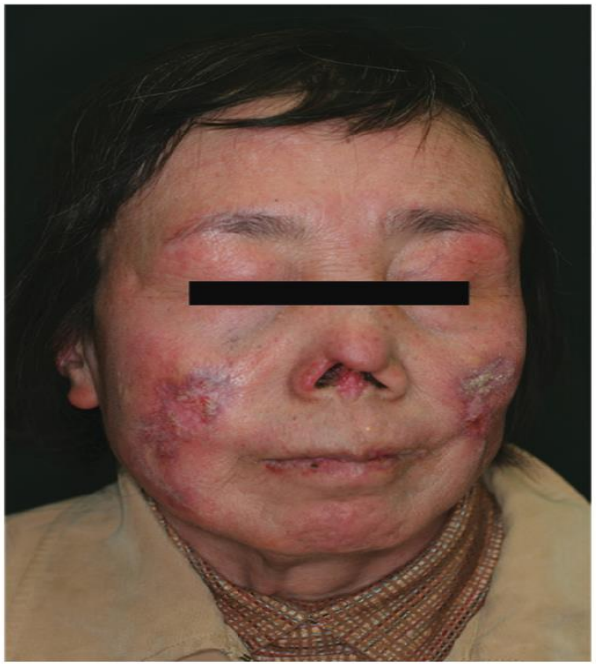
Gène/protéine	Âge à l'apparition	Fonction de la protéine	Voie associée à la signalisation de l'IFN de type I	Hérédité	Principales caractéristiques ajoutées au LES
TREX1/TREX1	Nouveaux-nés, enfants, adultes	Désoxyribonucléase	ADN cytosolique	Récessive autosomique	Engelures, glaucome, retard mental
SAMHD1/SAMHD1	Nouveaux-nés, enfants	Contrôle du pool de dNTP (± nucléase)	ADN cytosolique (± ARN cytosolique)	Récessive autosomique	Engelures, maladie de Moya-Moya, glaucome, retard mental
TMEM173/STING	Enfants, adultes	Adaptatrice de cGAS	ADN cytosolique (± ARN cytosolique)	Dominante autosomique	Pneumopathie interstitielle, fibrose pulmonaire, vascularite cutanée
RNASEH2A/RNASEH2A *RNASEH2B*/RNASEH2B *RNASEH2C*/RNASEH2C	Nouveaux-nés, enfants	Ribonucléase	ARN cytosolique : hybrides d'ADN	Récessive autosomique	Paraparésie, retard mental
IFIH1/MDA5	Nouveaux-nés, enfants, adultes	Senseur d'ARNdb	ARN cytosolique	Dominante autosomique	Paraparésie, glaucome, vascularite
DDX58/RIG-I	Enfants, adultes	Senseur d'ARNdb	ARN cytosolique	Dominante autosomique	Glaucome, syndrome de Singleton-Merten
ACP5/TRAP	Nouveaux-nés, enfants, adultes	Phosphatase	Inconnue	Récessive autosomique	SPENCD, cytopénies, vascularite, retard de croissance
C1QA,B,C/C1QA,B,C	Enfants, adultes	Voie canonique du complément	Inconnue	Récessive autosomique	Infections, lésions cutanées

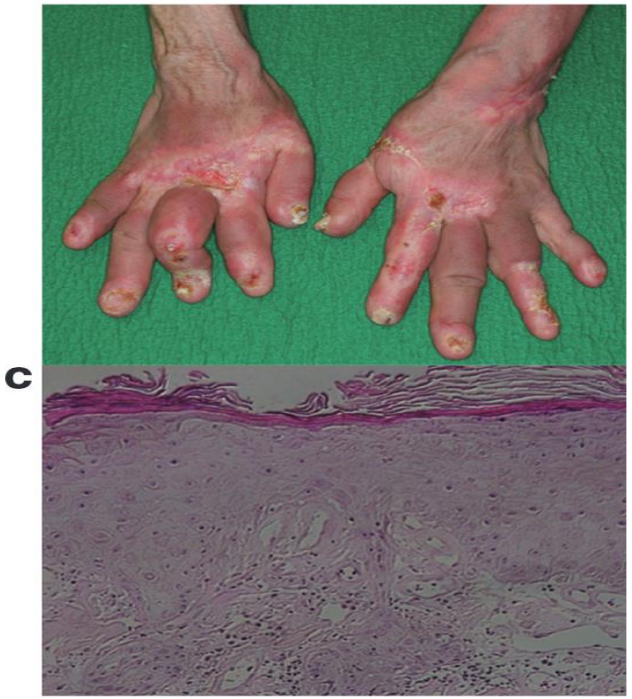
IFN : interféron ; SPENCD : spondyloenchondrodysplasie ; dNTP : désoxyribonucléotide ; cGAS : GMP cyclique-AMP synthase.

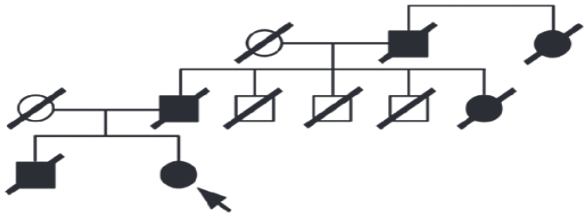
Arnaud et al. JBS 2018

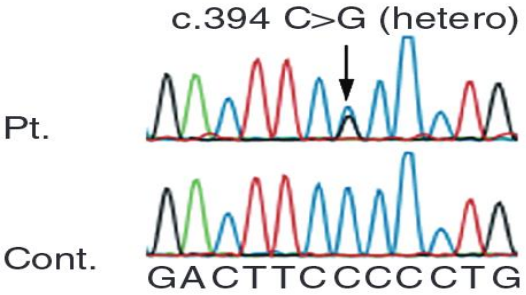
Lupus monogéniques

TREX1 (familial chilblain lupus)





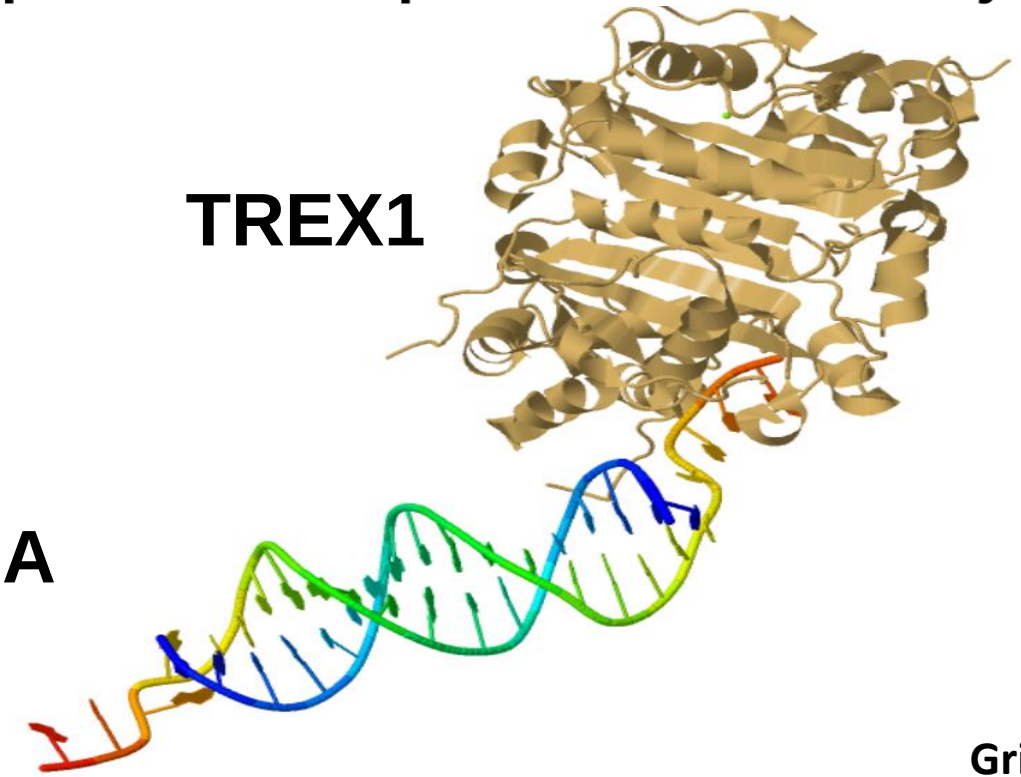




Sugiura et al. J Invest Derm 2012

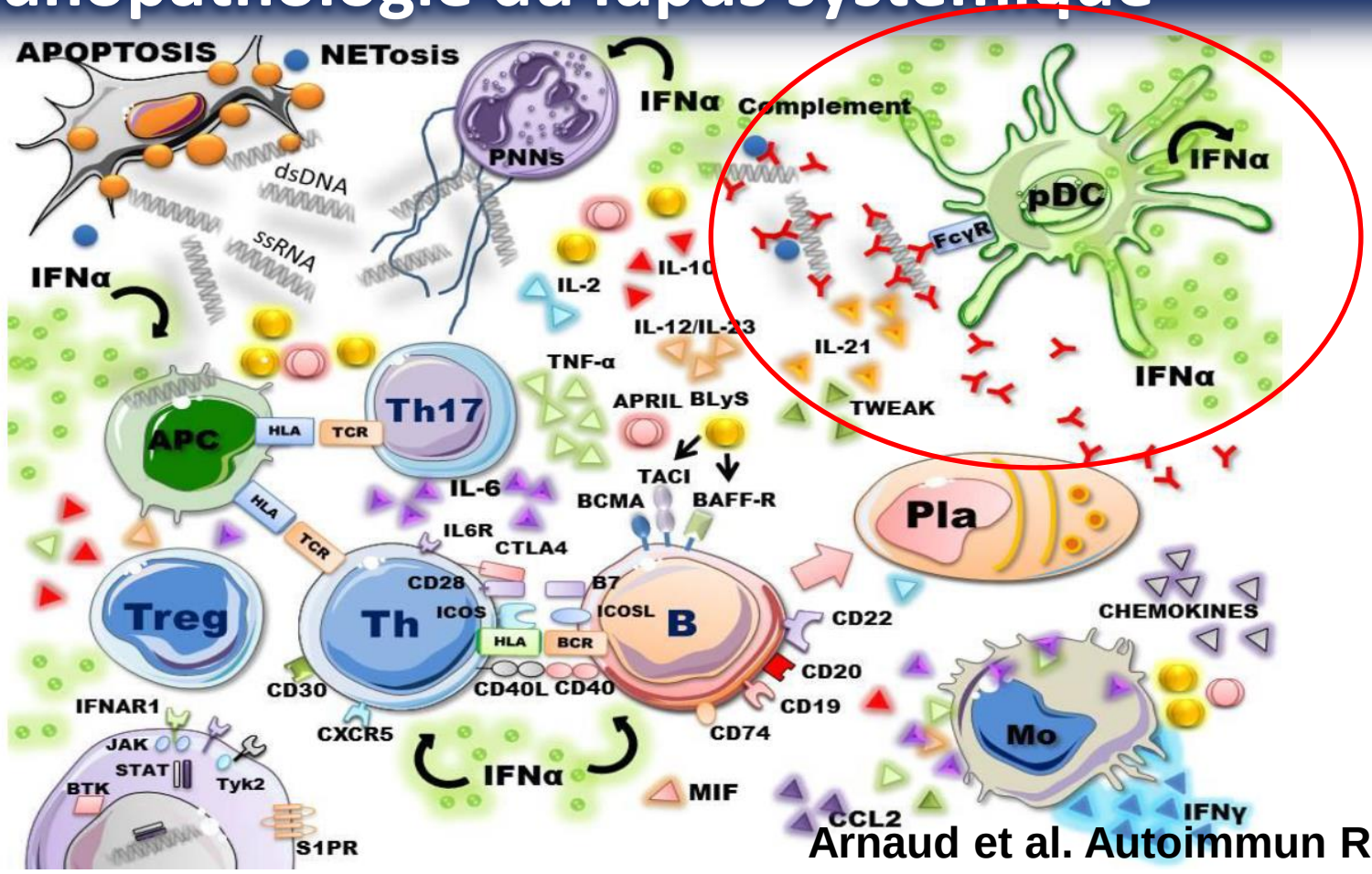
Lupus monogéniques

Exonuclease TREX1 degrades double-stranded DNA to prevent spontaneous lupus-like inflammatory disease



Grieves et al. PNAS 2015

Immunopathologie du lupus systémique



Arnaud et al. Autoimmun Rev 2018

Les « causes » du lupus

Génétique

(>110 gènes impliqués*)

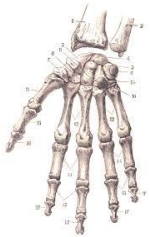
Hormones

(oestrogènes)

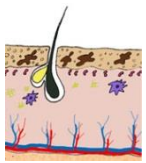
Environnement

(ex : UV, médicaments)

Système immunitaire

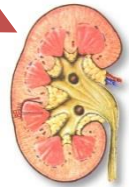


Articulations

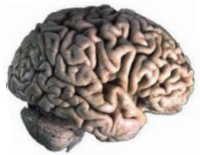


Peau

Séreuses



Rein

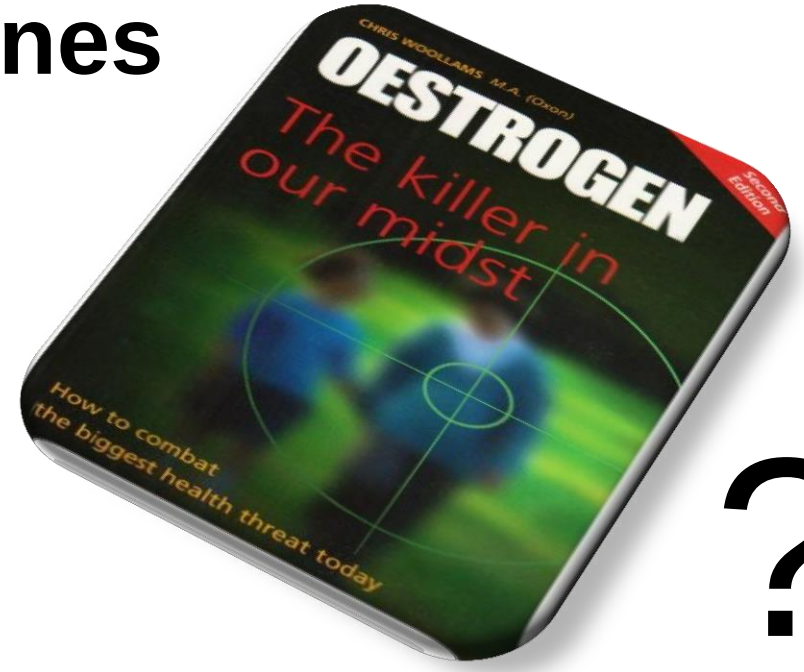


SNC

*Rares formes monogéniques

Les « causes » du lupus

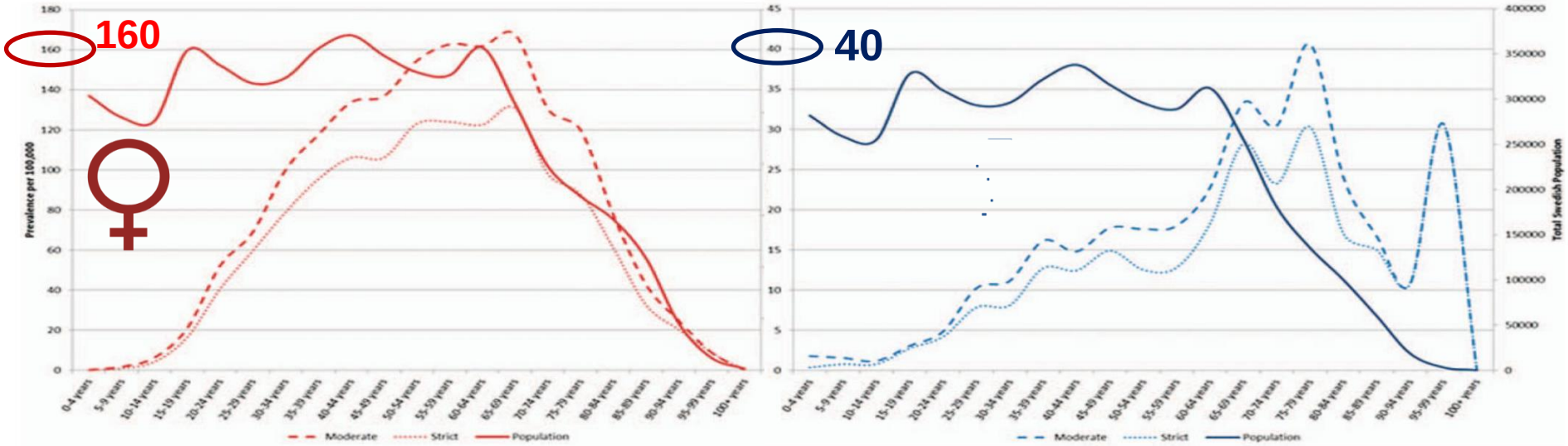
Comment évaluer le rôle des hormones



?

Prédominance féminine

Systemic Lupus Erythematosus Prevalence in Sweden in 2010: What Do National Registers Say?



Simard et al. Arthritis Care Research 2014

Dosages hormonaux

Sex Hormones and Systemic Lupus Erythematosus

Review and Meta-Analysis

Table 6. Sex hormone changes in SLE patients*

Hormone	Women	Men
DHEA/DHEAS	↓	Probably ↓
↓		
Progesterone	↓	Unknown
↓		
Testosterone	↓ *	Normal
↓		
Estradiol	↑ *	Normal
↓ (stimulates)		
Prolactin	↑ *	↑ *

* Compared with healthy controls. SLE = systemic lupus erythematosus; DHEA/DHEAS = dehydroepiandrosterone/dehydroepiandrosterone sulfate.

*** Significant difference between SLE patients and healthy controls**

McMurray et al. Arthritis Rheum. 2003

Dosages hormonaux

Table 2. Sex hormone profiles in patients with SLE and their matched controls*

	SLE patients (n = 71)	Matched controls (n = 25)	*P*
FSH			
Levels, median (range) units/liter	4.2 (1.2–30)	3.6 (1.9–16)	0.23
High FSH (>12.5 units/liter), no. (%)	11 (15.5)	1 (4)	0.18
LH			
Levels, median (range) units/liter	4.6 (1.3–20)	2.7 (1.6–7.1)	<0.0001
High LH (>9.6 units/liter), no. (%)	10 (14.1)	0 (0)	0.06
Prolactin			
Levels, median (range) mIU/liter	161 (23–1,022)	153 (47–339)	0.18
High prolactin (>278 mIU/liter), no. (%)	5 (7.0)	0 (0)	0.32
SHBG, median (range) nmoles/liter	32.0 (11–108)	29.0 (8.2–61)	0.33
Testosterone			
Levels, median (range) nmoles/liter	11.0 (4.0–32)	13.0 (3.4–27)	0.78
Low testosterone (<10 nmoles/liter), no. (%)	23 (32.4)	7 (28.0)	0.68
Bioactive testosterone			
Levels, median (range) nmoles/liter	6.3 (2.9–13)	7.2 (2.7–11)	0.20
Low bioactive testosterone, no. (%)†	24 (34)	2 (8)	0.02

* SLE = systemic lupus erythematosus; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone–binding globulin.
† Defined as <6.3 nmoles/liter for those ages 20–49 years and <4.4 nmoles/liter for those age ≥50 years.

Arnaud et al. Arthritis Rheum. 2017

Rôle des ostrogènes naturels et de synthèse

Reproductive and Menopausal Factors and Risk of Systemic Lupus Erythematosus in Women

	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI)
Pooled results (NHS + NHSII)				
Age at menarche, years				
≤10	–	–	–	2.1 (1.4–3.2)
11	–	–	–	1.2 (0.8–1.7)
12	–	–	–	1.0 (referent)
13	–	–	–	1.1 (0.8–1.6)
≥14	–	–	–	1.0 (0.7–1.5)
P for trend†				0.02
Oral contraceptive use				
Never	–	–	–	1.0 (referent)
Ever	–	–	–	1.5 (1.1–2.1)
Past	–	–	–	1.7 (1.2–2.3)
Current	–	–	–	–
PMH use§				
Never	23	550,867	1.0 (referent)	1.0 (referent)
Ever	65	916,454	1.9 (1.2–3.1)	1.9 (1.2–3.1)
Past	27	359,311	2.4 (1.3–4.2)	2.2 (1.3–3.9)
Current	38	557,143	1.7 (1.0–2.9)	1.7 (0.9–2.9)
Duration of PMH use§				
Never	23	550,867	1.0 (referent)	1.0 (referent)
<5 years' use	34	441,661	1.7 (1.0–3.0)	1.8 (1.0–3.0)
≥5 years' use	31	474,793	2.1 (1.2–3.8)	2.0 (1.1–3.6)

Prospective study n = 238 803 (1976-2003)
262 incident SLE cases

Costenbader et al. Arthritis Rheum. 2007

Rôle des ostrogènes de synthèse

Combined Oral Contraceptives in Women with Systemic Lupus Erythematosus

Table 1. Baseline Characteristics of the Study Subjects According to Treatment Group.*

Characteristic	Oral Contraceptives (N=91)	Placebo (N=92)
Age (yr)		
Mean	29.8	30.1
Range	18–39	18–39
Active disease (%)	23	25
SELENA-SLEDAI Instrument score		
Mean	3.01	3.39
Range	0–10	0–12
Renal disorder (%)	37	37
Low levels of complement (%)	29	25
Increased DNA binding (%)	32	22
Prednisone use (%)	56	55
Prednisone dose (mg/day)		
Mean	5.16	5.38
Range	0–30	0–30†

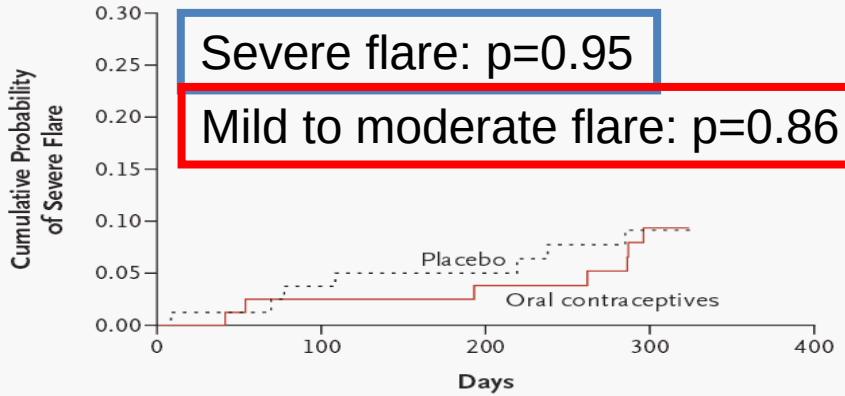


Figure 2. Kaplan–Meier Estimates of the Cumulative Probability of a Severe Flare in Subjects Receiving Oral Contraceptives and Placebo.

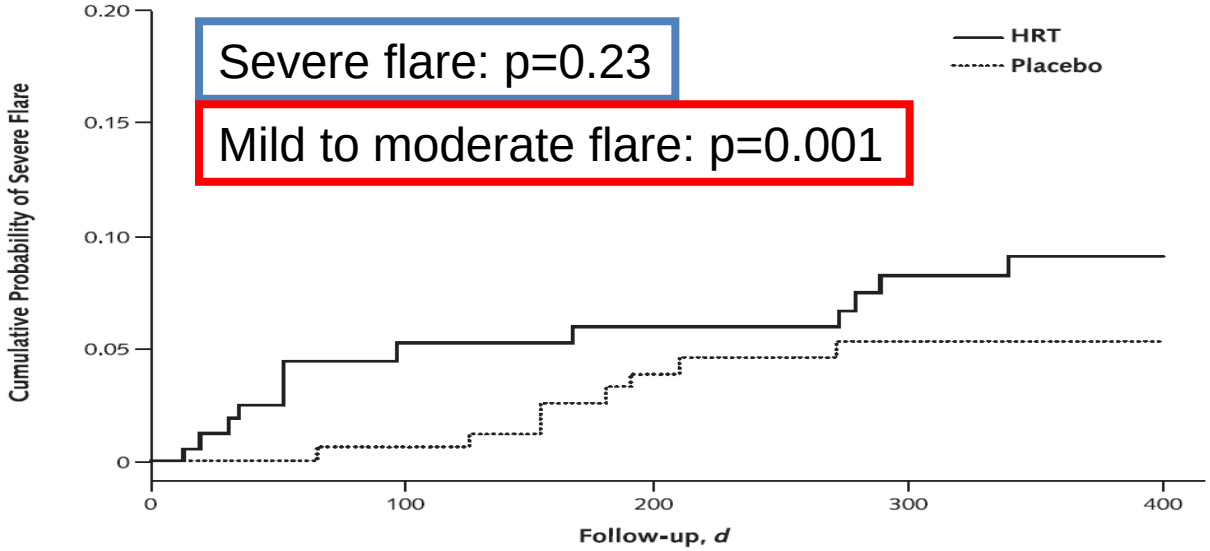
The difference between treatment groups in the 12-month rate of occurrence of severe flare was –0.0028 (P=0.95).

Buyon et al. NEJM 2005

Rôle des ostrogènes de synthèse

Annals of Internal Medicine | ARTICLE

The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus Erythematosus: A Randomized Trial



Patients at Risk, *n*					
HRT	174	148	143	136	130
Placebo	177	171	156	146	146

Buyon et al. Ann Intern Med. 2005

Rôle des ostrogènes

Modèles murins de lupus

Lupus

Estrogens
Murine GnRH
Anti-androgens (Male)
Organochlorine drugs

Lupus

KO Estro receptors (-/-)
Tamoxifen
Raloxifen
Anti-estrogen drugs

Carlsten et al. Clin Exp Immunol 1990
Walker et al. Arthritis Rheum. 1972

Un lien entre la génétique et les hormones ?

L'effet « dose-réponse » du chromosome X

♀ **Turner**
45 XO

0 case / 768 (SLE)
vs
4 / 10 000 (general pop)

♂ **Klinefelter**
47 XXY

235 cases / 10 000 (SLE)
vs
17 / 10 000 (general pop)

♀ **Trisomie X**
47 XXX

7 cases / 2826 (SLE)
vs
2 / 7074 (general pop)

Scofield et al. Arthritis Rheum. 2008 Liu et al. Arthritis Rheum. 2015

Les « causes » du lupus

Génétique

(>110 gènes impliqués*)

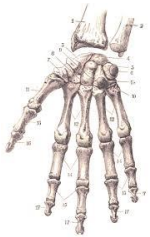
Hormones

(oestrogènes)

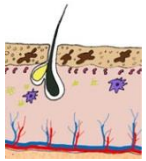
Environnement

(ex : UV, médicaments)

Système immunitaire

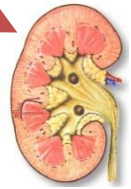


Articulations

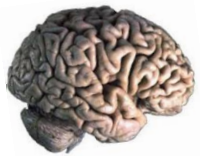


Peau

Séreuses



Rein



SNC

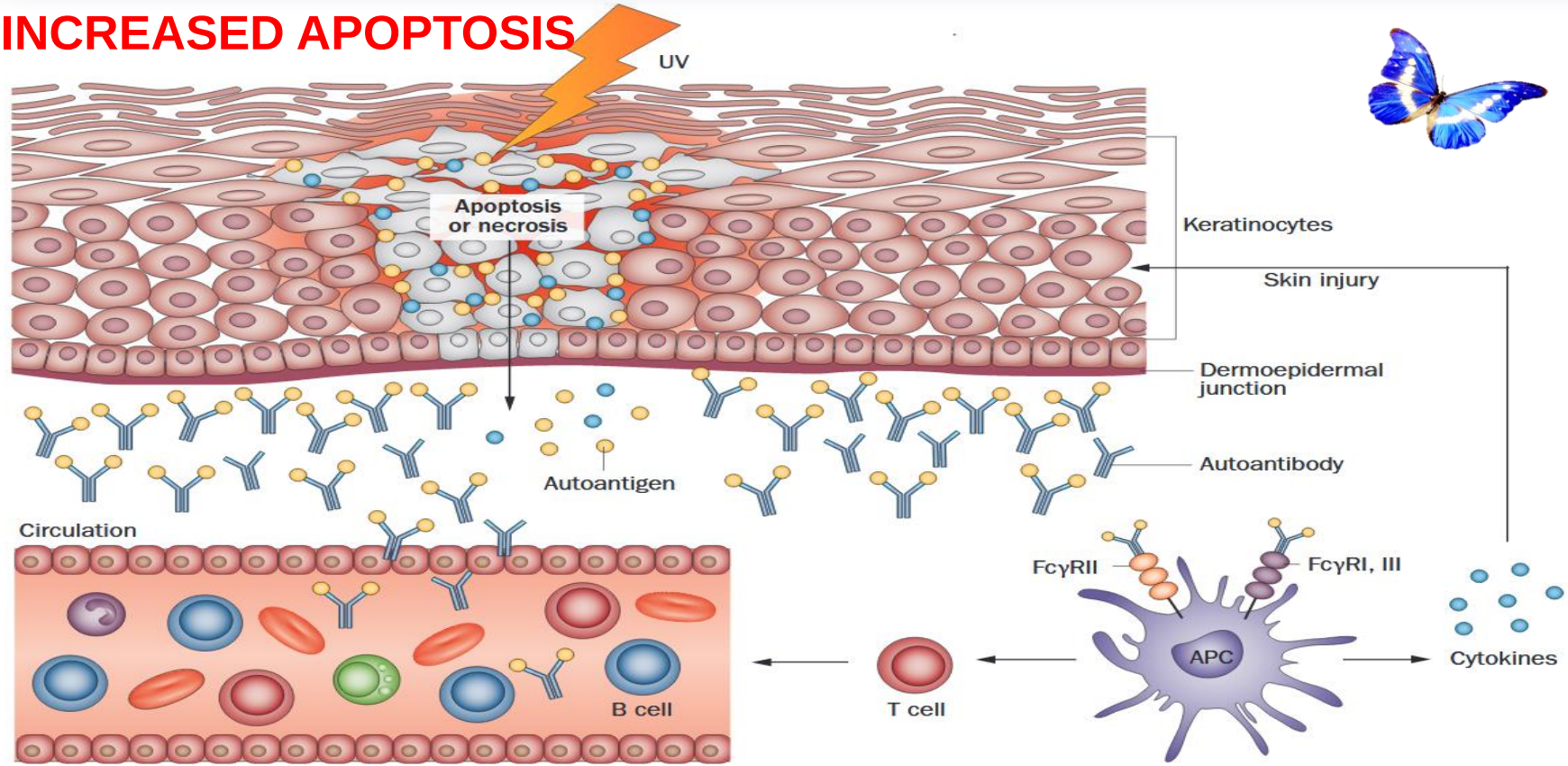
*Rares formes monogéniques

Environnement et lupus

Quels facteurs environnementaux ?

Le rôle délétère des UVs

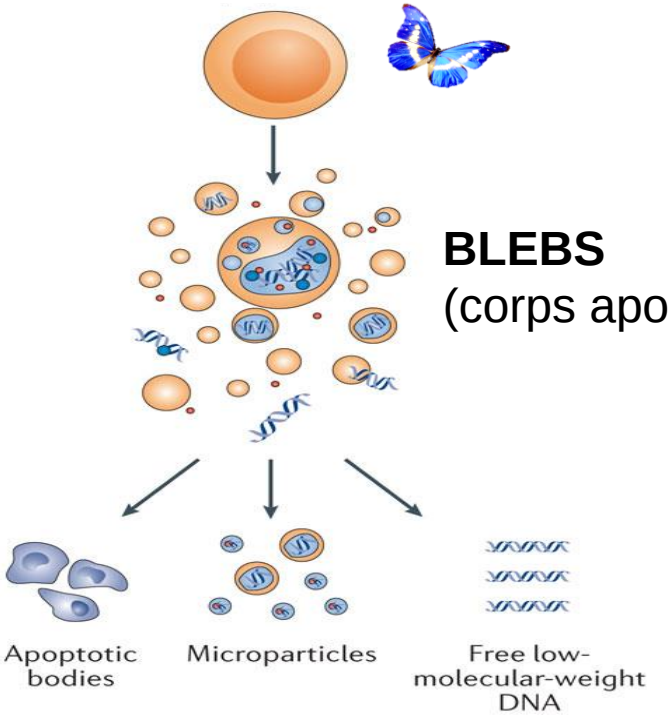
INCREASED APOPTOSIS



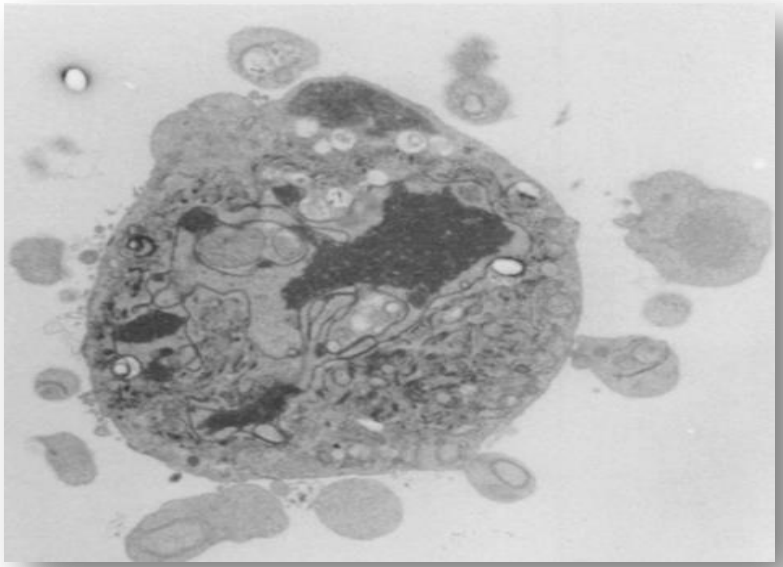
Deng et al. Nat Rev Rheumatol 2015

Principales sources d'auto-antigènes au cours du lupus

APOPTOSE



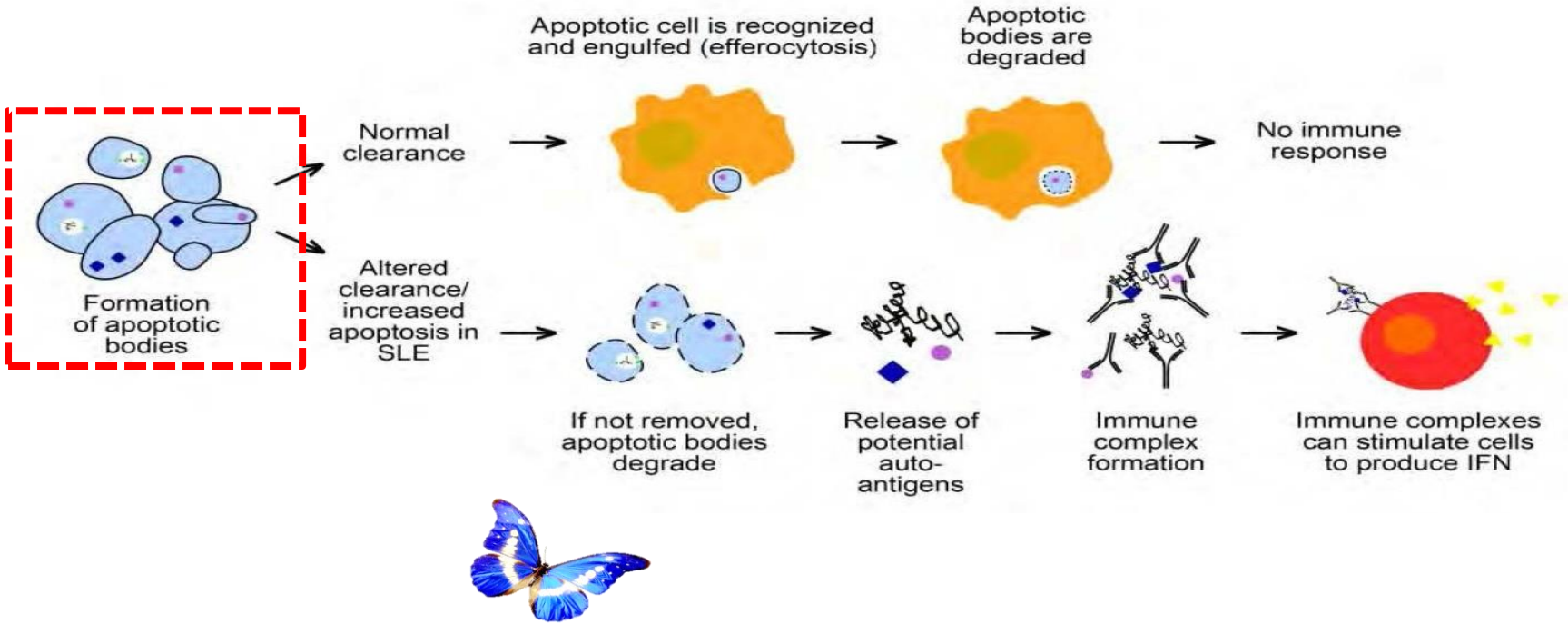
BLEBS
(corps apoptotiques)



Casciola-Rosen et al. J Exp Med 1994

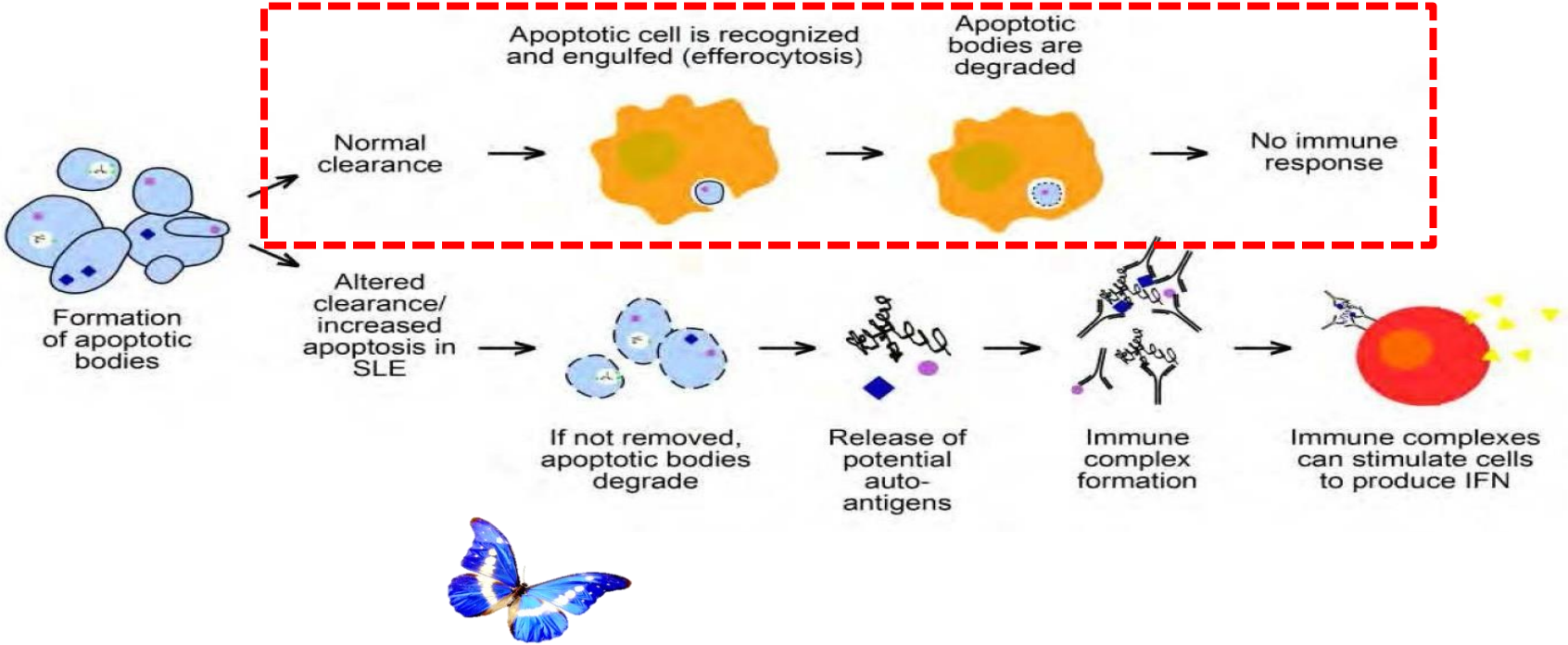
Pisetsky et al. Nat Rev Rheumatol 2015

Le rôle de l'apoptose au cours du lupus

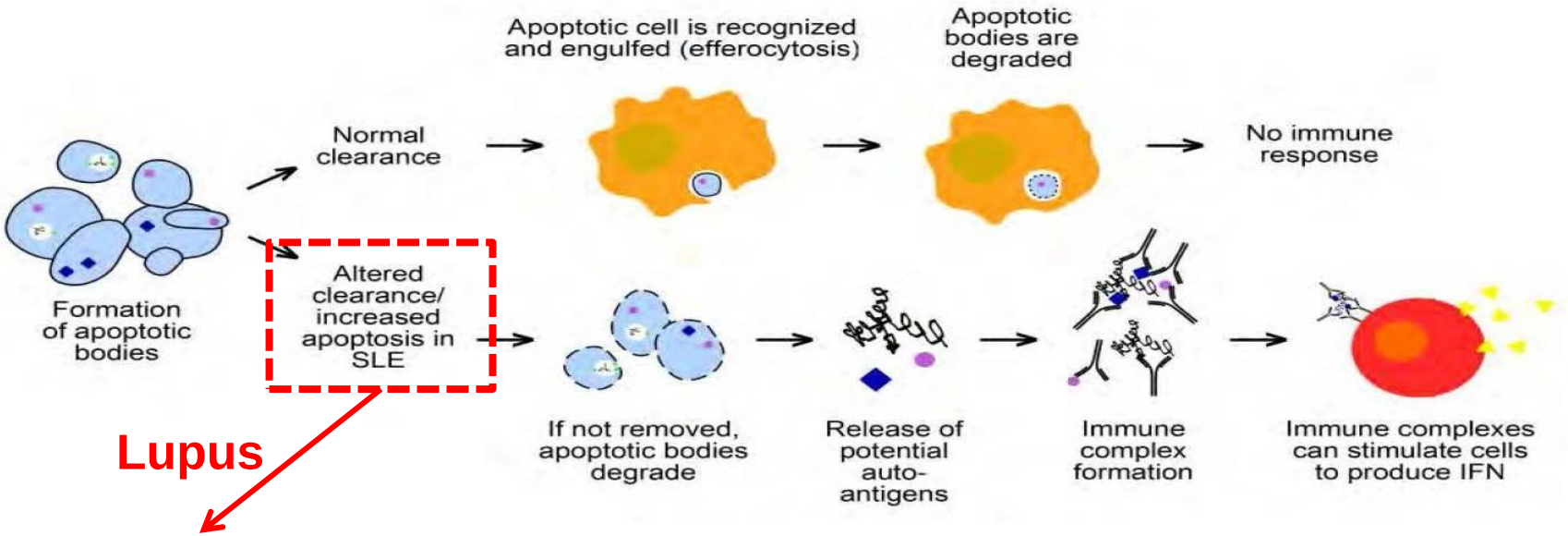


Le rôle de l'apoptose au cours du lupus

Réponse physiologique => clearance



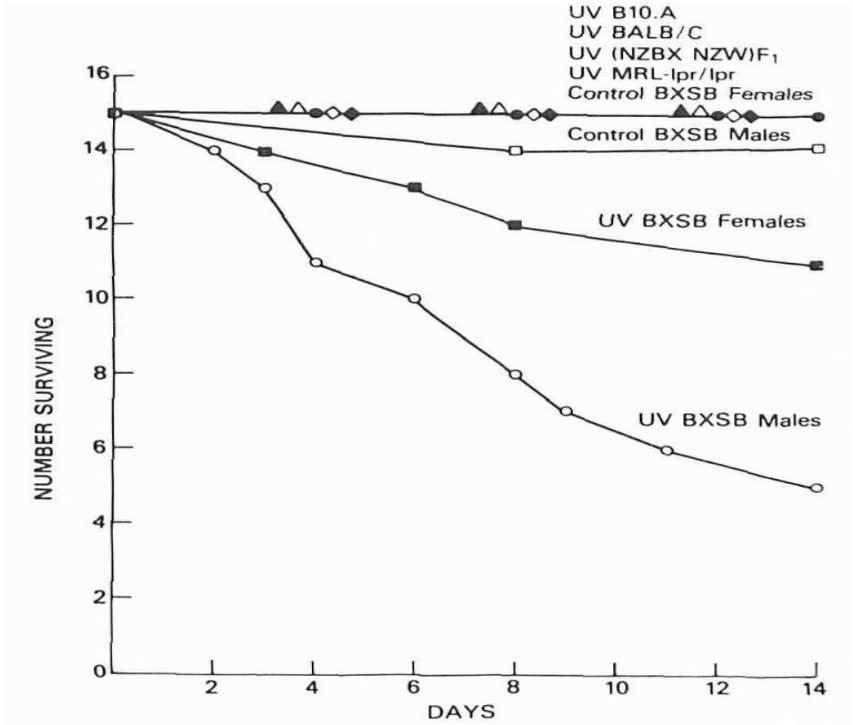
Le rôle de l'apoptose au cours du lupus



Déficit en complément
Polymorphisme des FcγR
Activité DNAse I diminuée

Le rôle délétère des UVs

Le rôle des UV chez lupus-prone mice



Ancel et al. J Invest Derm 1985

Environnement et lupus

Exposition aux UV et risque de lupus

	Patients ($n=258$) n (%)	Controls ($n=263$) n (%)	OR (95% CI)[a]
Skin characteristics			
Skin tone			
Fair or very fair	187 (72)	209 (79)	0.72 (0.48, 1.1)
Olive, dark or very dark	71 (28)	54 (21)	1.0 (referent)
Reaction to sun—2 h, midday			
Tan or darken without burning	50 (20)	56 (22)	1.0 (referent)
Sunburn	101 (39)	140 (54)	0.88 (0.55, 1.4)
Sunburn with blistering or rash	88 (34)	55 (21)	2.1 (1.3, 3.6)
Other	17 (7)	9 (3)	2.4 (0.96, 6.0)
Outdoor work (⩾20 h/week, ⩾2 months/year)			
In 12 months before diagnosis (patients) or past 12 months (controls)	32 (12)	16 (6)	1.9 (1.0, 3.7)
Total years, mean (S.D.)	1.2 (3.5)	1.6 (3.6)	($P=0.29$)
0	185 (72)	181 (69)	1.0 (referent)
1–4	54 (21)	50 (19)	1.0 (0.67, 1.6)
⩾5 or more	18 (7)	32 (12)	0.62 (0.32, 1.2)
Outdoor work in the 12 months before diagnosis, among people whose reaction to the midday sun is to:[b]			
Tan or darken without burning	4 (8)	5 (9)	0.75 (0.18, 3.2)
Sunburn	14 (14)	8 (6)	2.7 (1.0, 6.9)
Sunburn with blistering or rash	13 (15)	1 (2)	7.9 (0.97, 64.7)

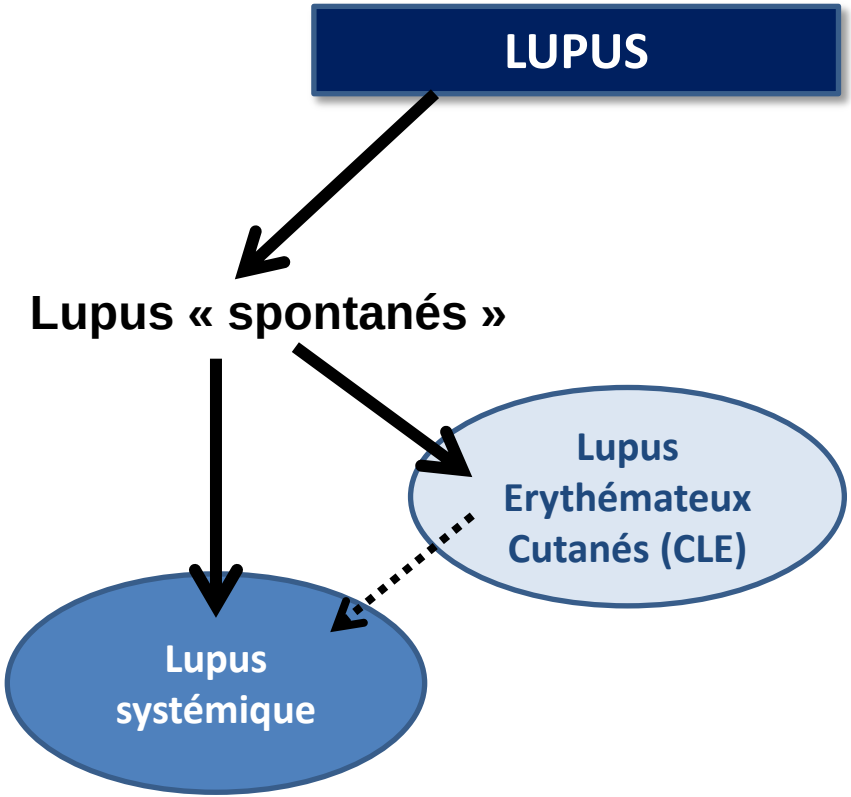
Cooper et al. Rheumatology 2010

Environnement et lupus

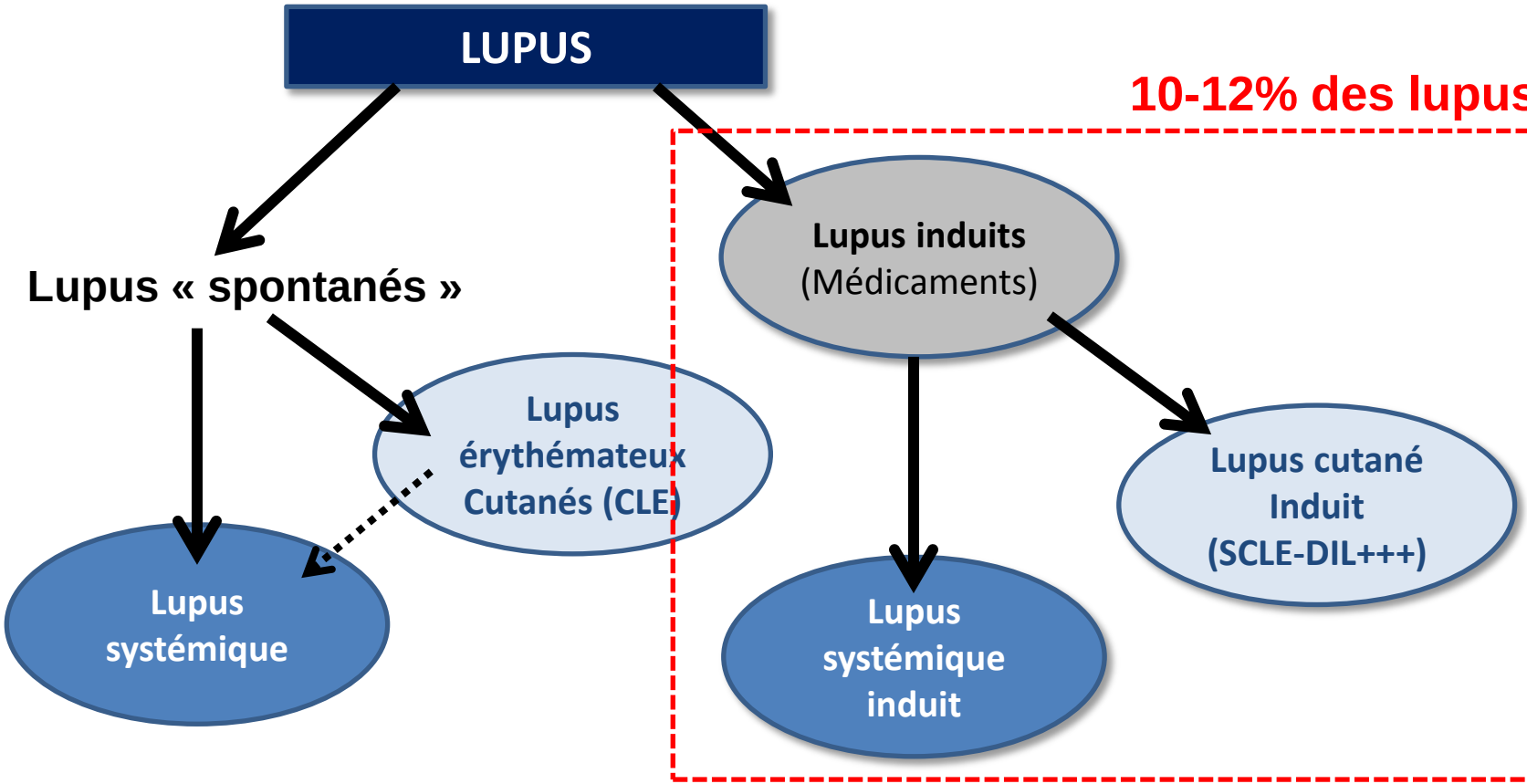
Clinical manifestations	At first visit (%)	During follow-up (%)
Arthritis	69	84
Malar rash	40	58
Fever	36	52
Photosensitivity	29	45
Nephropathy	16	39
Serositis	17	36
Neuro involvement	12	27
Oral ulcers	11	24
Thrombocytopenia	9	22
Adenomegaly	7	12
Discoid lupus	6	10
Myositis	4	9
Hemolytic anemia	4	8
Pulmonary involvement	3	3

Cervera et al. Medicine 1993

Typologie des lupus…

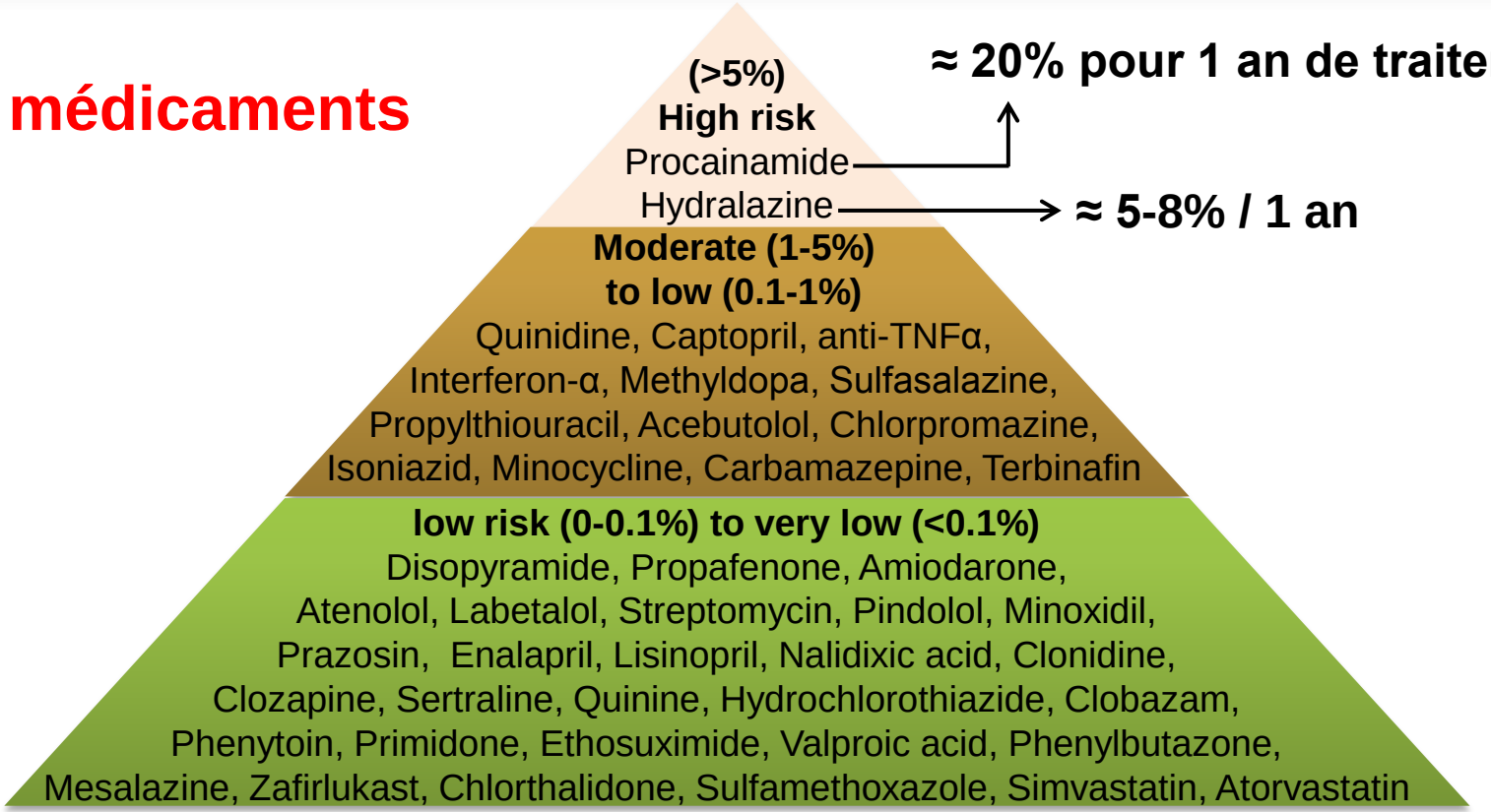


Lupus induits



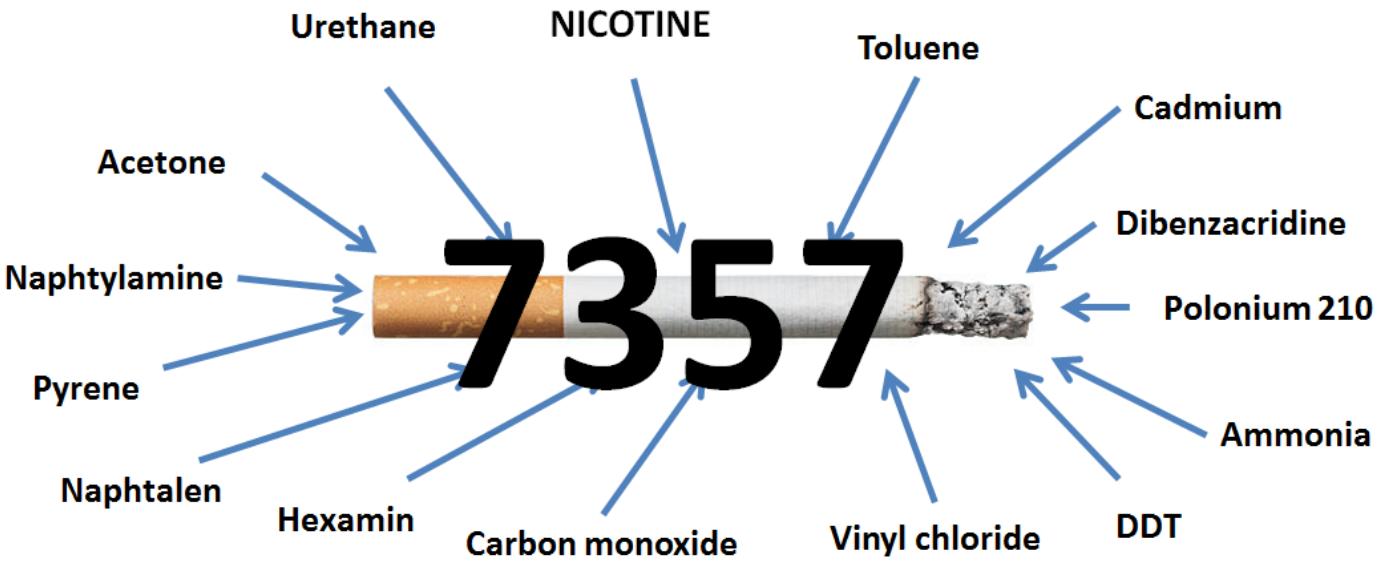
Lupus induits

> 100 médicaments



Arnaud et al. Annals of Rheum Disease 2019

Exposition à la cigarette



NUMBER OF CHEMICAL COMPOUNDS DETECTABLE IN CIGARETTE SMOKE

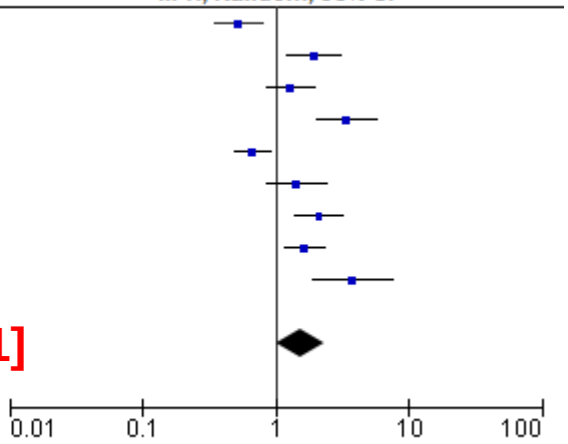
Exposition à la cigarette

EVER versus NEVER smokers

Study or Subgroup	SLE cases Events	SLE cases Total	Controls Events	Controls Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Reidenberg et al. (1993)	67	195	97	195	11.4%	0.53 [0.35, 0.79]	1993
Nagata et al. (1995)	54	282	32	292	11.0%	1.92 [1.20, 3.09]	1995
Hardy et al. (1998)	67	139	118	281	11.4%	1.29 [0.85, 1.93]	1998
Cooper et al. (2001)	77	125	40	125	10.7%	3.41 [2.03, 5.74]	2001
Ghaussy et al. (2001)	102	265	171	355	11.9%	0.67 [0.49, 0.93]	2001
Bengtsson et al. (2002)	51	85	105	205	10.8%	1.43 [0.86, 2.39]	2002
Kiyohara et al. (2009)	53	151	86	424	11.4%	2.13 [1.41, 3.20]	2009
Ekblom-Kullberg et al. (2013)	153	205	552	862	11.8%	1.65 [1.17, 2.33]	2013
Zou et al. (2014)	37	260	11	260	9.5%	3.76 [1.87, 7.54]	2014
Total (95% CI)		**1707**		**2999**	**100.0%**	**1.52 [1.00-2.31]**	
Total events	661		1212				

Heterogeneity: Tau² = 0.35; Chi² = 66.78, df = 8 (P < 0.00001); I² = 88%

Test for overall effect: Z = 1.98 (P = 0.05)



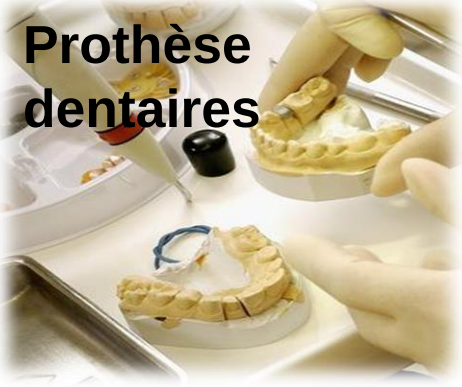
Arnaud et al. Autoimmunity Rev 2019

Environnement et lupus

Silice et lupus

Sable (silice)

Activation lymphocyte



Kiyohara et al. J Rheum 2012

Environnement et lupus

Silica and SLE

Exposures and activities[a]	Patients (n = 258) n (%)	Controls (n = 263) n (%)	OR (95% CI)[b]
Occupational			
Silica dust[c]	40 (16)	27 (10)	1.6 (0.90, 2.7)
Artist, working with paints, dyes or developing film	14 (5)	4 (2)	3.9 (1.3, 12.3)
Repairing or cleaning machinery or metal	15 (6)	8 (3)	1.9 (0.76, 4.7)
Stains, varnishes or paint strippers[d]	12 (5)	10 (4)	1.4 (0.54, 3.6)
Sterilizing dental equipment	6 (2)	2 (1)	3.9 (0.76, 20.0)
Mercury (⩾once per week)	7 (3)	3 (1)	3.1 (0.77, 12.7)
Nail polish or applications	9 (3)	1 (0)	10.2 (1.3, 81.5)
Gasoline—taxi, bus or truck driver or job pumping gas	10 (4)	15 (6)	0.76 (0.32, 1.8)
Pesticides[e]	9 (3)	9 (3)	1.1 (0.43, 3.0)
Drawing blood, giving injections	14 (5)	18 (7)	0.97 (0.45, 2.1)
Dry cleaning	5 (2)	4 (2)	1.5 (0.38, 5.6)
Non-occupational			
Pottery or ceramic work—ever[f]	59 (23)	42 (16)	1.7 (1.1, 2.7)
Total days—never	199 (77)	221 (84)	1.0 (referent)
5–25	19 (7)	19 (7)	1.2 (0.62, 2.4)
⩾26	39 (15)	22 (8)	2.2 (1.2, 3.9)
Home renovation with drywall—ever[g]	49 (19)	40 (15)	1.3 (0.83, 2.1)
Stained or leaded glass—ever[f]	8 (3)	3 (1)	3.0 (0.76, 11.6)
Combined silica exposure[h]			
Any	111 (43)	88 (33)	1.6 (1.1, 2.3)
Number of exposure scenarios—0	147 (57)	175 (67)	1.0 (referent)
1	79 (31)	69 (26)	1.4 (0.97, 2.1)
2	27 (10)	17 (6)	1.9 (0.97, 3.7)
3	5 (2)	2 (1)	3.7 (0.67, 20.1)

Cooper et al. Rheumatology 2010

Environnement et lupus

Prospective Risk of Rheumatologic Disease Associated with Occupational Exposure in a Cohort of Male Construction Workers

Table 3 Occupational Exposure- and Smoking-associated Risks of Rheumatologic Disease: Multivariate Analysis

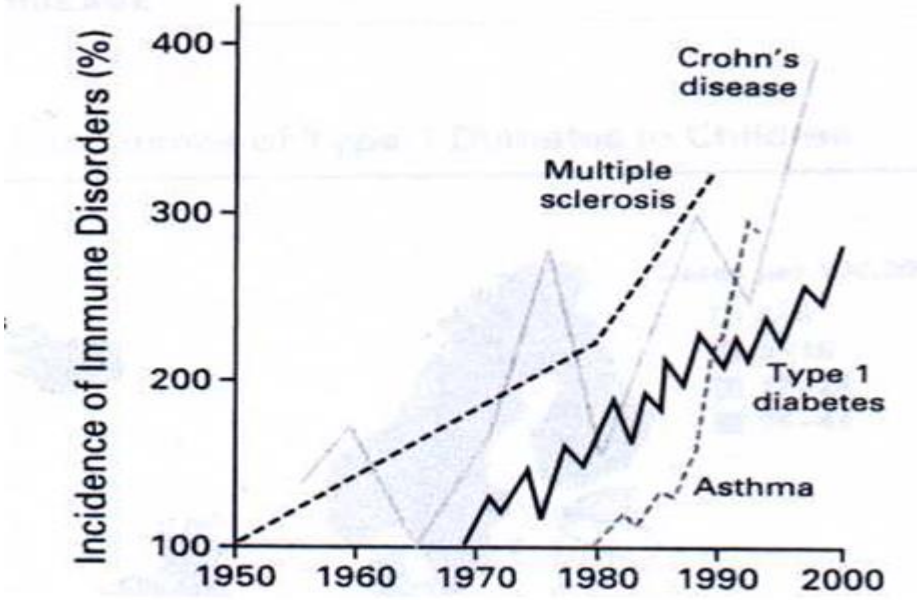
	Adjusted Risk Estimates for Rheumatologic Disease by Disease Type							
	Seropositive RA		Seronegative RA		Any RA		SLE, SSc, DM	
Exposure	n	RR (95% CI)	n	RR (95% CI)	N	RR (95% CI)	n	RR (95% CI)
Dust type								
Neither dust	182	1.0 (Referent)	74	1.0 (Referent)	273	1.0 (Referent)	47	1.0 (Referent)
Silica	127	1.28 (1.02-1.61)	57	1.46 (1.03-2.07)	195	1.33 (1.11-1.60)	42	1.76 (1.16-2.68)
Other inorganic	158	1.27 (1.02-1.57)	64	1.28 (0.92-1.79)	245	1.32 (1.11-1.57)	39	1.19 (0.78-1.82)
Smoking								
Never	82	1.0 (Referent)	50	1.0 (Referent)	147	1.0 (Referent)	34	1.0 (Referent)
Ever smoker	385	2.41 (1.89-3.07)	145	1.52 (1.10-2.12)	566	1.99 (1.66-2.40)	94	1.73 (1.15-2.60)

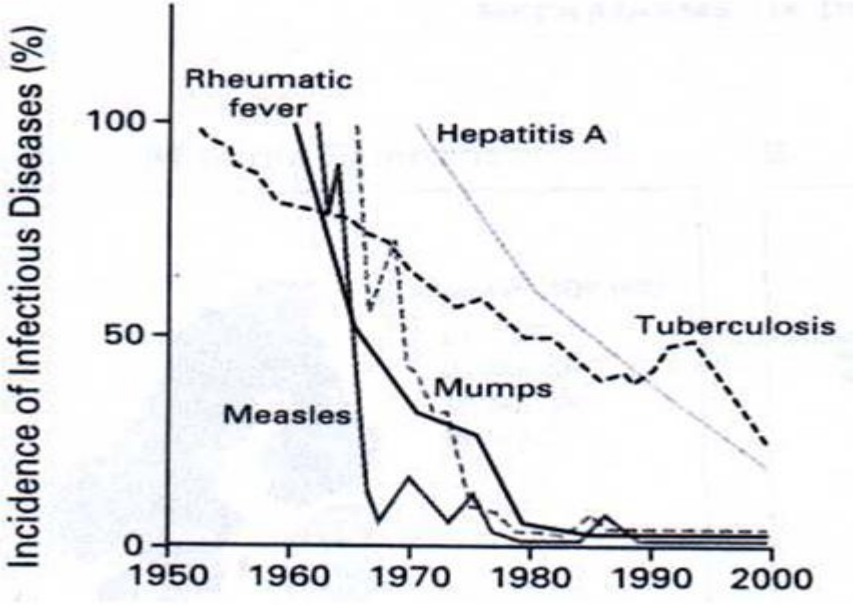
All risk estimates adjusted for age (10-year increments), smoking status, and both of the job exposure matrix exposure categories shown (silica and other inorganic dust).
CI = confidence interval; DM = dermatomyositis; RA = Rheumatoid arthritis; RR = relative risk; SLE = Systemic lupus erythematosus; SSc = Systemic sclerosis.

Blanc et al. Am J Med 2015

Environnement et lupus

L'hypothèse hygiéniste

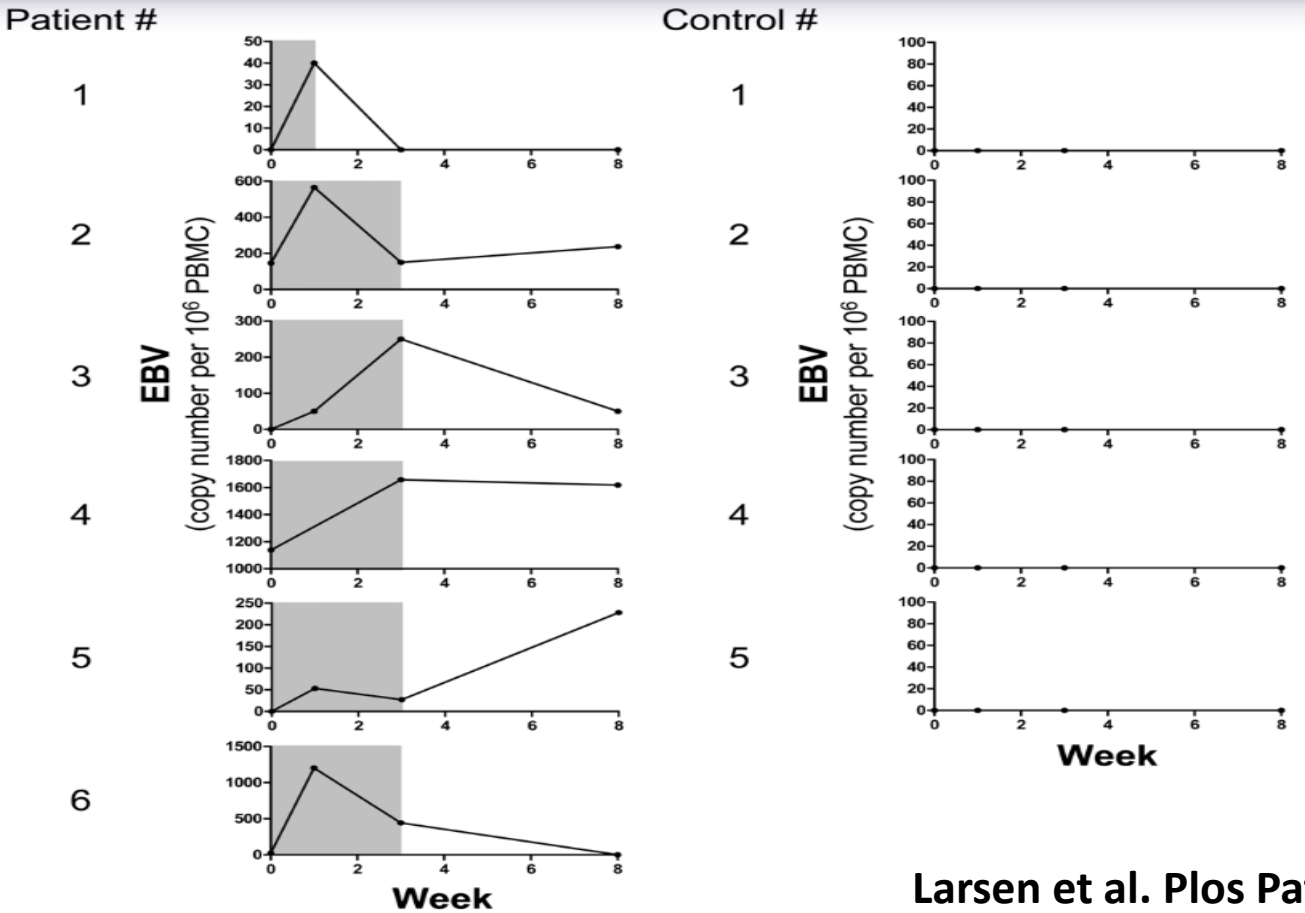




Bach JF New Engl J Med 2002

Infection à EBV et lupus

high disease activity

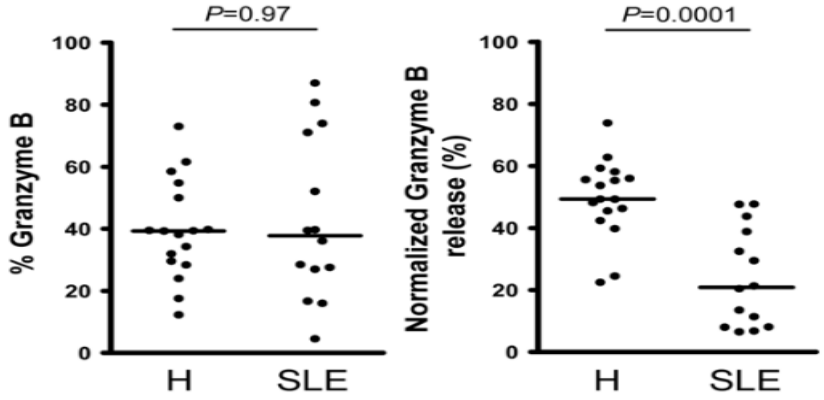


Larsen et al. Plos Pathogen 2011

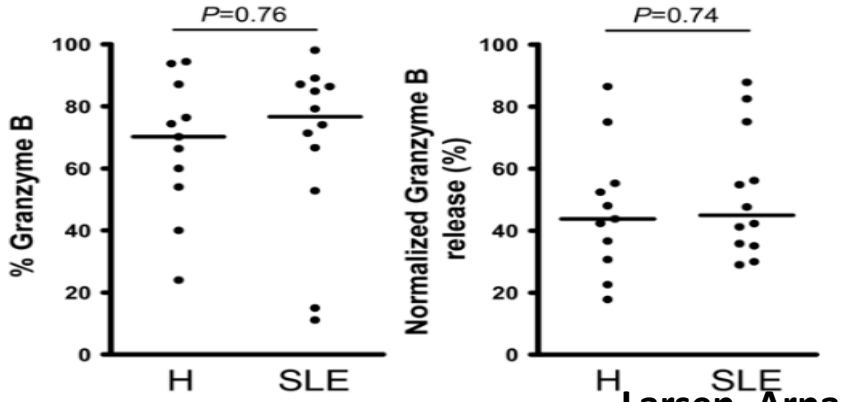
Infection à EBV et lupus

Exhausted Cytotoxic Control of Epstein-Barr Virus in Human Lupus

EBV



CMV



Larsen, Arnaud et al. Plos Pathogen 2011

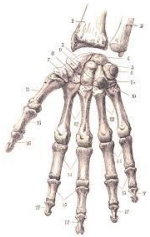
Une interaction multifactorielle complexe

Génétique
(>110 gènes impliqués*)

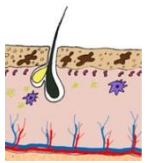
Hormones
(oestrogènes)

Environnement
(ex : UV, médicaments)

Système immunitaire

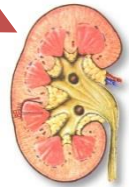


Articulations



Peau

Séreuses



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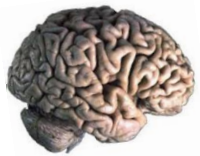


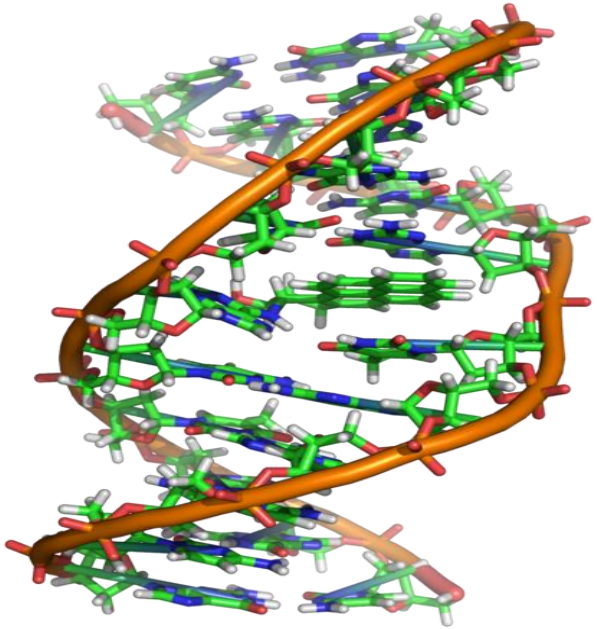
SNC

*Rares formes monogéniques

Génétique ou environnement ?

Nottingham	**Total 25 / 100 000** Afro-Caribbean 207 Asian (Chinese) 93 Asian (Indian) 49 Whites 20
Leicester	**Total 26 / 100 000** Asian 64 Whites 20
Birmingham	**Total 28 / 100 000** Afro-Caribbean 112 Asian (Indian) 47 Whites 21

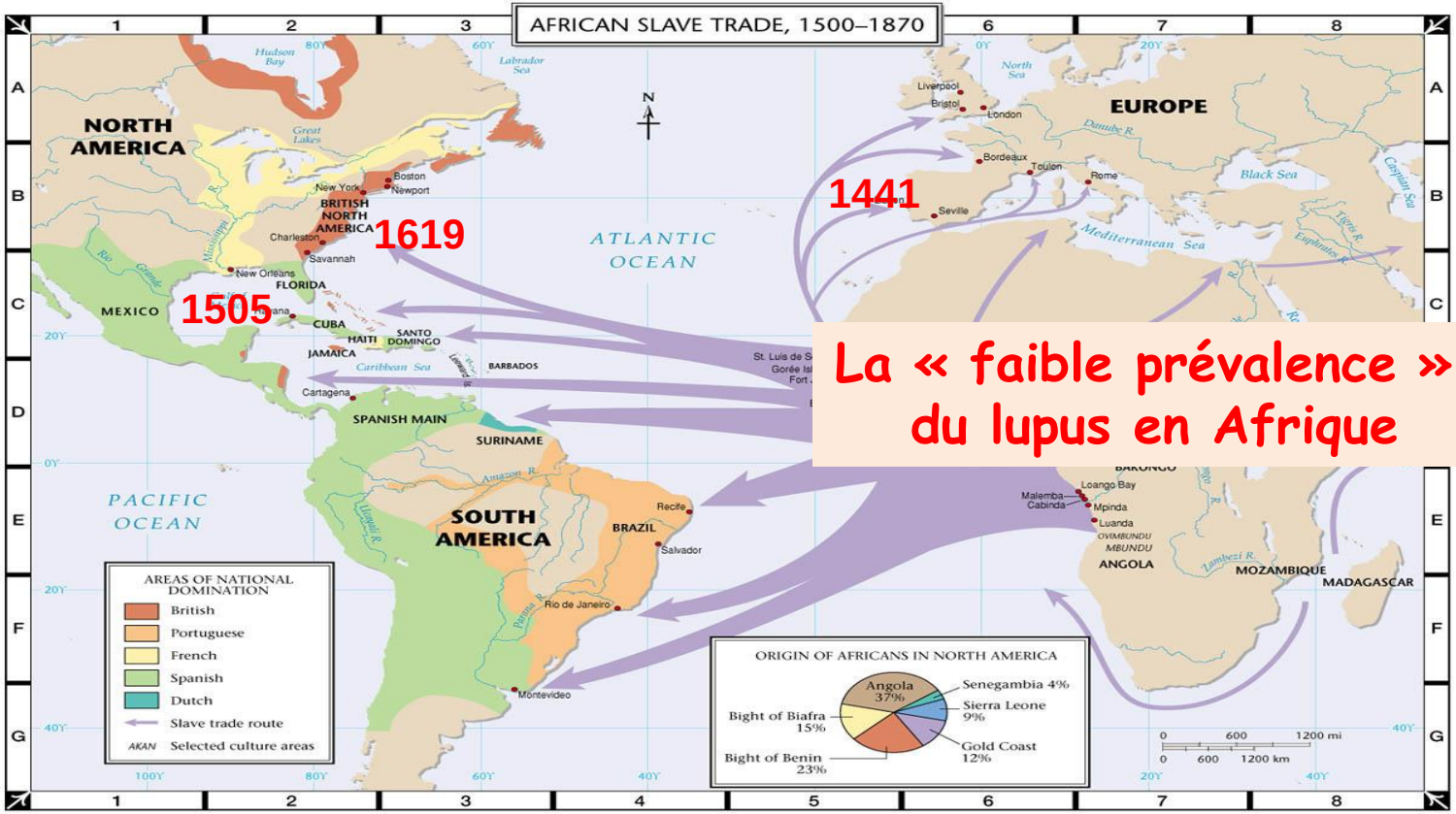
Génétique ou environnement ?



ou…

Génétique ou environnement ?

Modification du risque chez les migrants



La « faible prévalence » du lupus en Afrique

Génétique ou environnement ?

L'absence de donnée fiable en Afrique

Table 1. Systemic lupus erythematosus (SLE) in populations of African ancestry*

Country, state, or city (ref.)	No. of SLE cases	Population-based	Years studied	ACR criteria	Incidence in females	Prevalence in females
West Africa						
Ghana (39)	11	No	1983–1989	1971	NA	NA
Guinea (33)	1	No	1971	None	NA	NA
Nigeria (31, 35)	3	No	?, ?	None	NA	NA
Ivory Coast (34)	9	No	1972–1983	1971	NA	NA
Gabon (36)	1	No	1968	None	NA	NA
Congo Republic (37)	3	No	1961–1962	None	NA	NA
Senegal (32, 38)	4	No	1973–1975, 1959	None	NA	NA
Africa, other						
Zimbabwe (18–20, 23, 24)	71	No	1962–1967, ?, ?, 1979–1983	None, 1971, 1982	NA	NA
South Africa (16, 17, 21, 22, 25, 27)	287	No	1984–1990, ?, ?, 1975–1987, 1969–1975, 1960–1972	None, 1971, 1982	NA	NA
Uganda (26, 28)	26	No	1968–1978, ?	1971, none	NA	NA
Kenya (29)	1	No	1961	None	NA	NA
Ethiopia (30)	4	No	1971–1978	None	NA	NA

ETUDE AFRILUP

Bae et al. Arthritis Rheum 1998

Génétique ou environnement ?

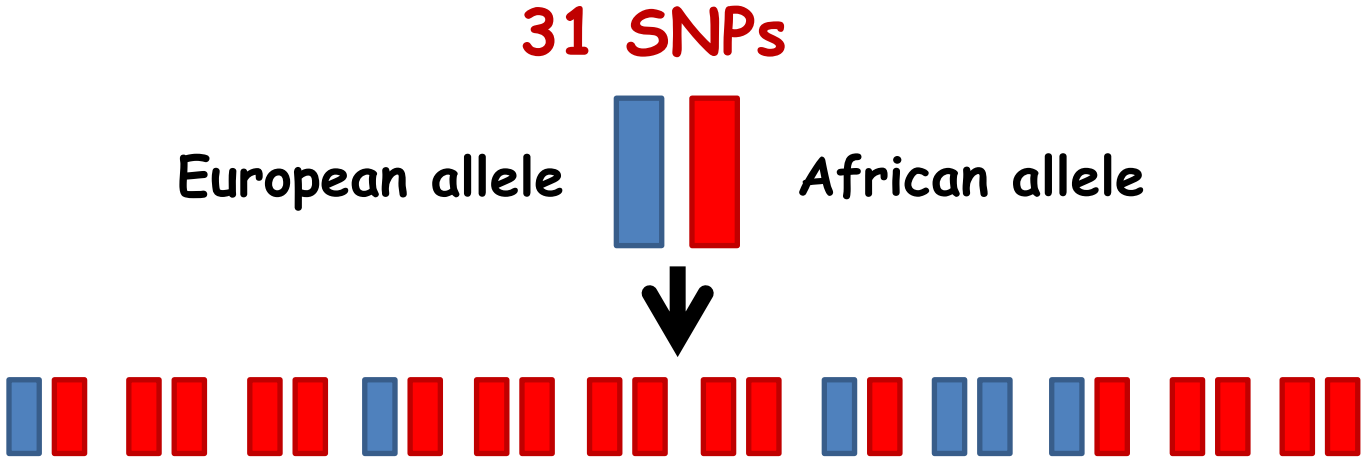
Systemic lupus erythematosus in migrants from west Africa compared with Afro-Caribbean people in the UK

SLE has a high prevalence in Afro-Caribbean populations but has been reported to be rare in west Africa. We assessed prevalence (per 100 000) of SLE in women in an area of south London and estimated it to be 177 (95% CI 135–220) in Afro-Caribbeans, 110 (58–163) in west Africans, and 35 (26–43) in Europeans. The high prevalence of SLE in recent migrants from west Africa suggests that the disease is not rare in west Africa, and that there is a genetic basis for the high risk of SLE in people of west African descent compared with other groups.

Molokhia et al. Lancet 2001

Génétique ou environnement ?

Relation of risk of systemic lupus erythematosus to west African admixture in a Caribbean population



Molokhia et al. Hum Genet 2003

Génétique ou environnement ?

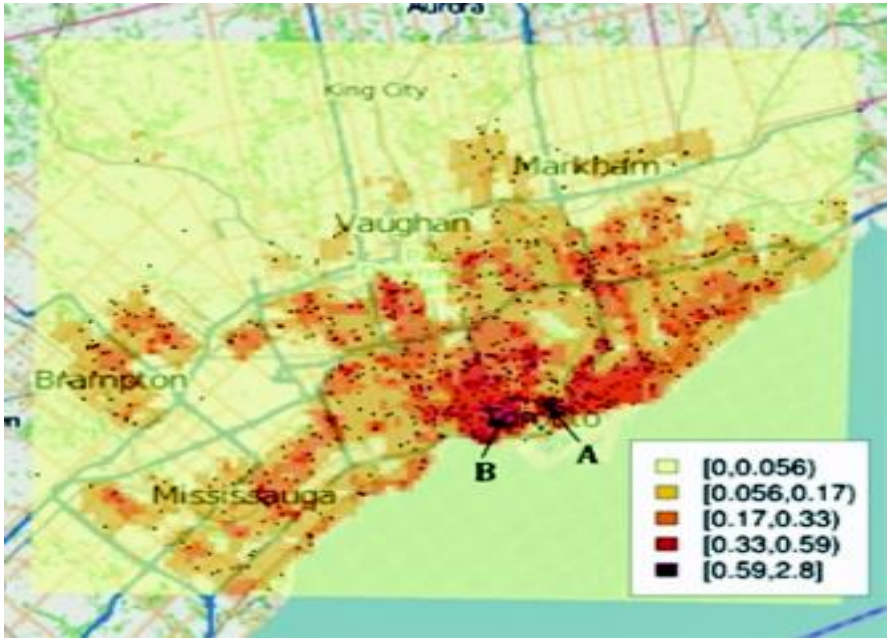
Relation of risk of systemic lupus erythematosus to west African admixture in a Caribbean population

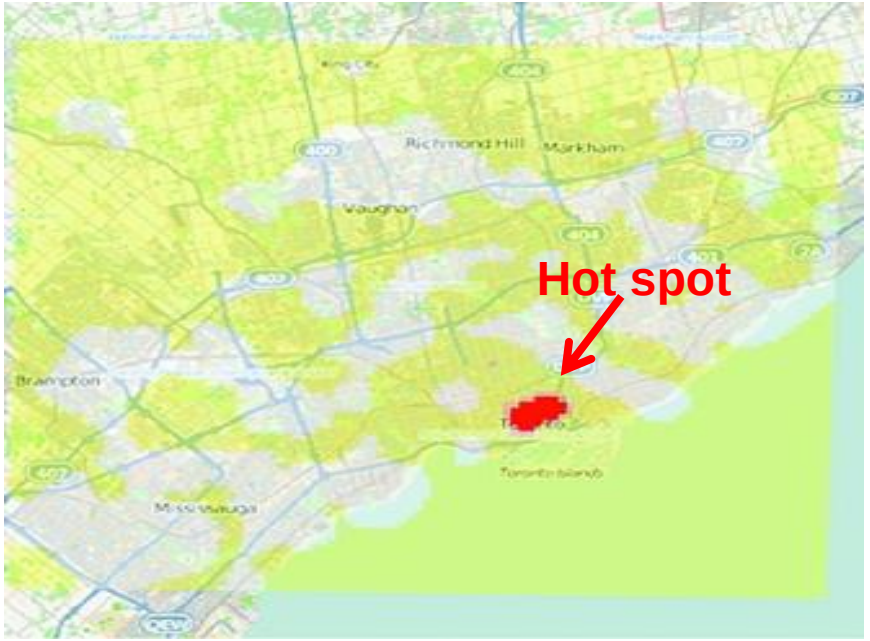
Factor	Odds ratio associated with unit change in African admixture	95%CI
Univariate analyses: risk factors examined one at a time, with age and sex as only other variables in the model		
African admixture	32.5	2.0–517
Lived at age 12 in household lacking water supply	2.2	1.1–4.4
Age completed full-time education[a]	1.5	0.9–2.4
Multivariate analysis		
African admixture	28.4	1.7–485
Lived at age 12 in household lacking water supply	2.7	1.2–5.8
Years of education	2.0	1.1–3.3

Molokhia et al. Hum Genet 2003

Une interaction complexe

A Hot Spot for Systemic Lupus Erythematosus, but Not for Psoriatic Arthritis, Identified by Spatial Analysis Suggests an Interaction Between Ethnicity and Place of Residence





Al-Maini et al. Arthritis Rheum 2013

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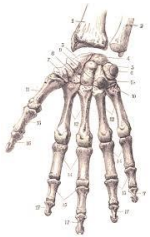

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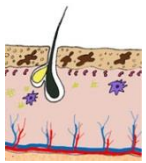

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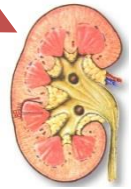

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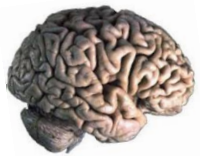

SNC

*Rares formes monogéniques

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Service de rhumatologie, Hôpitaux Universitaires de Strasbourg

Centre National de Référence des Maladies Systémiques Autoimmunes Rares