

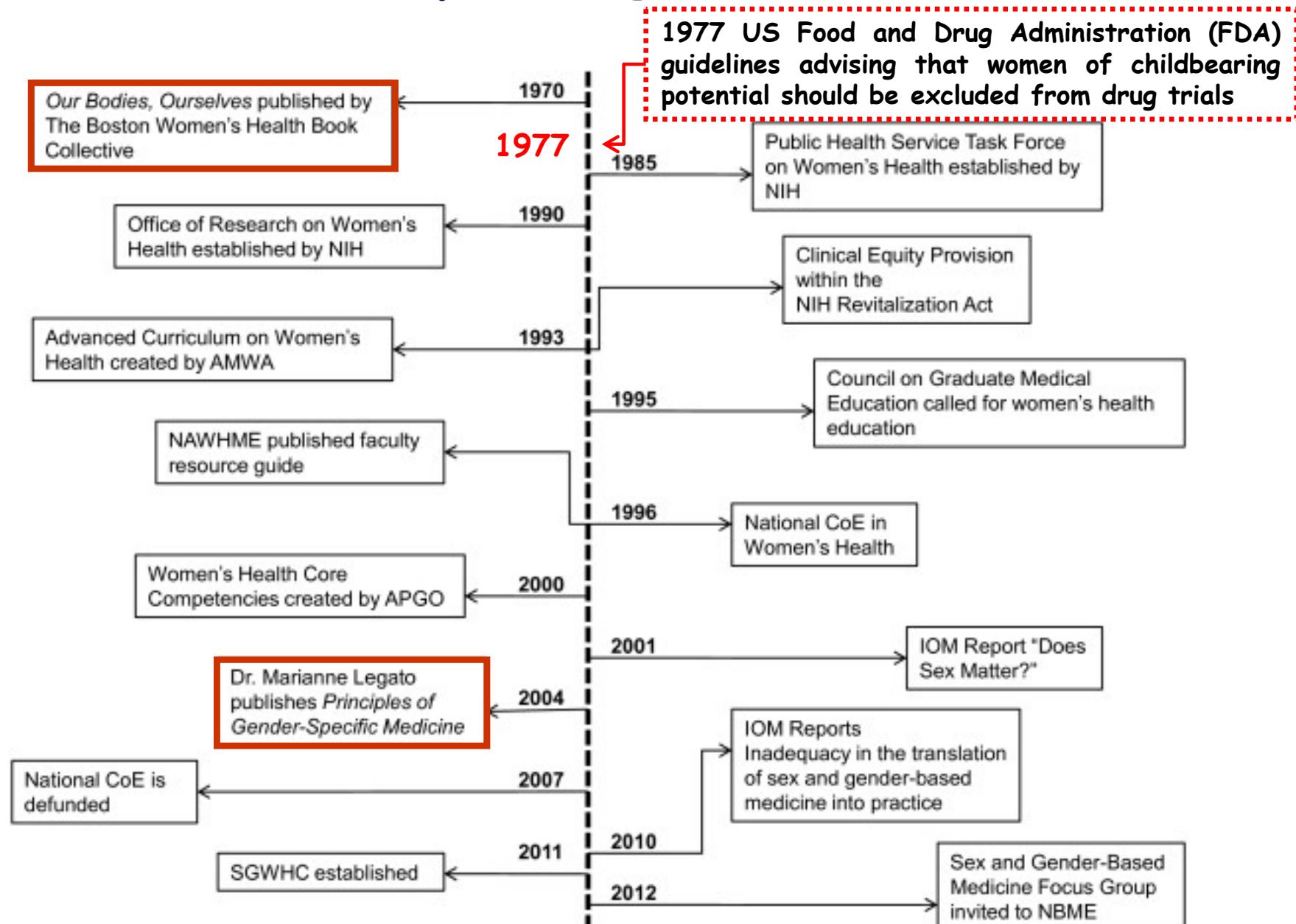


Medicina di genere in Allergologia

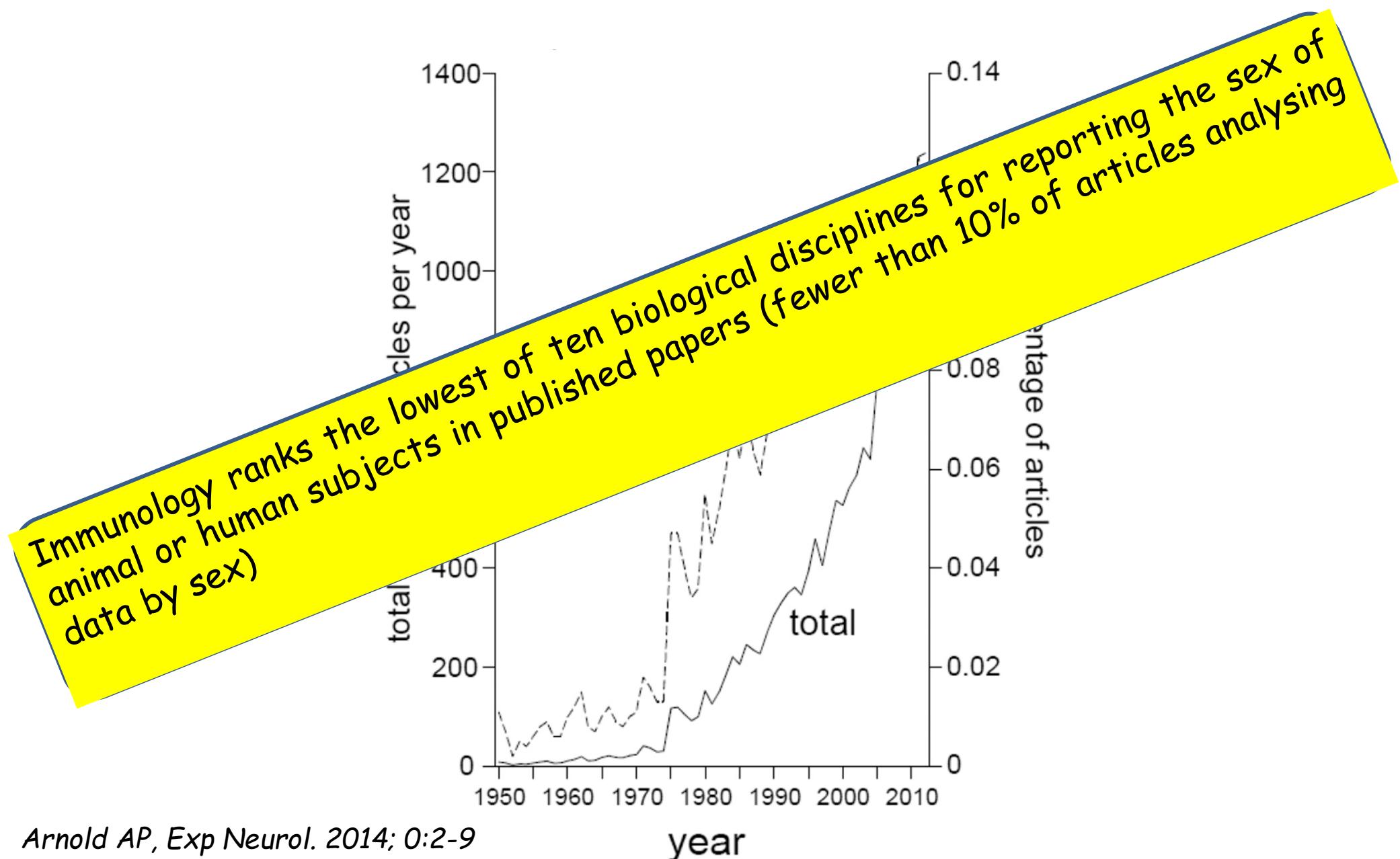
Prof.ssa Erminia Ridolo
Allergologia e Immunologia Clinica
Università di Parma



The road map of gender medicine



Sex differences and Medline-PubMed between 1950 and 2012



Il sesso è una variabile biologica da considerare negli studi allergo-immunologici

The unequally distribution between sex of specific immune response

nature

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Saturday 22 February 2014

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letters to nature

Nature 214, 1224 - 1225 (17 June 1967); doi:10.1038/2141224a0



Influence of Sex on Immunoglobulin Levels

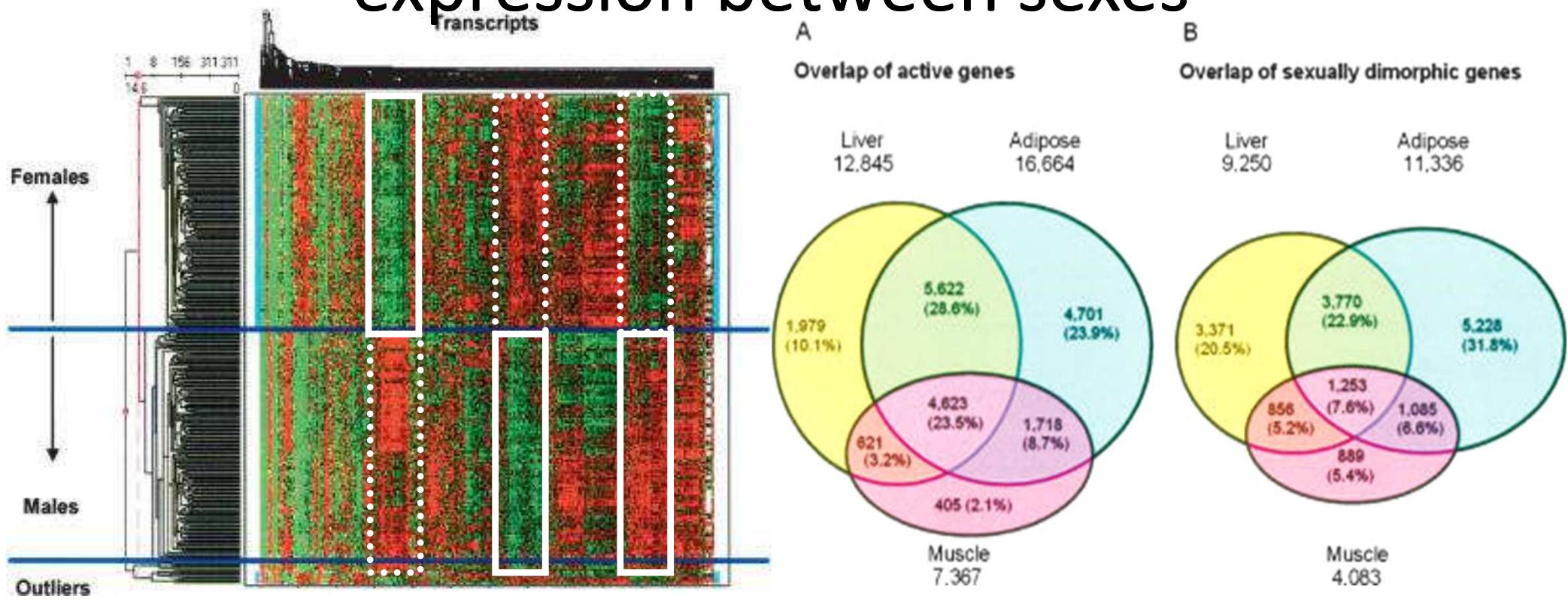
MICHAEL BUTTERWORTH, BARBARA MCCLELLAN & MATHEA ALLANSMITH

Department of Statistics, Department of Medical Microbiology, Stanford University, Stanford, California.

WE have determined the IgG, IgA, and IgM levels of 315 normal adults and 503 children of various ages¹. To find out whether differences exist between males and females, we compared the levels for the sexes within various age groups, breaking these down into "fine" and "coarse" subgroups. There were fourteen fine groups of about thirty children each and five coarse groups of about 100 children each. The subjects were laboratory personnel, blood donors, college students, school-children, babies, and inmates of a home for recently abandoned children, all apparently healthy. Immunoglobulins were determined by a single radial immunodiffusion method² using commercial antibody-agar plates standardized against purified immunoglobulins. The standardization curves used were the least-squares linear regressions of log mg/100 c.c. versus the log ring diameter. This relationship fitted the results better than the semilogarithmic one used by others²⁻⁴. The males and females in each group were compared by Student's *t* test. We used log mg/100 c.c. for the *t* tests and to calculate the means, because the distributions of the three major immunoglobulins among adults are approximately log normal.

1. Allansmith, M., in *Human Development*, 19 (W. B. Saunders, Philadelphia, Pennsylvania, 1966).
2. Fahey, J. L., and McKelvey, E. M., *J. Immunol.*, **94**, 84 (1965). | [PubMed](#) | [ISI](#) | [ChemPort](#) |
3. Stiehm, E. R., and Fudenberg, H. H., *Pediatrics*, **37**, 715 (1966). | [PubMed](#) | [ISI](#) | [ChemPort](#) |
4. Kohler, P. F., and Farr, R. S., *Nature*, **210**, 1070 (1966). | [Article](#) | [PubMed](#) | [ISI](#) | [ChemPort](#) |

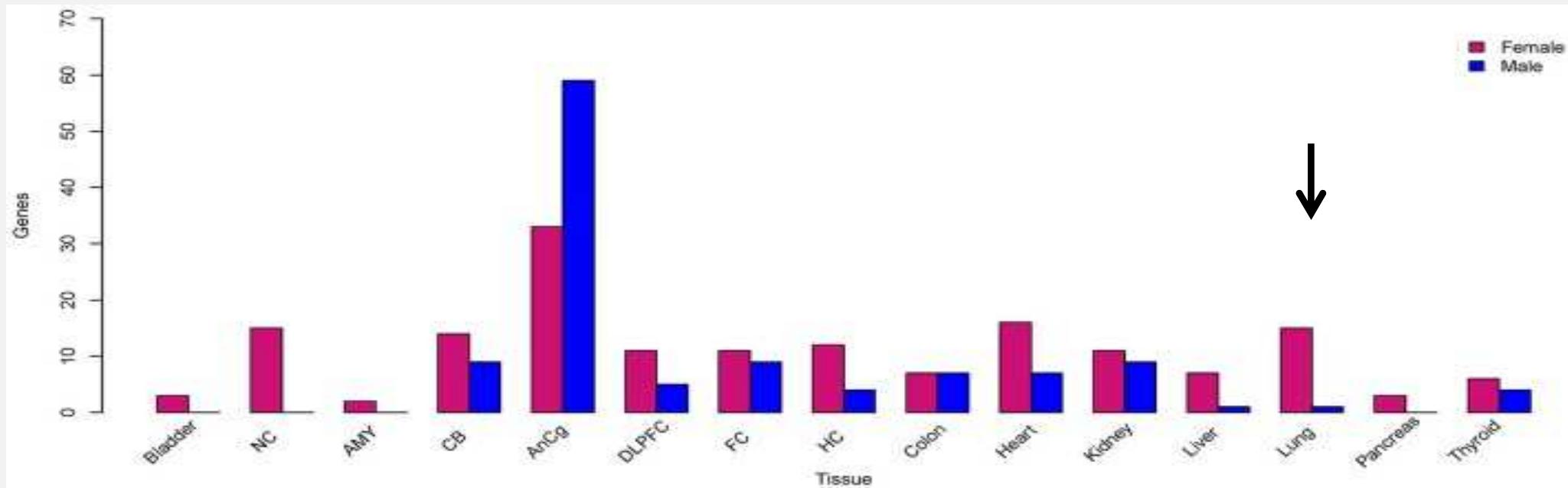
Sexual dimorphism and differences in gene expression between sexes

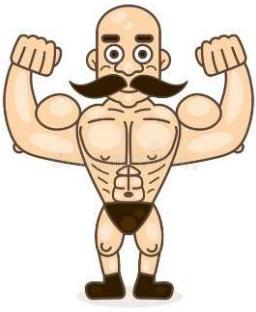


BUT...

- i) the degree of sexual dimorphism ranges of active genes depends on the tissue(i.e. 14% in the brain, 70% in the liver)
- ii) some genes display evidence of clustering not only on the sex chromosomes, but also on several autosomes

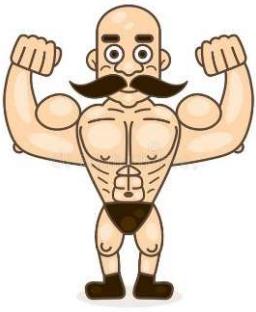
Lungs express different genes in males and females





Is the male sex the stronger sex ?

- The incidence of infections and severe infection is higher in men than women for viral, bacterial, fungal and parasitic diseases.
- The prevalence of sexually transmitted infections (STIs) such as HIV and HSV-2 is higher among woman.

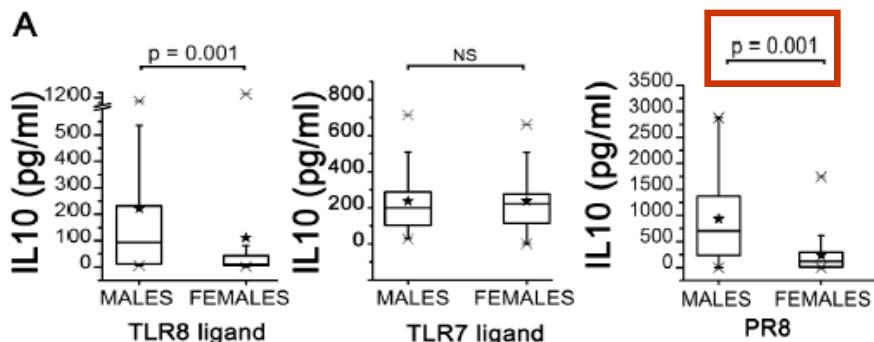
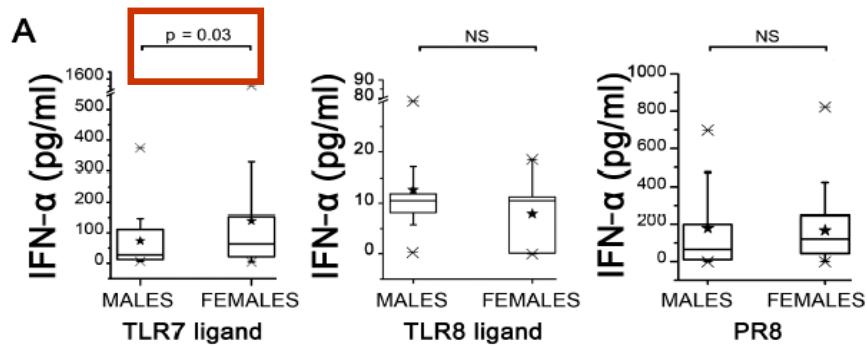


Is the male sex the stronger sex ?

OPEN ACCESS Freely available online

PLOS one

Sex Differences in the Response to Viral Infections: TLR8 and TLR9 Ligand Stimulation Induce Higher IL10 Production in Males



Is female sex really disadvantaged?

How gender influences immunological mechanisms in health



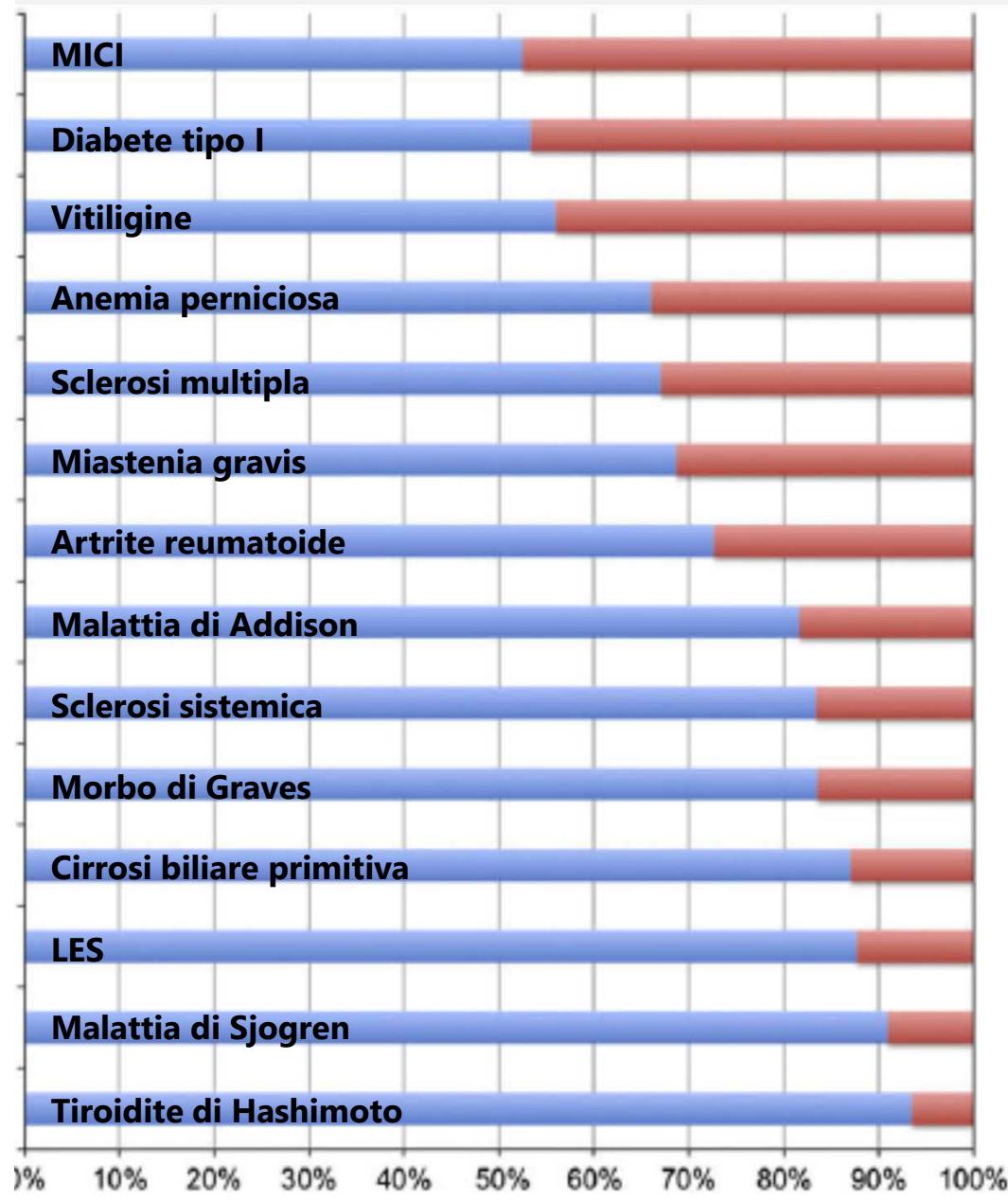
- antibody production and in particular IgM
- cell-mediated responses after immunization
- CD4+ T cell counts, C4/CD8 ratio
- T_H1 responses
- ILCs2



- inflammatory response to infectious organisms
- CD8+ counts but reduced cytotoxic potential
- Tregs
- T_H17

Outcome and survival rates from illnesses — such as those caused by infectious diseases, sepsis, trauma or injury — are better in women than in men

The disadvantage to be a female: the “gender gap” in autoimmune disease

Gender prevalence ratios for selected autoimmune diseases^a

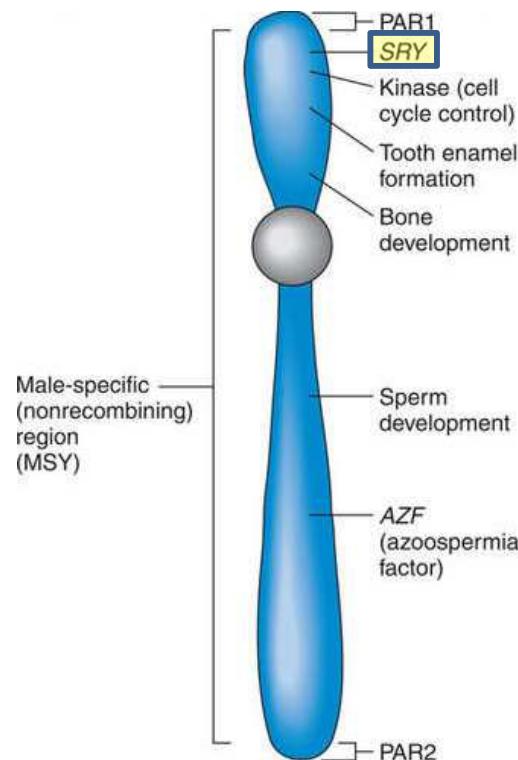
Autoimmune disease	Ratio (female/male)
Hashimoto's thyroiditis/hypothyroidism	50:1
SLE	9:1
Sjögren's syndrome	9:1–20:1
Antiphospholipid antibodies	9:1
Primary biliary cirrhosis	9:1
Mixed connective tissue disease	8:1
Chronic active hepatitis	8:1
Grave's disease/hyperthyroidism	7:1
Rheumatoid arthritis	3:1–4:1
Scleroderma	3:1–4:1
Myasthenia gravis	2:1–3:1
Multiple sclerosis	2:1
Autoimmune thrombocytopenic purpura	2:1
Type 1 Diabetes mellitus	1:1–2:1
Ulcerative colitis	1:1
Autoimmune myocarditis	1:1.2

^a Modified from Fairweather and Rose [55] and McCarthy [4].

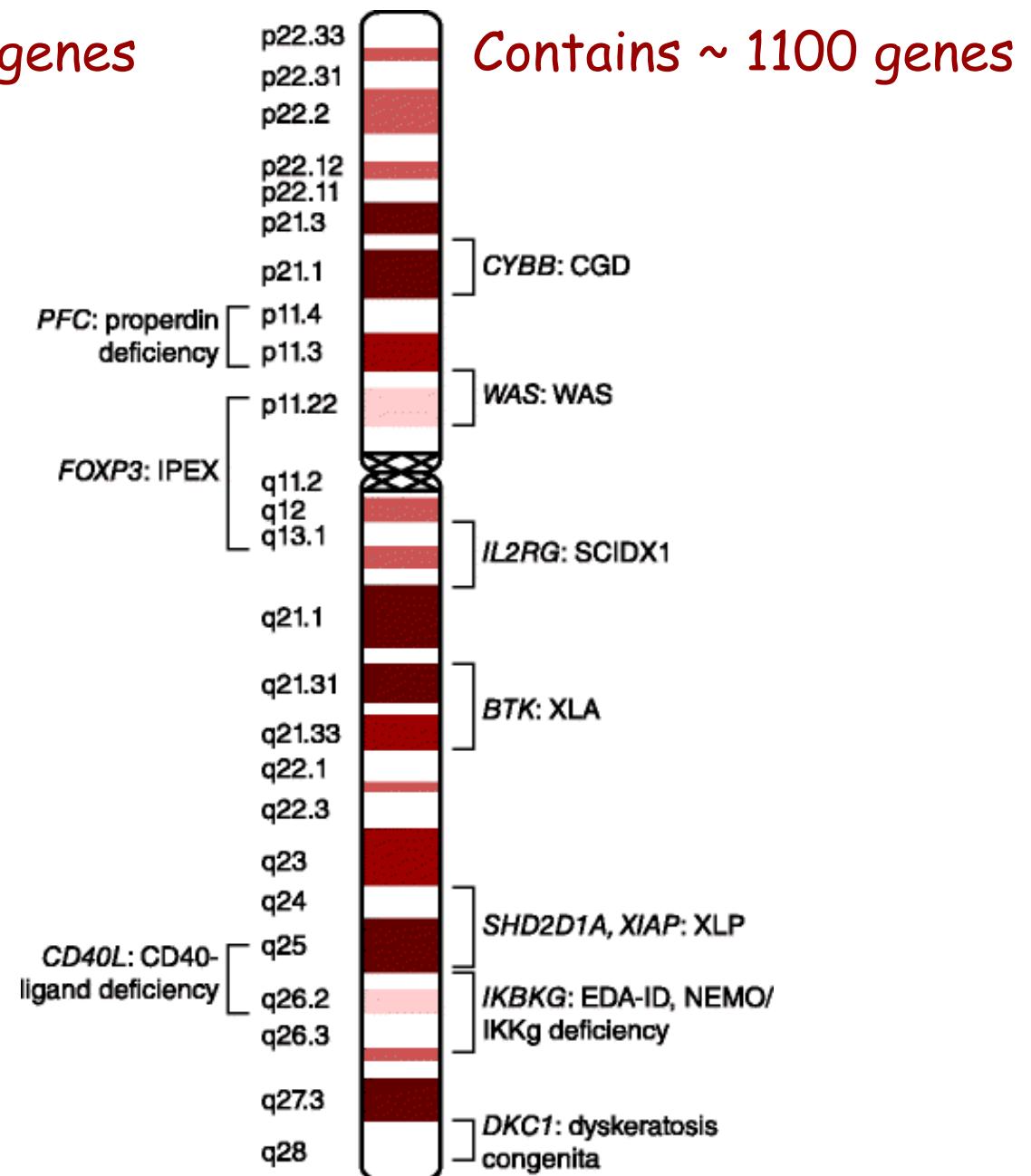
■ female
■ male

Sexual dimorphism and immune system

Several genes clue for the immune function map on X chromosome



Contains ~ 100 genes

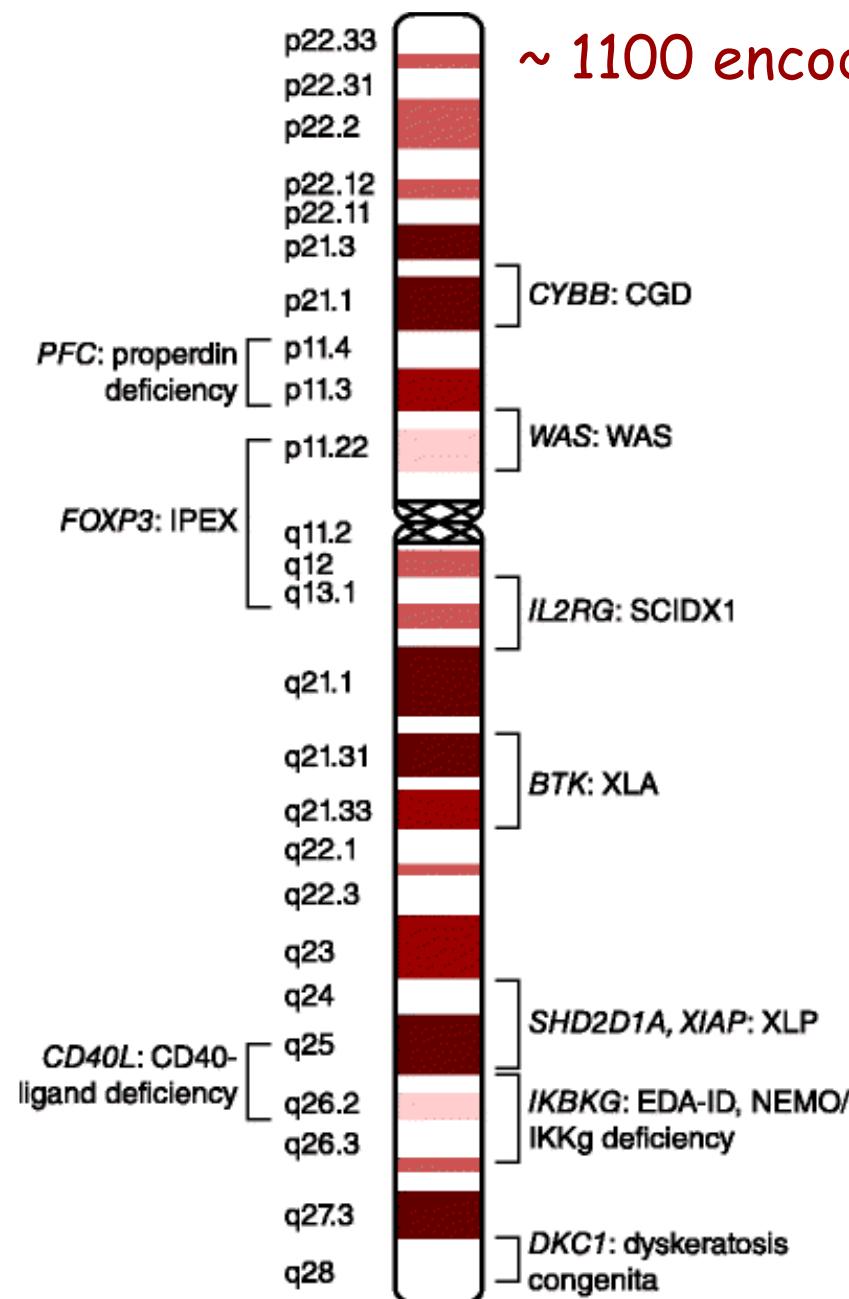


Several genes clue for the immune function map on X chromosome

a Receptors & associated proteins

AR	Androgen receptor
AGTR2	Angiotensin receptor 2
CSF2RA	Colony-stimulating factor 2 receptor α (granulocyte-macrophage)
GPCR	G-protein coupled receptors 23, 50, 101, 112, 119, T74 and CX-chemokine receptor 3
CYSLTR1	Cysteinyl leukotriene receptor 1
IL-1RAP1	Interleukin-1 (IL-1) receptor accessory protein-like 1
IL-1RAP2	IL-1 receptor accessory protein-like 2
IL-2RG	IL-2 receptor γ -chain
IL-3RA	IL-3 receptor α -chain
IL-9R	IL-9 receptor
IL-13RA1	IL-13 receptor $\alpha 1$ -chain
IL-13RA2	IL-13 receptor $\alpha 2$ -chain
IRAK	IL-1 receptor-associated kinase
NGFRAP1	Nerve-growth-factor receptor associated protein 1
TLR7	Toll-like receptor 7
TLR8	Toll-like receptor 8

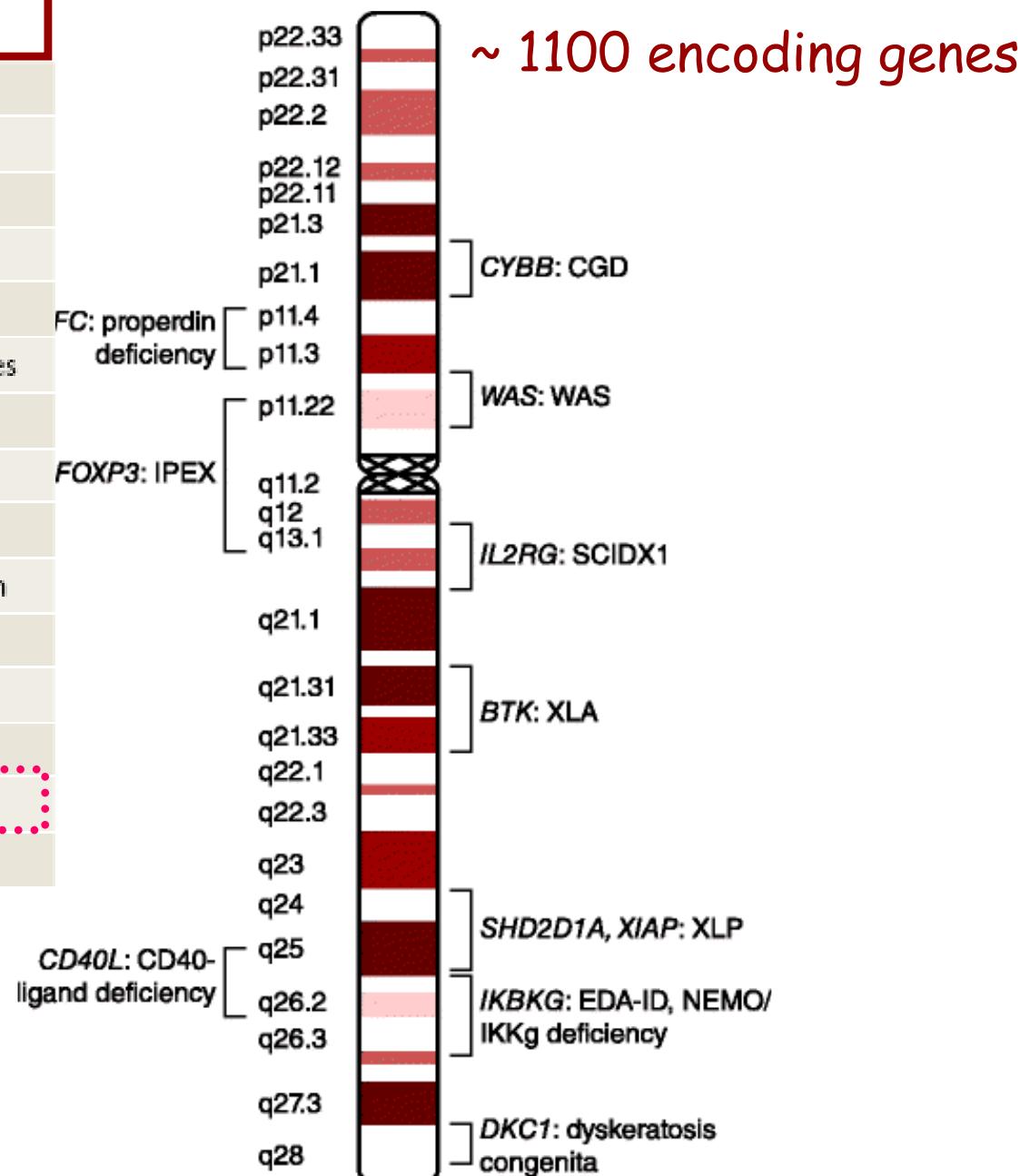
~ 1100 encoding genes



Several genes clue for the immune function map on X chromosome

b Immune-response related proteins

XSCID	X-linked severe combined immunodeficiency
ELK1	Involved in B-cell development
EPAG	Early lymphoid activation protein
GATA1	GATA-binding protein 1
GTD	Gonadotropin deficiency
IDDMX	X-linked susceptibility to insulin-dependent diabetes
IGBP1	CD79A, immunoglobulin binding protein 1
IGSF1	Immunoglobulin superfamily member 1
ITGB1BP2	Integrin-β ₁ -binding protein 2
CD99	Also known as MIC2; associated with T-cell function
MTCP1	Mature T-cell proliferation 1
PFC	Properdin P factor, complement
TIMP1	Tissue inhibitor of metalloproteinase 1
CD40L	CD40 ligand
Z39IG	An immunoglobulin superfamily protein

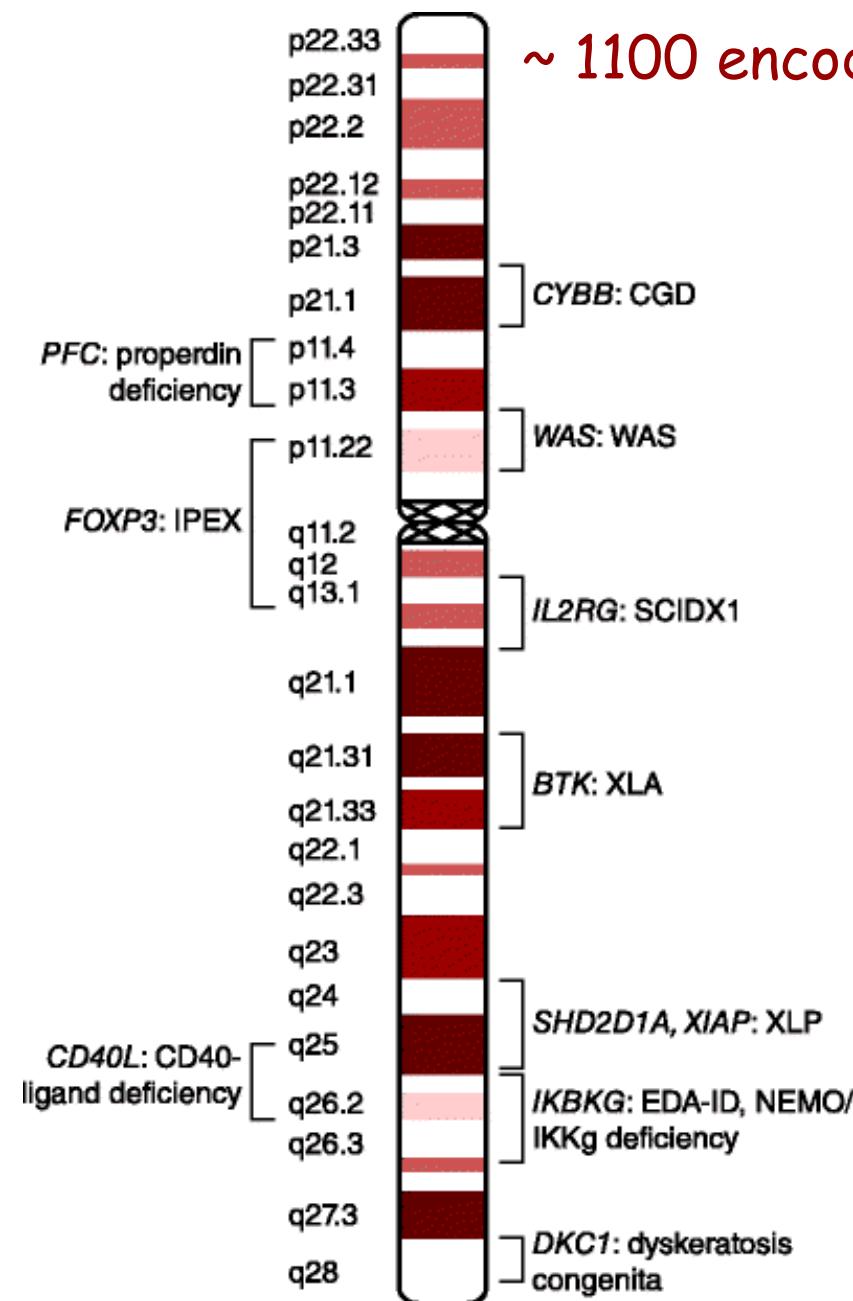


Several genes clue for the immune function map on X chromosome

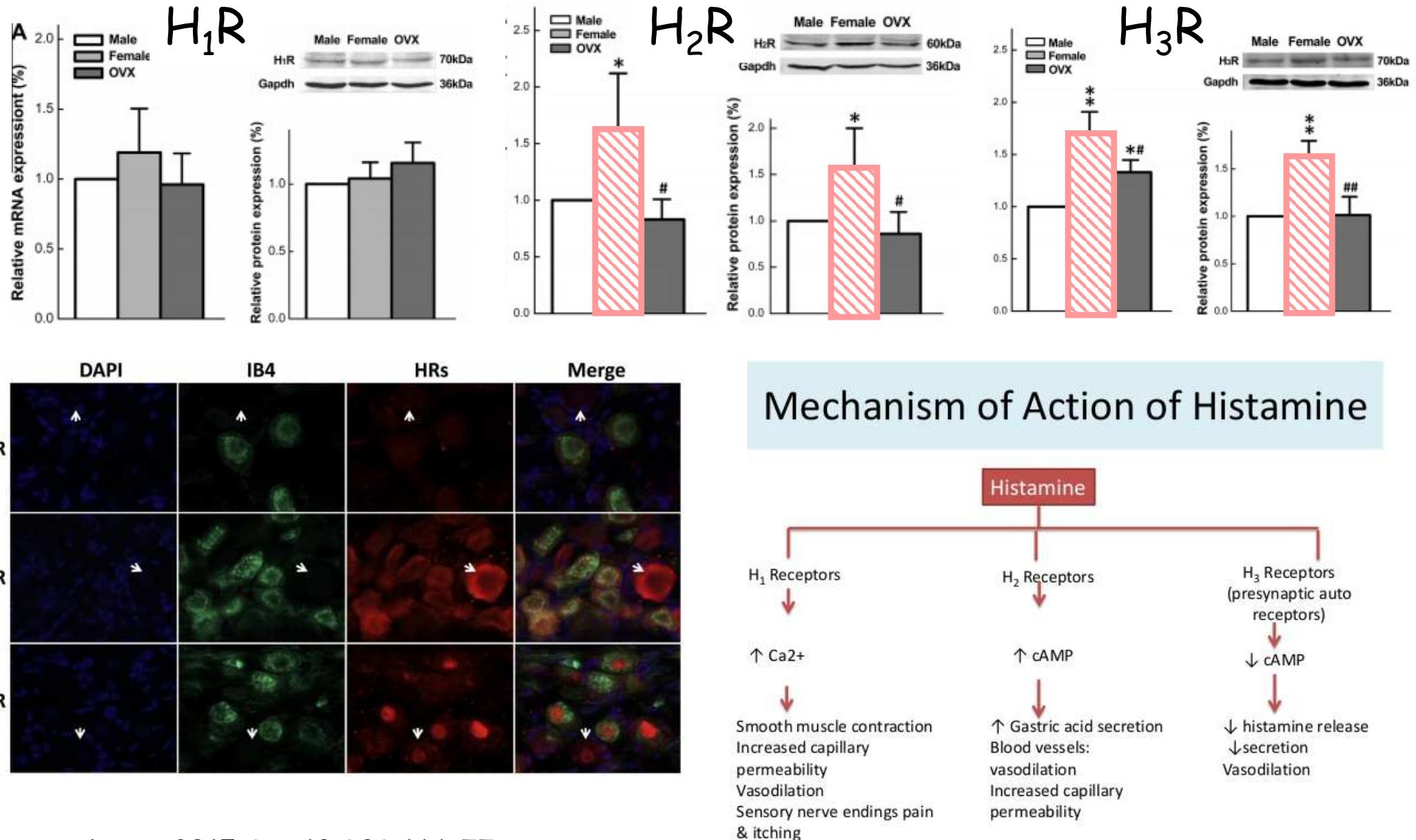
c Transcriptional & translational control effectors

RHOGAP	RAS homologue (RHO) GTPase activating proteins 4, 6
CDC42GEF	Cell-division cycle 42 guanine-nucleotide-exchange factors 6, 9
ETK	Also known as BMX
BTK	Bruton agammaglobulinaemia tyrosine kinase
CDX4	Caudal homeobox transcription factor 4
TRAP170	A co-factor for SP1 transcription factor activation
DUSP	Dual specificity phosphatases 9, 21
EEF	Eukaryotic translation elongation factors 1α13, β4
EIF	Eukaryotic translation initiation factor 1A*, 2a
FOXP3	Forkhead box P3 (associated with the development and function of regulatory T cells)
GAB3	Growth-factor-receptor-bound protein 2-associated binding protein 3
HDAC	Histone deacetylases 6, 8
IKK γ	IκB kinase; also known as NEMO
MAPKKK15	Mitogen-activated protein kinase kinase kinase 15
NF κ BRF	Nuclear factor- κ B (NF- κ B) repressing factor
NRK	NF- κ B-inducing kinase-related kinase
NXF	Nuclear RNA export factors 2, 3, 4, 5
PAK3	p21 (also known as CDKNIA)-activated kinase 3
PPP	Protein phosphatases 1, 2*, 6
PRKCI	Protein kinase C ι
S6K	Ribosomal protein S6 kinase
SWI/SNF	SWI/SNF-related, matrix associated, actin-dependent regulator of chromatin
STK9	Serine/threonine kinase 9
TAFI	TATA-box-binding protein-associated factor 1, TFIID subunit
UBE1	Ubiquitin-activating enzyme E1
UBE2A	Ubiquitin-conjugating enzyme E2A
USP	Ubiquitin-specific proteases 9*, 11, 26, 27, 511
WASP	Wiskott–Aldrich syndrome protein

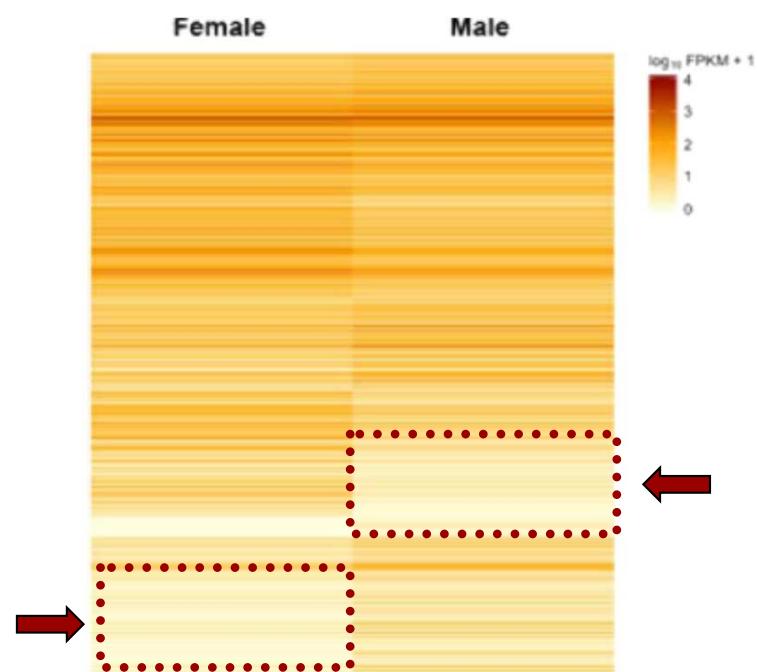
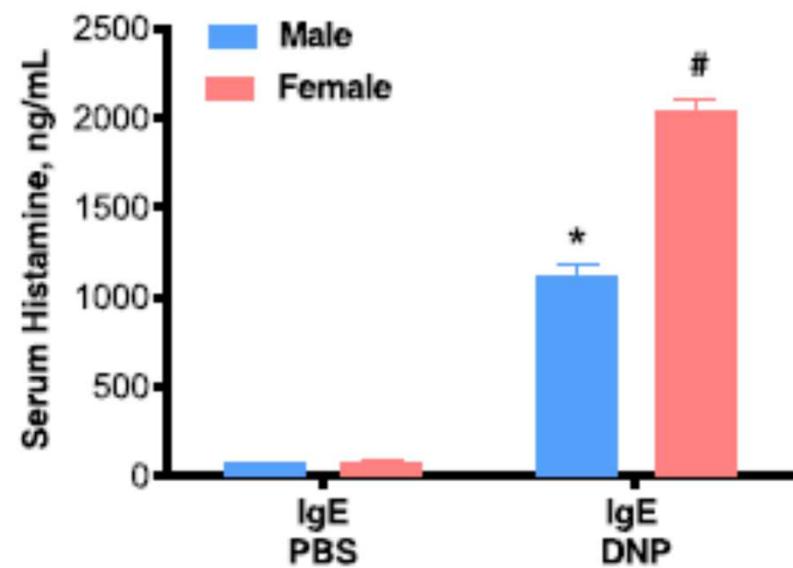
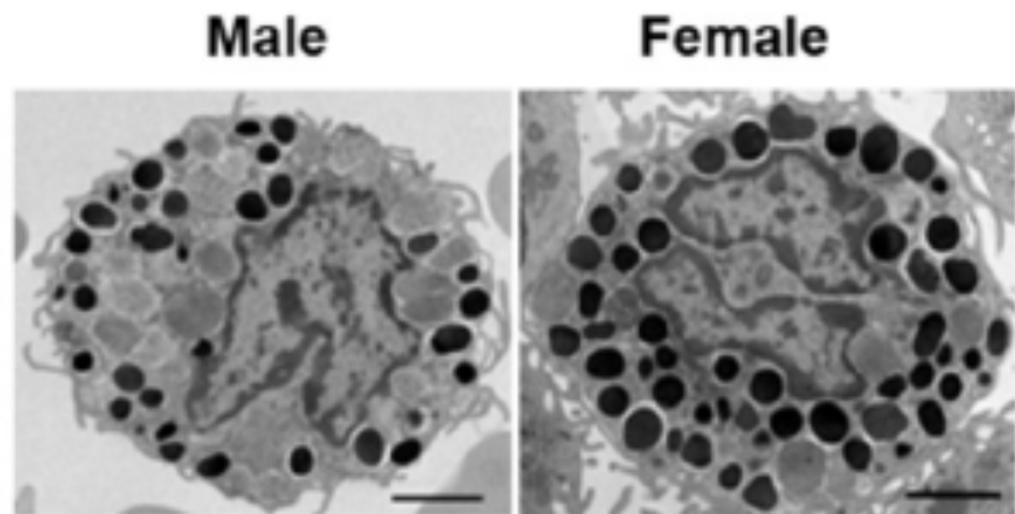
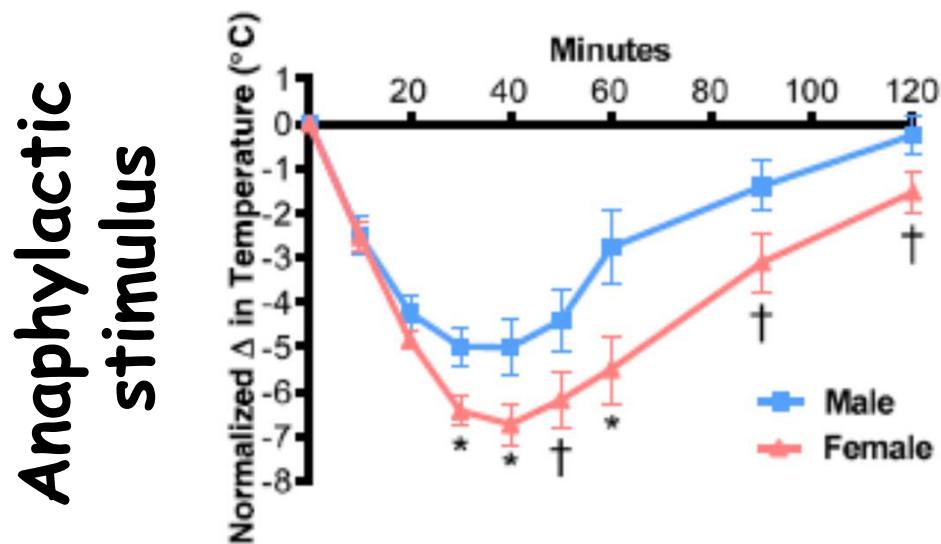
~ 1100 encoding genes



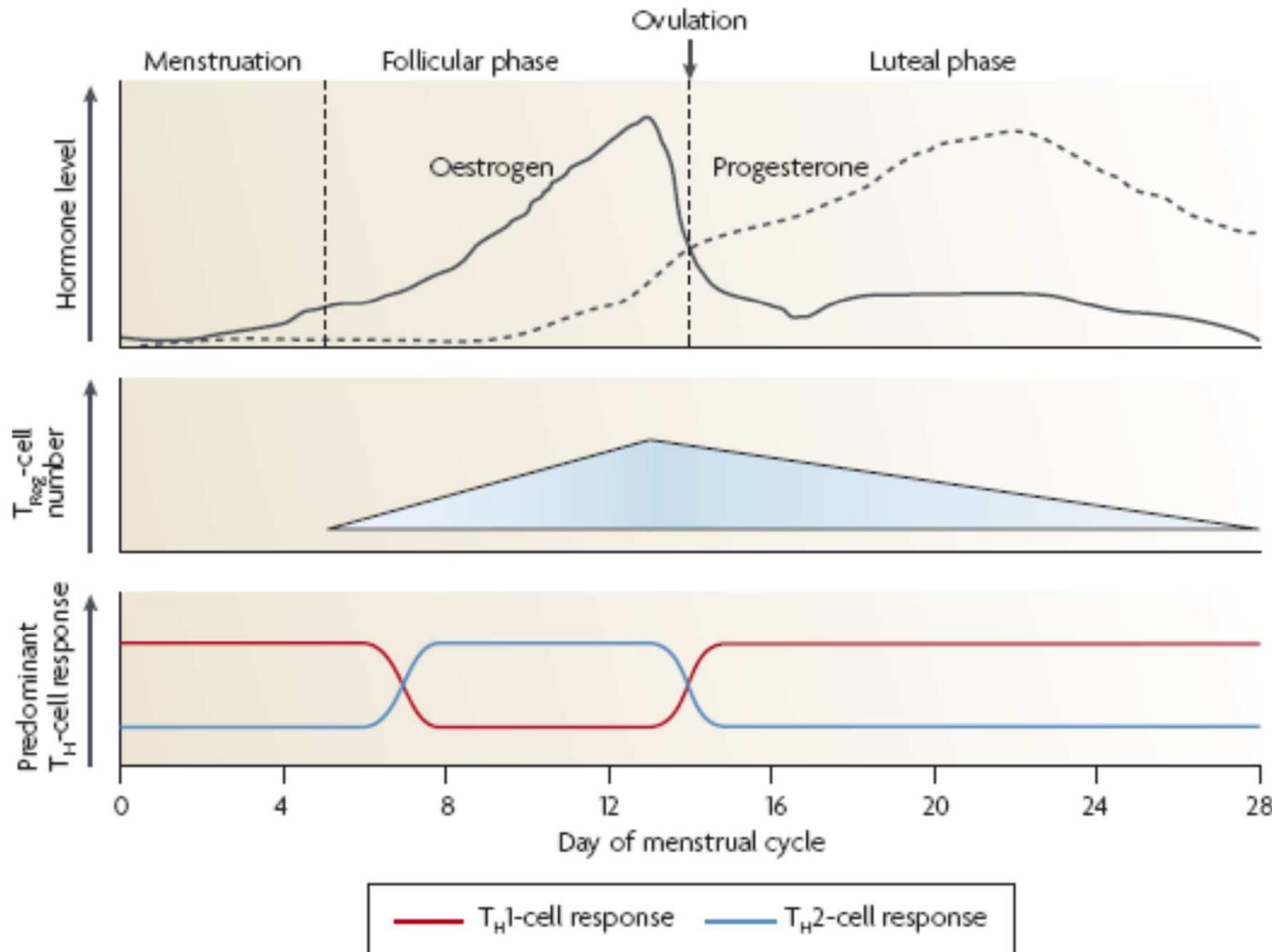
Sexual dimorphism in the expression of Histamine Receptors



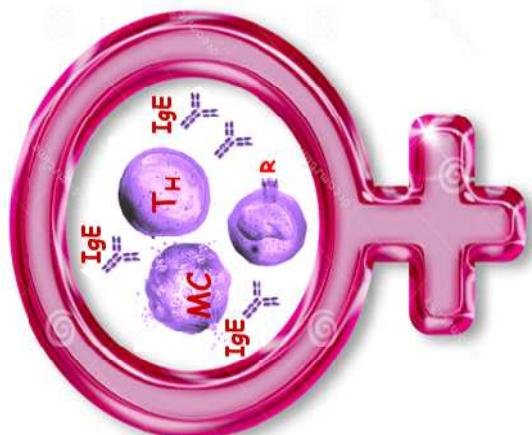
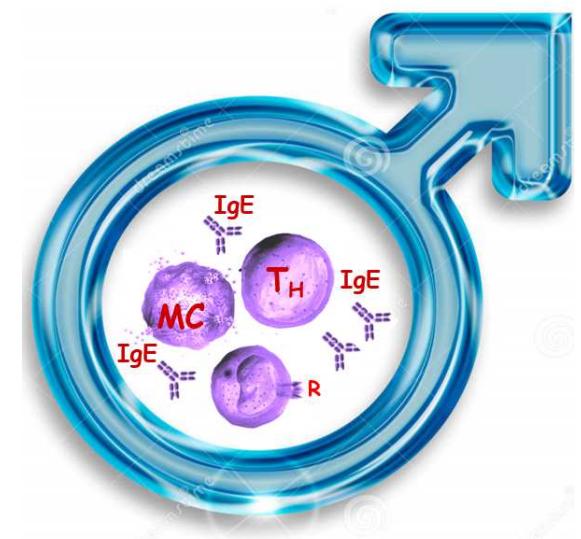
MCs functions depend on sex



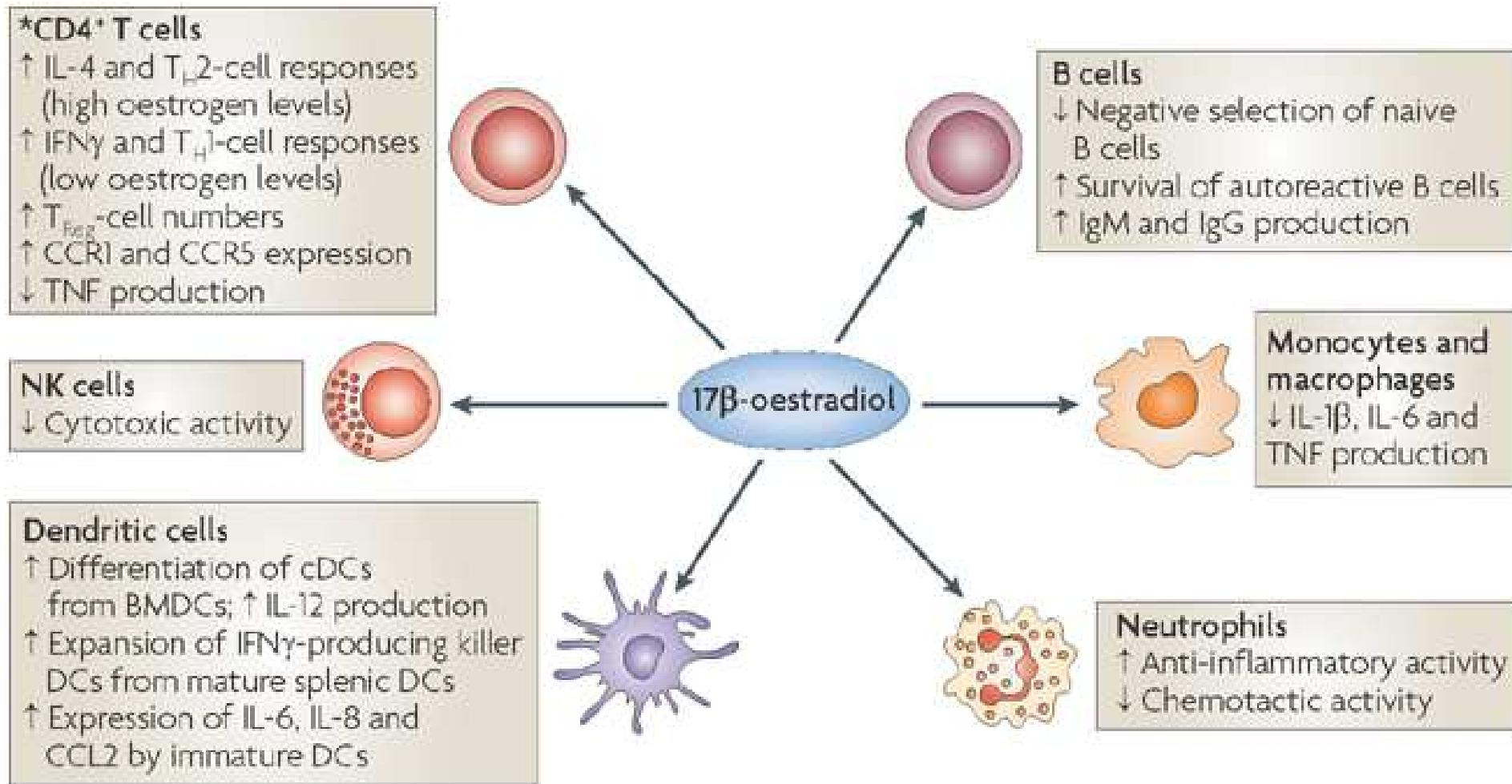
Hormones play several physiological roles

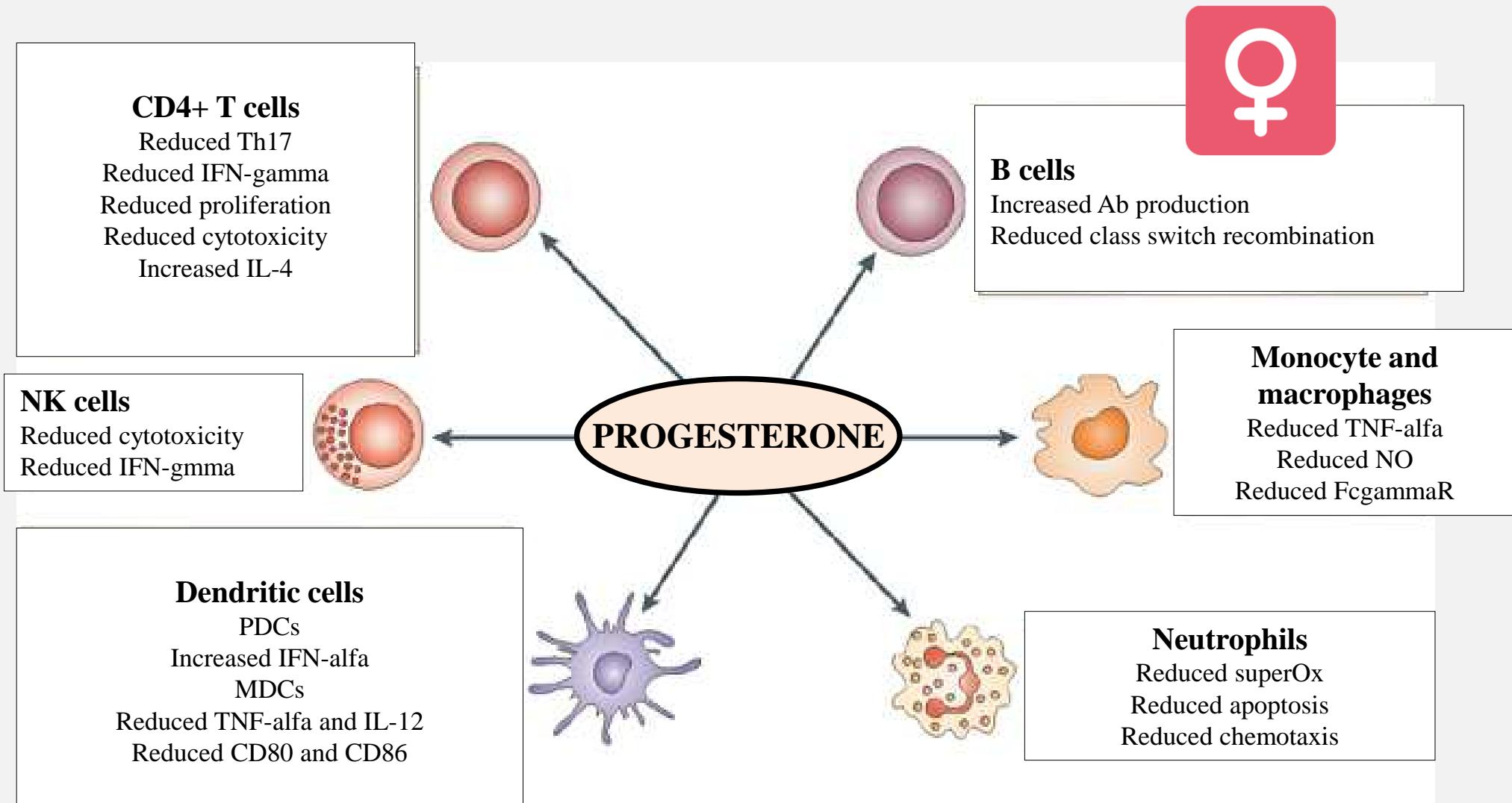


- The male sex hormone testosterone is usually immunosoppressive, while the female hormone estrogen has a tendency to be immunoenhancing.
- Estrogen and progesterone enhance type 2 and suppress type 1 responses in female, while testosterone suppress type 2 response, but with an uneven pattern for type 1 responses in male.

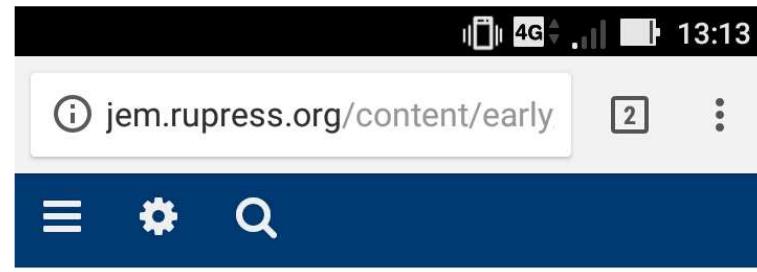


Estrogens polarize T cells towards the T_H2 phenotype





Sex, ILC2s and asthma



JEM The Journal of
Experimental Medicine

Brief Definitive Report
**Androgen signaling
negatively controls group
2 innate lymphoid cells**

Sophie Laffont, Eve Blanquart, Magali Savignac,
Claire Cénac, Gilles Laverny, Daniel Metzger,
Jean-Philippe Girard, Gabrielle T. Belz,
Lucette Pelletier, Cyril Seillet, Jean-Charles Guéry

DOI: 10.1084/jem.20161807 | Published May 8, 2017



Article

Figures & Data

Info

Metrics

Sexual dimorphism in allergy



Asma	Prevale nell'infanzia (1,5 volte)	Prevale dall'adolescenza all'età adulta
Rinite allergica	Prevale nell'infanzia	Prevale dall'adolescenza all'età adulta
Dermatite atopica	Prevale dopo i 65 aa	Prevale fino ai 65 aa
Dermatite da contatto		Prevale nelle donne
Orticaria		Prevale nelle donne
Allergia ai farmaci		Prevale nelle donne
Allergia al veleno di imenotteri	Prevale negli uomini	



Gender Medicine

Congestive heart failure in elderly patients
Edited by Professors C. G. M. de Brujin, J. H. G. M. Busschots, and J. C. M. Verheyen
Volume 7, 2001, 432 pp.
ISBN 0-444-50833-2
Ergonomics in Design Series, Volume 2
Edited by Professors C. G. M. de Brujin, J. H. G. M. Busschots, and J. C. M. Verheyen
Volume 16, 2001, 432 pp.
ISBN 0-444-50834-0
GENDER MEDICINE
Edited by Professors C. G. M. de Brujin, J. H. G. M. Busschots, and J. C. M. Verheyen
Volume 15, 2001, 432 pp.
ISBN 0-444-50835-9
ELSEVIER

Mortality Changes in Intensive Care

+39,437/439,755 (99.93)
1755 (0.07)

der difference = 1219-1221.
Med. 1994; 150: 1219-1221.

© 2010, Pages 109-114

3. Naleway AL, Vollmer WM, Frazier EA, et al. Gender differences in asthma management and quality of life. *J Asthma*. 2006;43:549-552.

Gender Differences in the Prevalence of Hypertension

Gender Differences in the Prevalence of Hypertension

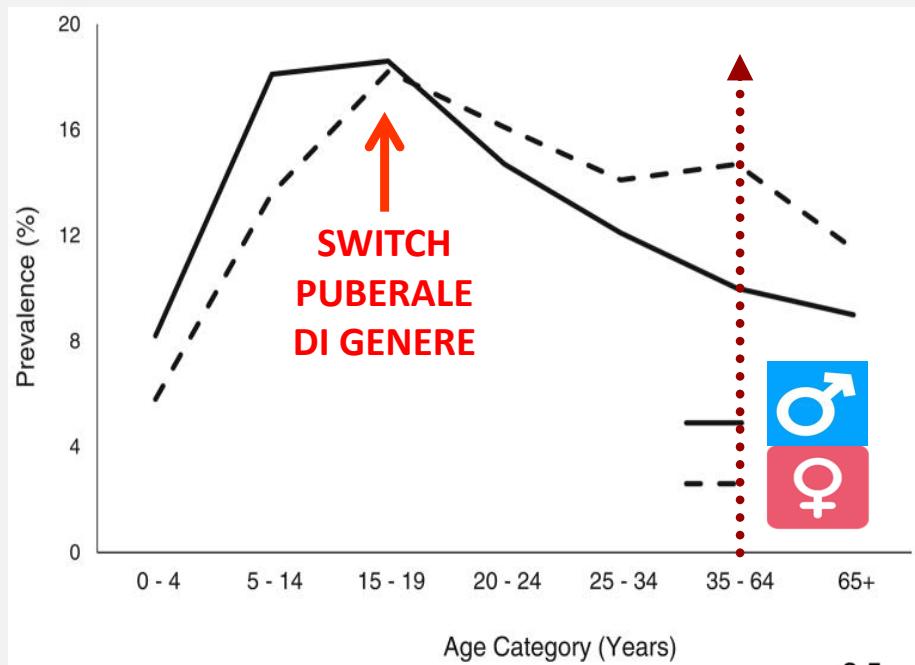
**L. Woods, MD, MEd¹; Kelly B.
Bethesda Family Medicine Residency Program, Cincinnati,
Good Samaritan Hospital, Cincinnati, Ohio**

2. Woods SE, Sorscher J, King J, Hasselfeld K. Young adults admitted for asthma: Does gender influence outcomes? *J Women's Health (Larchmt)*. 2003;12:481–

5. Trawick DR, Holm C, Wirth J. Influence of gender on rates of hospitalization, hospital course, and hypercapnea in high-risk patients admitted for asthma: A 10-year retrospective study at Yale-New Haven Hospital. *Chest*. 2001;119:115–119.

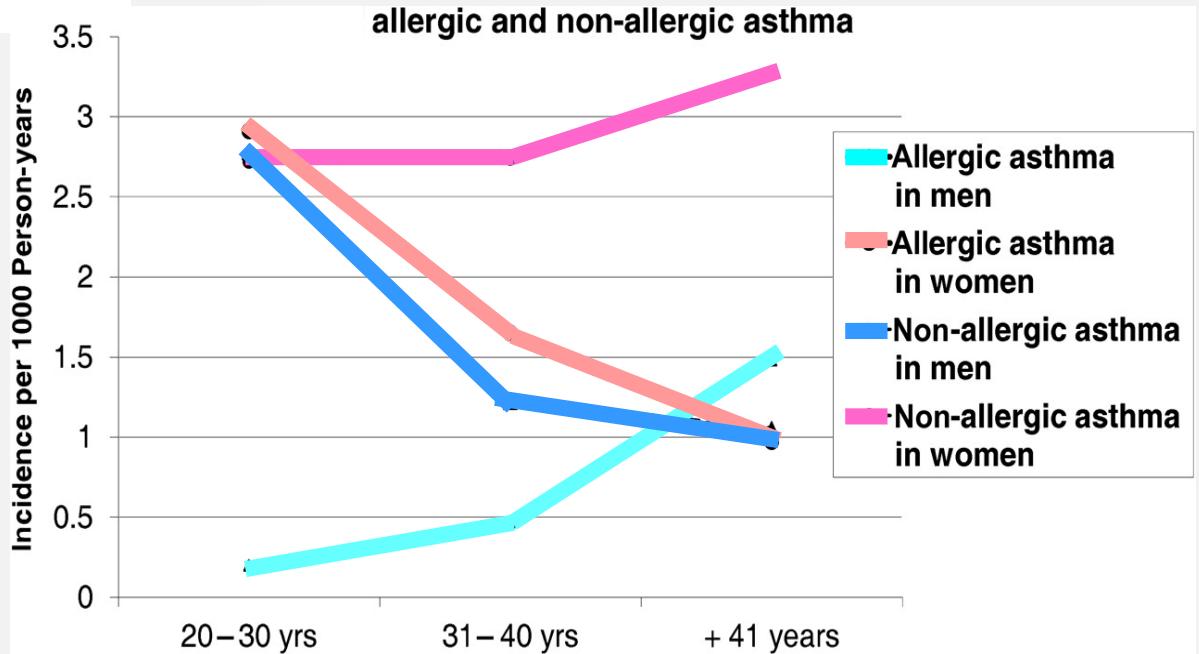
6. Osborne ML, Vollmer WM, Linton KL, Buist AS. Characteristics of patients with asthma within a large HMO: A comparison by age and gender. *J Respir Crit Care Med.* 1998;157:123–128.

7. Agency for Healthcare Research and Quality (AHRQ). HCUP facts and figures, 2006. http://www.hcup-us.ahrq.gov/reports/factsandfigures/HAR_2006.pdf. Accessed April 2, 2009.

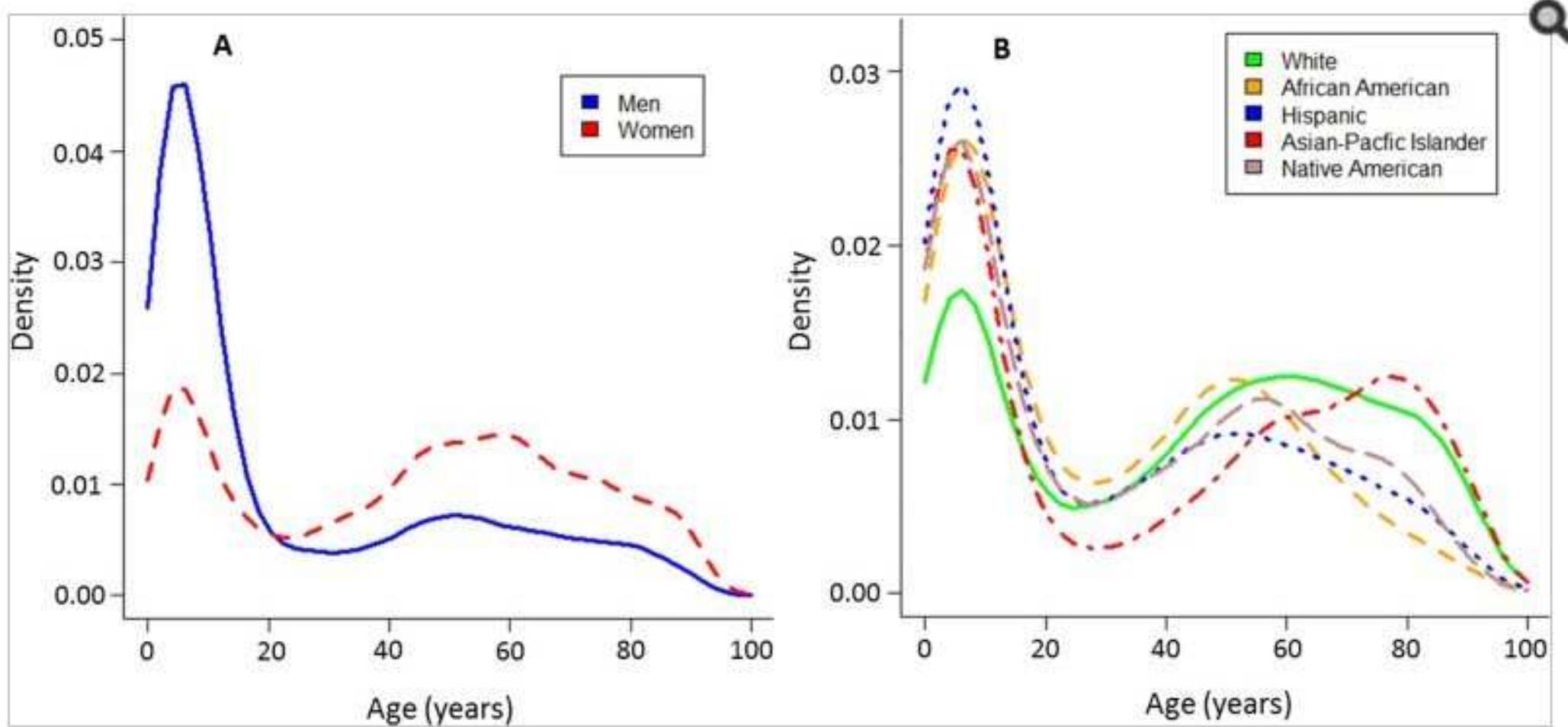


- Durante l'infanzia la prevalenza dell'asma è maggiore nel sesso maschile fino all'adolescenza, in cui si assiste a un'inversione di tendenza

- Nell'età adulta le donne presentano incidenza di asma più alta rispetto agli uomini
- Oltre alla PREVALENZA, nelle donne adulte aumentano anche la GRAVITA' e la MORTALITA' per asma bronchiale (OMS: circa 180mila morti/anno, di cui il 64% donne)



Besides incidence, prevalence and severity..



Asthma hospitalization increases in middle age women



HIGHER PREVALENCE IN WOMEN



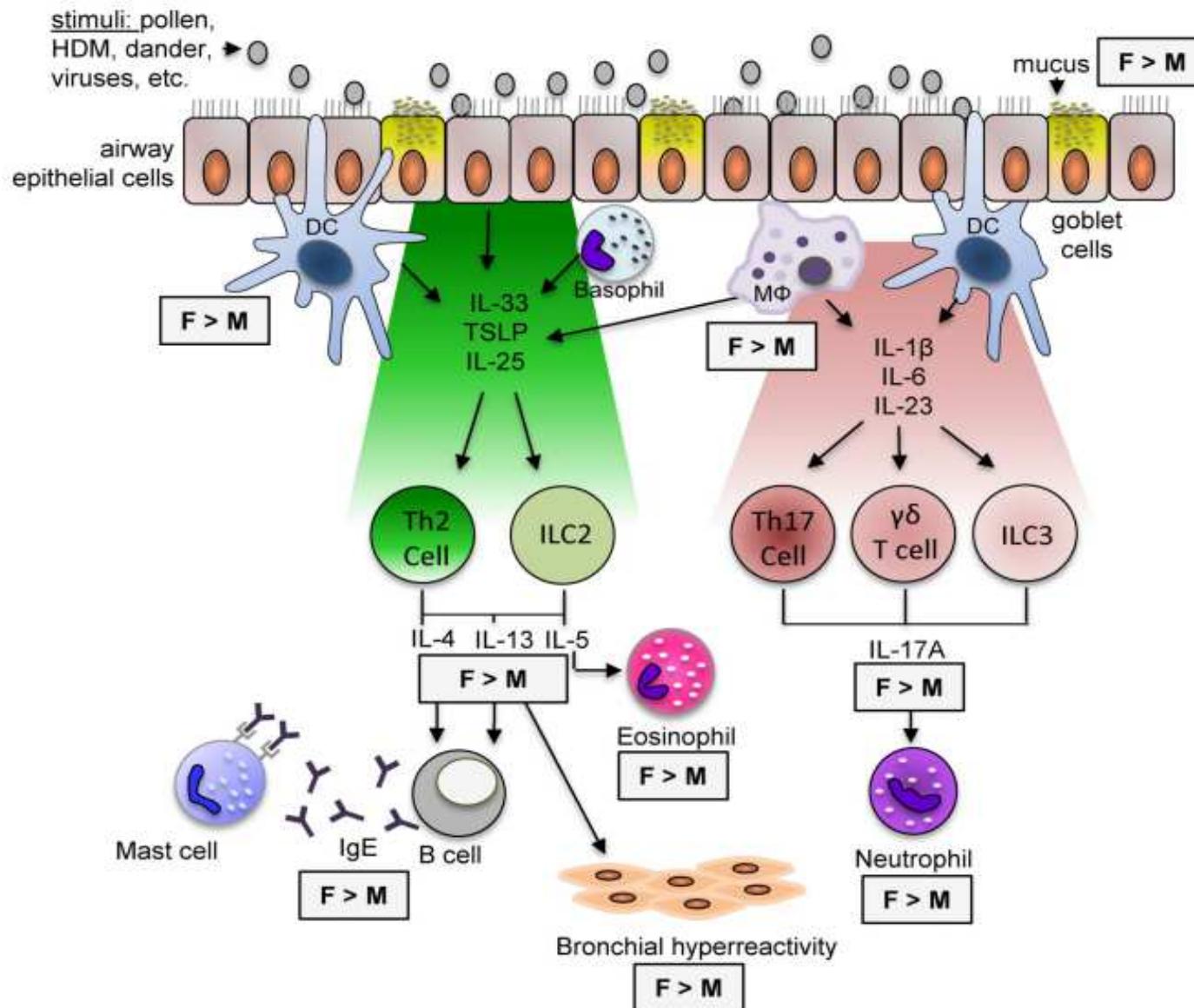
FEMALE PATIENTS ARE MORE
SYMPTOMATIC AND USE
MORE MEDICATIONS

Sex Differences in Severe Asthma: Results From Severe Asthma Network in Italy-SANI

Results: Almost 2/3 of severe asthmatics were female. Late-onset asthma, obesity and gastroesophageal reflux were more frequent in females than in males, while previous smoking habits and nasal polyposis were more frequent in males. Females had poor asthma control and a higher number of severe exacerbations leading to hospitalization, in comparison to males. Biomarkers of type 2 inflammation (blood eosinophil, exhaled nitric oxide, and serum immunoglobulin E levels) were significantly higher in males than in females. The type 2 profile (defined by a combination of these 3 biomarkers) was significantly more frequent in males than in females. In multivariate analysis, late-onset asthma and a normal body mass index were only independent variables associated with the type 2 profile, while male sex and age showed only a trend toward the association with the type 2 profile.

Conclusions: Significant differences may be observed between male and female patients with severe asthma, influencing the asthma pheno-endotyping in both sexes.

..asthma is different in woman



Meccanismi alla base delle differenze immunologiche fra i due sessi:

➤ Dysanapsis

Crescita non armonica e sincrona del parenchima e delle vie aeree



- Dopo i 18 aa i polmoni femminili sono più piccoli e più leggeri dei polmoni maschili, con vie aeree più piccole in relazione al volume polmonare rispetto agli uomini.
- Nell'età pediatrica si verifica la condizione opposta (VEMS/CVF a favore delle femmine).

Espressione genica sesso-correlata nell'asma

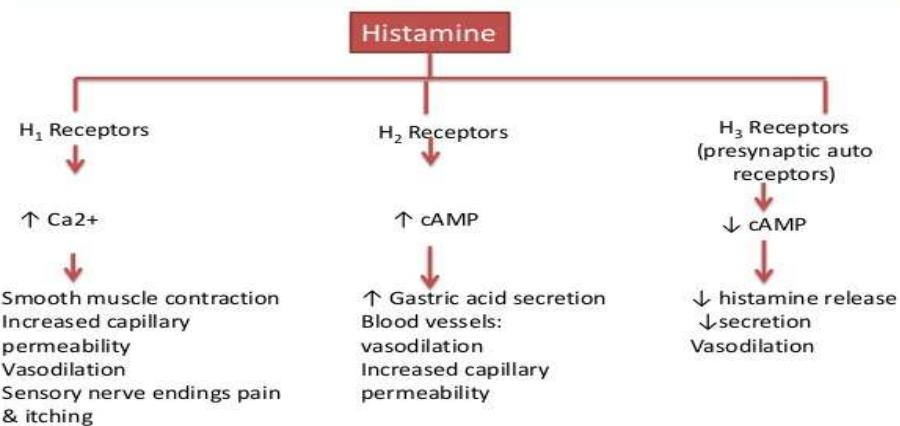
- SNPs nel gene della **linfopoietina stromale timica**:

-rs1837253 protegge solo gli uomini
-rs2289276 protegge solo le donne [1]

- **Periostina sierica**: è negativamente correlata al FEV1 nelle donne asmatiche gravide [2]



Mechanism of Action of Histamine



▪ Recettori istaminergici nei topi:

- H₂R e H₃R maggiormente espressi nel sesso femminile;
- H₁R ugualmente espresso in entrambi i sessi [3]

▪



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Allergy. 2010 December; 65(12): 1566–1575. doi:10.1111/j.1365-2101.2010.02415.x.

TSPL Polymor SNPs in TSPL ith Asthma in a Sex-Specific Fashion

Gary Laskin¹

rs1837253

protective
in males

Eduardo Soto-Quiros²
Ingo Ruczinski³
Kathleen C. Barnes⁴, Jennifer D. Wilk¹⁰, George R. O'Connor⁵, Michael James Gauderman¹¹,
Hita Vora¹¹, James W. Baurley¹¹, Frank Gilliland¹¹, Catherine Liang¹, Jody S. Sylvia¹,
Barbara J. Klanderman^{1,4}, Sunita S. Sharma^{1,2,4}, Blanca E. Himes^{1,3,12}, Cara J.
Bosslet¹, Scott Celedón^{1,2,3}

P. Kim^{2,4}, Jessica A. Mathias⁹,

A. Mathias⁹,
James Gauderman¹¹,
Hita Vora¹¹, James W. Baurley¹¹, Frank Gilliland¹¹, Catherine Liang¹, Jody S. Sylvia¹,
Barbara J. Klanderman^{1,4}, Sunita S. Sharma^{1,2,4}, Blanca E. Himes^{1,3,12}, Cara J.
Bosslet¹, Scott Celedón^{1,2,3}

high risk
in females

¹ Charles R. Drew University of Medicine and Women's Hospital, Los Angeles, California, USA, ² Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts, ³ Center for Genomic Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, ⁴ Harvard Medical School, Boston, Massachusetts, ⁵ Division of Pediatric Pulmonology, Hospital Nacional de Niños, San José, Costa Rica, ⁶ Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland, ⁷ Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, ⁸ Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, ⁹ Genomics Section, Inherited Disease Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, ¹⁰ The National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, MA, Boston University School of Medicine, Boston, MA, ¹¹ Department of Preventive Medicine, University of Southern California, Los Angeles, California, ¹² Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA, ¹³ Paediatric Respiratory, Imperial School of Medicine at National Heart and Lung Institute, Royal Brompton Hospital, London, United Kingdom

Finestre di maggiore vulnerabilità all'asma nel sesso femminile

Pubertà: l'asma è più comune e severa nelle donne durante e dopo la pubertà. La prevalenza è maggiore nelle donne con menarca precoce

Ovulazione: le esacerbazioni dell'asma iniziano più spesso in fase pre-ovulatoria (28%). L'ovulazione può fungere da trigger per le crisi asmatiche nelle donne vulnerabili

Mestruazioni: l'asma può peggiorare durante la fase peri-mestruale ("asma catameniale") in maniera più severa e problematica rispetto al peggioramento peri-ovulatorio. In una piccola % di pazienti con asma grave possono essere un fattore scatenante la **Near Fatal Asthma**

Gravidanza: il decorso clinico dell'asma è variabile (30% peggiora, 25% migliora, 30% immutato), con un generale miglioramento durante le ultime 4 settimane di gestazione

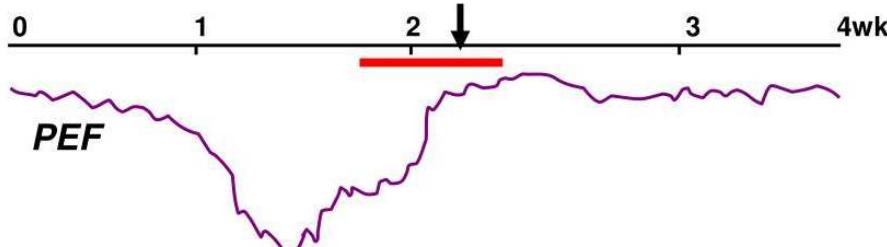
Puerperio: i cambiamenti che avvengono durante la gravidanza di solito si risolvono entro 3 mesi dal parto

Menopausa: il rischio aumenta in pre-menopausa

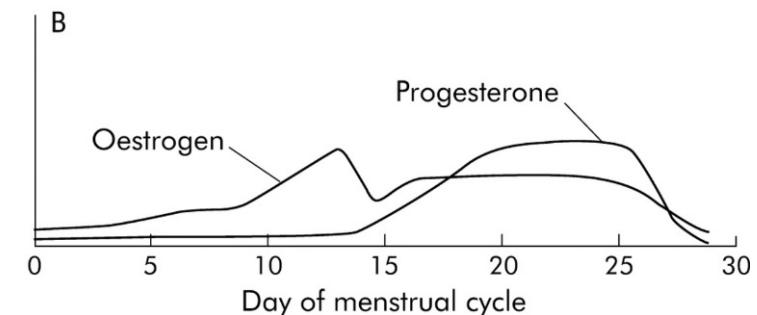
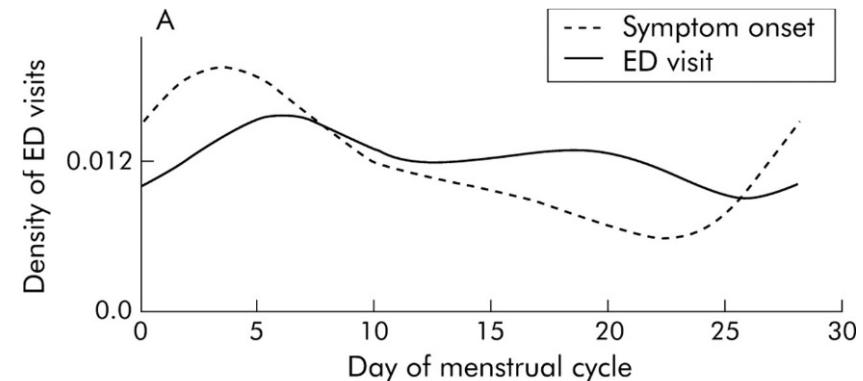
Terapia ormonale sostitutiva: effetti controversi (aumento del rischio di ricovero, aumentata durata dell'ospedalizzazione)

Premenstrual/perimestral asthma (catamenial asthma)

- Worsening of asthma ~7days premenstrually
- Recovers with menstruation



Beynon H et al: Lancet 1988

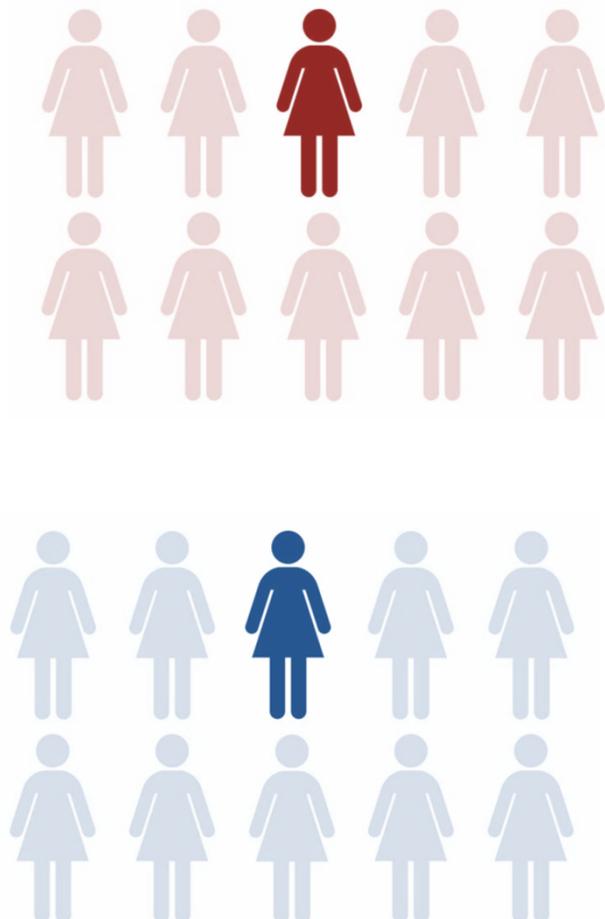


Brenner BE et al. Thorax 2005.

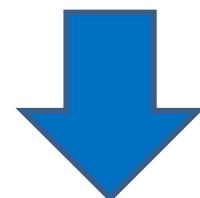
Reference	No. of pts	Study design	Prevalence of PMA (%)	Objective measures
Rees ^[2]	81	Questionnaire, retrospective	33	None
Hanley ^[3]	102	Questionnaire, retrospective	35	PEF in selected patients
Gibbs et al. ^[4]	91	Questionnaire, retrospective	40	PEF in selected patients
Eliasson et al. ^[5]	57	Questionnaire, retrospective	33	None
Agarwal & Shar ^[6]	100	Questionnaire, retrospective	23	PEF in selected patients
Shames et al. ^[7]	32	Questionnaire, prospective	28	PEF and methacholine challenge in all patients
Forbes et al. ^[8]	481	Questionnaire, retrospective	8	None

PEF = peak expiratory flow.

Asthma and Pregnancy



Il 10% delle donne gravide soffre di asma bronchiale



Il 10% delle gravide con asma ha una riacutizzazione durante la gravidanza



1/3. • migliora
• non subisce cambiamenti
• peggiora

Gluck J.C. et Al. The effect of pregnancy on the course of asthma. Immuno Allergy Clin N Am 2006

Murphy, Semin Respir Crit Care, Asthma during Pregnancy: Exacerbations, Management, and Health Outcomes for Mother and Infant. 2017

Hormonal changes

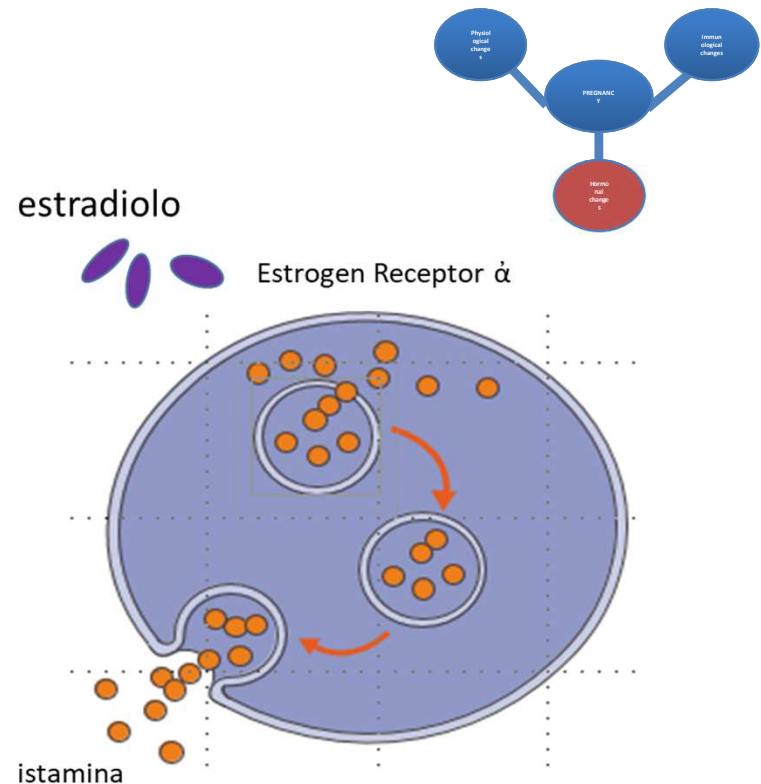
Healthy pregnant women

17 β oestradiol	↑↑
Progesterone	↑↑
Testosterone	↑
DHEAS	↑
Cortisol	↑↑

↑↑: Highly increased

↑: Increased

↑ =: Slightly increased



Gli estrogeni inducono una degranulazione mastocitaria non IgE dipendente.

Le mast cellule esprimono Estrogen receptor alfa e l'estradiolo ne aumenta l'espressione.

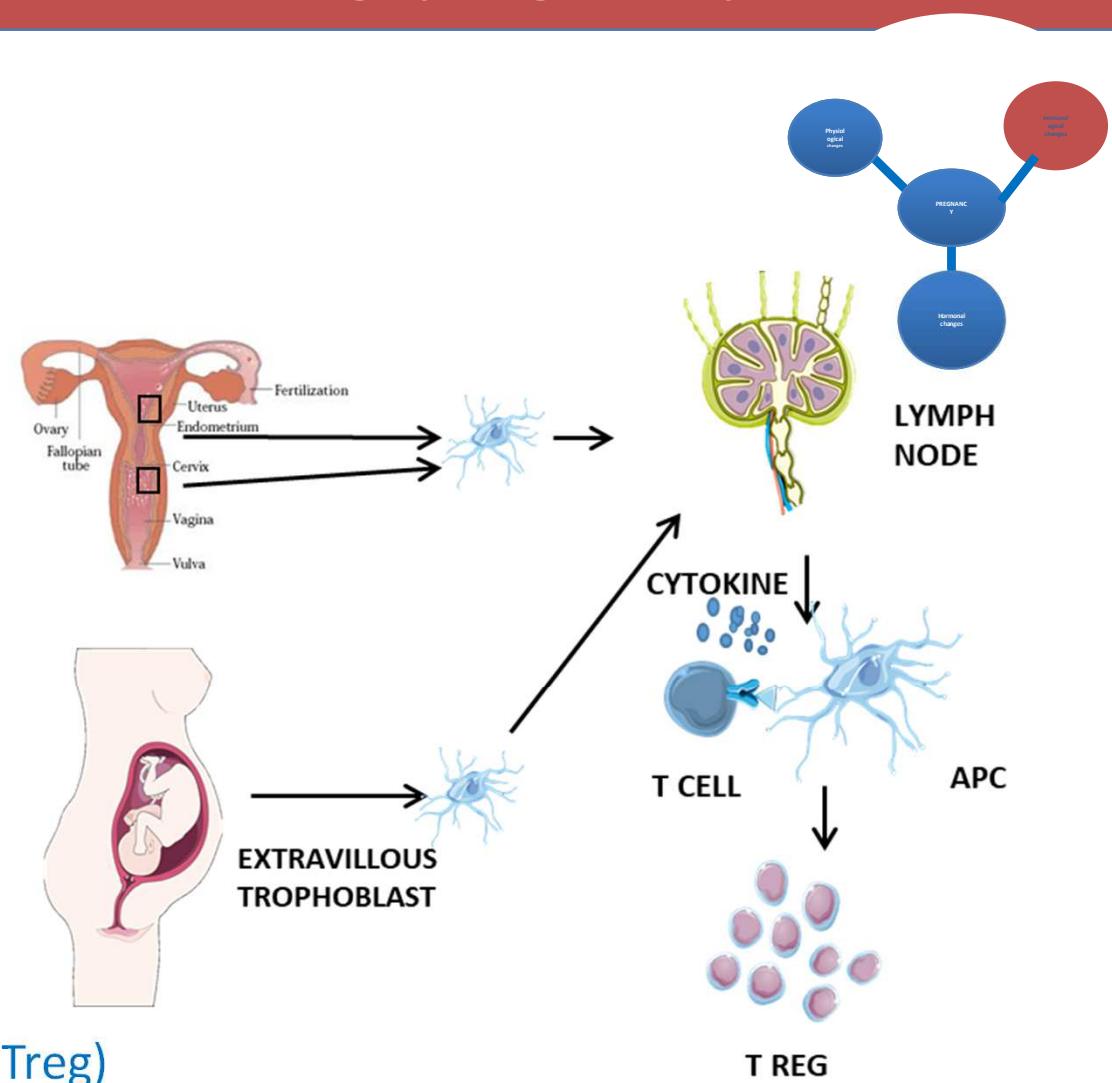
The immune system during pregnancy

Pregnancy represents an unique immune tolerant condition

WHY????? FETO MATERNAL TOLERANCE

Physiological immunosuppression protects the fetus from maternal immunoreponse against paternal antigens expressed by the fetus

→ Increase T Regulatory cells (Treg)



Saito S et al Semin Immunopathol 2007
Somerset DA. et al. Immunology 2004

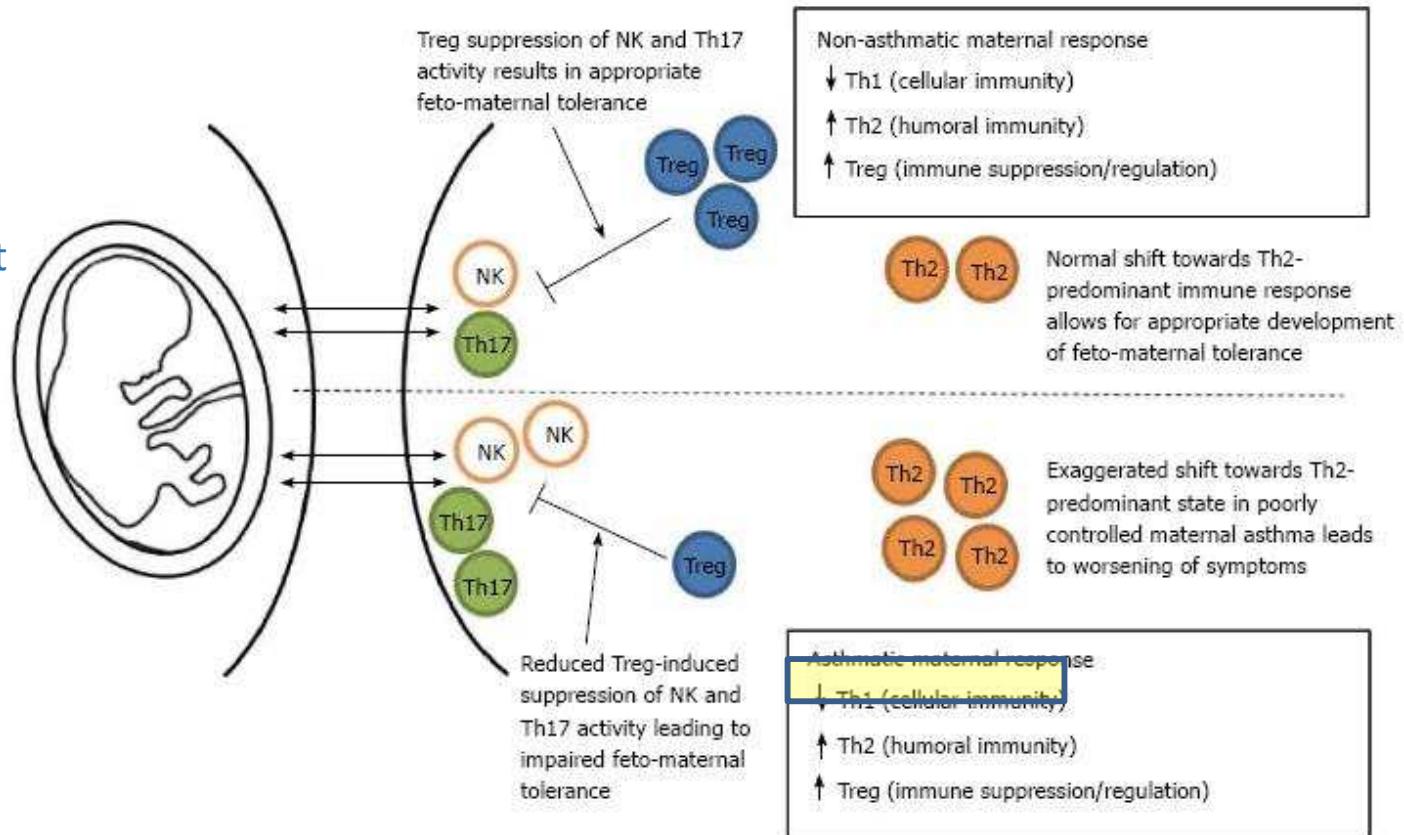
Other immunological changes in pregnancy : Th1, Th2, Th17

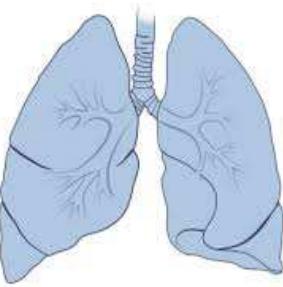
Successfull pregnancy is a Th2 related phenomenon and asthma itself is primary a Th2 mediated disease

Increased numbers of Th17 proinflammatory cells in pregnant asthmatic women



Impaired intrauterine growth





Il progesterone induce un incremento del 50% della ventilazione/minuto

15% tasso metabolico materno

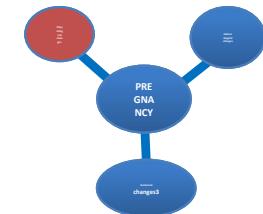
produzione di CO₂ di circa il 60 %

20% consumo di ossigeno

Il progesterone induce rilascio della muscolatura liscia dello sfintere esofageo con GERD nel 30 % delle gravidanze.

capacità funzionale residua (FRC)

alcalosi respiratoria compensatoria



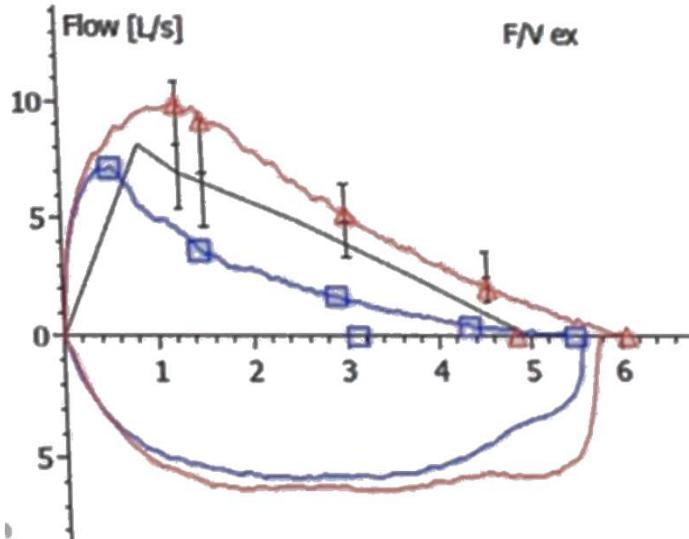
iperventilazione in oltre il 60-70 % delle gravidanze.



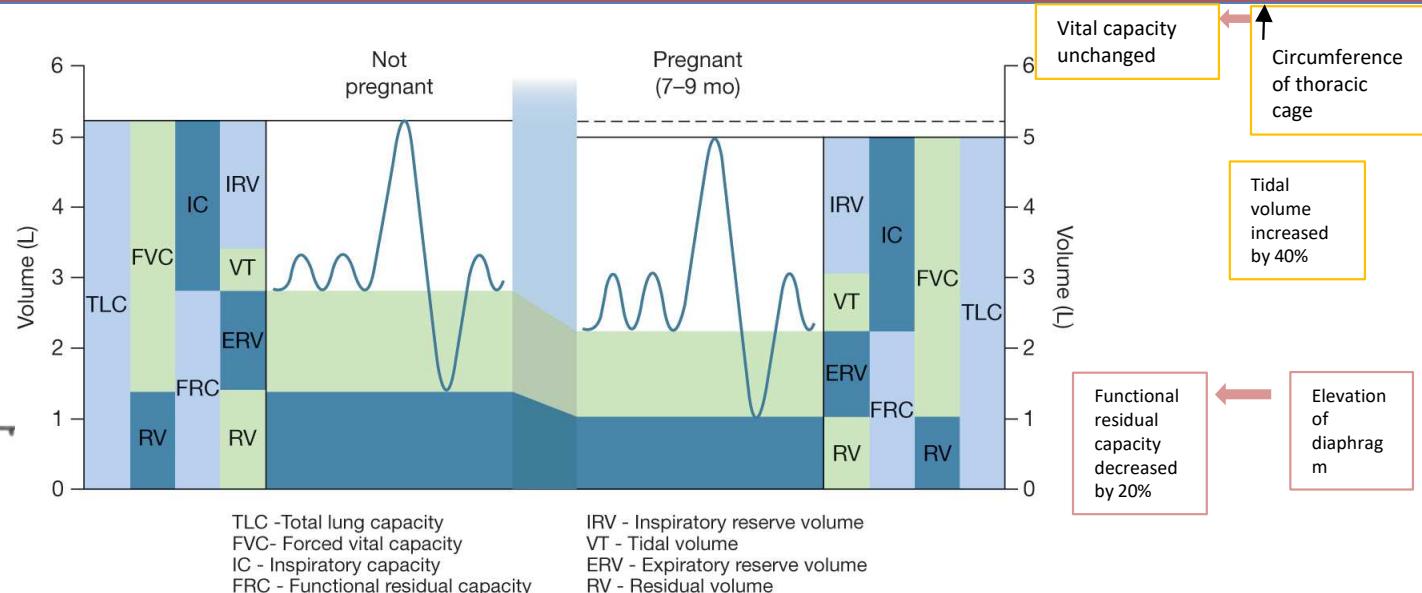
Dispnea in gravidanza

Changes in dynamic lung volumes during pregnancy

No change in FEV₁, FVC, PEF or FEV₁/FV



Changes in static volumes during (late) pregnancy



Differente prevalenza della rinite allergica fra i due sessi



Infanzia



Adolescenza e età adulta
(tranne in Asia)



Possibile influenza geografica (> prevalenza nel sesso maschile in Kuwait e Iran; > nel sesso femminile in Brasile e Arabia Saudita)

Le differenze sesso-correlate non sono ancora chiare → **necessari ulteriori studi!**

Differente prevalenza delle atopie fra i due sessi

Infanzia	Età adulta	Anziani
Prevalgono in Centro America rispetto all'Europa, ma non significative differenze sesso-correlate		

Dati contrastanti. Non è chiaro se vi sia un ruolo ormonale o immunologico



DERMATITI DA CONTATTO

- Nickel → più frequente nelle **donne**
- Balsamo di Perù → più frequente negli **uomini**

ORTICARIA SPONTANEA CRONICA (non rientra fra le allergie) → più frequente nelle **donne**

Take-home message



- Il sesso incide sulla suscettibilità alle malattie allero-immunologiche attraverso **meccanismi ormonali, genetici e anatomici**.
- **Asma**: nell'infanzia è più suscettibile il sesso maschile fino all'adolescenza (**switch puberale**). Nell'età adulta sono **più suscettibili le donne** (> prevalenza, gravità e mortalità), soprattutto in alcune finestre di vulnerabilità (per es. asma catameniale).
- **Rinite allergica**: durante l'infanzia prevale nel sesso maschile; prevale nel sesso femminile dall'adolescenza in poi. Non chiari i meccanismi.
- **Atopie**: dati controversi per l'infanzia; nell'età adulta prevalgono le donne (soprattutto nickel); fra gli anziani prevalgono gli uomini.