I° Congresso Nazionale Gruppo di Studio SIN
Neurologia di Genere :
Un diverso modo di pensare
alle malattie del sistema nervoso

Roma, 4 Maggio 2019

Genetica e medicina di genere

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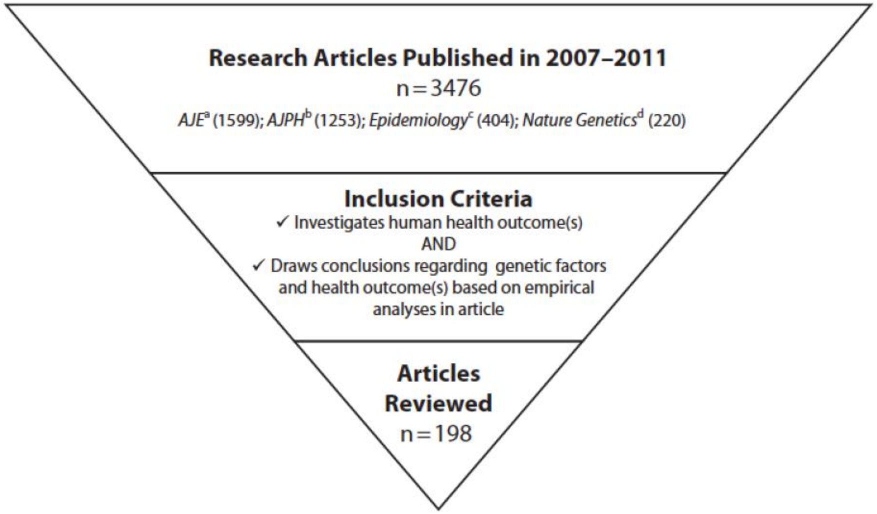
Regione Lombardia

Sex, Gender, Genetics, and Health

Susan E. Short, PhD, Yang Claire Yang, PhD, and Tania M. Jenkins, MA

This article addresses 2 questions. First, to what extent are sex and gender incorporated into research on genetics and health? Second, how might social science understandings of sex and gender, and gender differences in health, become more integrated into scholarship in this area? We review articles on genetics and health published in selected peer-reviewed journals. Although sex is included frequently as a control or stratifying variable, few articles articulate a conceptual frame or methodological justification for conducting research in this way, and most are not motivated by sex or gender differences in health. Gender differences in health are persistent, unexplained, and shaped by multilevel social factors. Future scholarship on genetics and health needs to incorporate more systematic attention to sex and gender, gender as an environment, and the intertwining of social and biological variation over the life course. Such integration will advance understandings of gender differences in health, and may yield insight regarding the processes and circumstances that make genomic variation relevant for health and well-being. (*Am J Public Health*. 2013;103:S93–S101. doi:10.2105/AJPH.2013.301229)



Research Articles Published in 2007–2011
n=3476
AJE[a] (1599); *AJPH*[b] (1253); *Epidemiology*[c] (404); *Nature Genetics*[d] (220)

Inclusion Criteria
✓ Investigates human health outcome(s)
AND
✓ Draws conclusions regarding genetic factors and health outcome(s) based on empirical analyses in article

Articles Reviewed
n=198

[a] *American Journal of Epidemiology* (*AJE*) publishes 2 issues/month, for 12 months (24 issues/year).
[b] *American Journal of Public Health* (*AJPH*) publishes 1 issue/month, for 12 months (12 issues/year).
[c] *Epidemiology* publishes 1 issue every 2 months (6 issues/year).
[d] *Nature Genetics* publishes 1 issue/month, for 12 months (12 issues/year).

FIGURE 1—Selection process of articles reviewed, 2007–2011.

TABLE 1—Summary of Incorporation of Sex or Gender in Research Articles on Genetics and Health

Variable	All Journals,[a] No. (Proportion)	Public Health Journals,[b] No. (Proportion)
Total number of articles	198	139
Single sex/gender analysis sample		
Total	35	32
Reproductive or sex-specific outcome[c]	12 (0.34)	10 (0.31)
Non-sex-specific health outcome	23 (0.66)	22 (0.69)
Multiple sex/gender analysis sample		
Total	163	107
Level of inclusion		
Sex/gender in title	2 (0.01)	0 (0.00)
Sex/gender in abstract	19 (0.12)	18 (0.13)
Type of inclusion		
Match on sex in sampling	20 (0.12)	14 (0.10)
Control/adjust for sex in analysis	93 (0.57)	62 (0.45)
Incorporate sex with twin design	16 (0.10)	15 (0.11)
Stratify analysis by sex	34 (0.21)	22 (0.16)
Interact sex with genetic variant	12 (0.07)	6 (0.04)
No mention of treatment of sex/gender in analysis	28 (0.17)	10 (0.07)

Note. All articles were published between 2007 and 2011. Ten studies did not clearly indicate which sex(es) or gender(s) they included and are presumed not to be single sex or gender studies.
[a] All Journals includes *American Journal of Epidemiology*, *American Journal of Public Health*, *Epidemiology* and *Nature Genetics*.
[b] Public Health Journals excludes *Nature Genetics*.
[c] Breast cancer was coded as non-sex-specific health outcome.

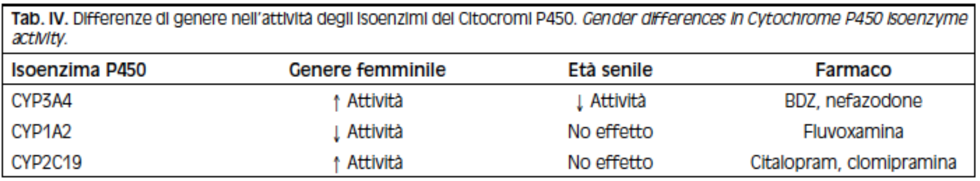
Supplement 1, 2013, Vol 103, No. S1 | American Journal of Public Health

I FATTI:

Le donne vivono più a lungo degli uomini ma si ammalano di più (*paradosso donna*)

La dimensione e la composizione corporea è diversa tra maschi e femmine

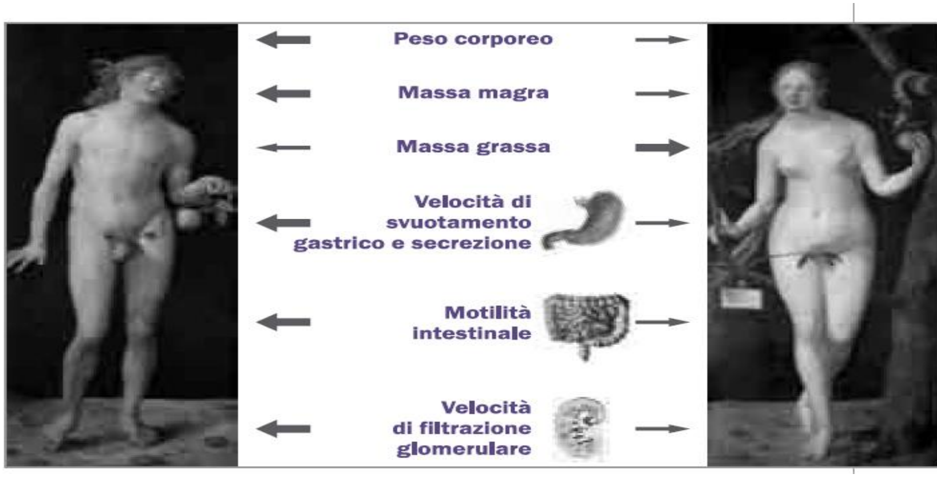
La farmacocinetica e la farmacodinamica è diversa tra uomini e donne (*le donne presentano più eventi avversi degli uomini al consumo dei farmaci*)



Tab. IV. Differenze di genere nell'attività degli isoenzimi del Citocromi P450. *Gender differences in Cytochrome P450 isoenzyme activity.*

Isoenzima P450	Genere femminile	Età senile	Farmaco
CYP3A4	↑ Attività	↓ Attività	BDZ, nefazodone
CYP1A2	↓ Attività	No effetto	Fluvoxamina
CYP2C19	↑ Attività	No effetto	Citalopram, clomipramina

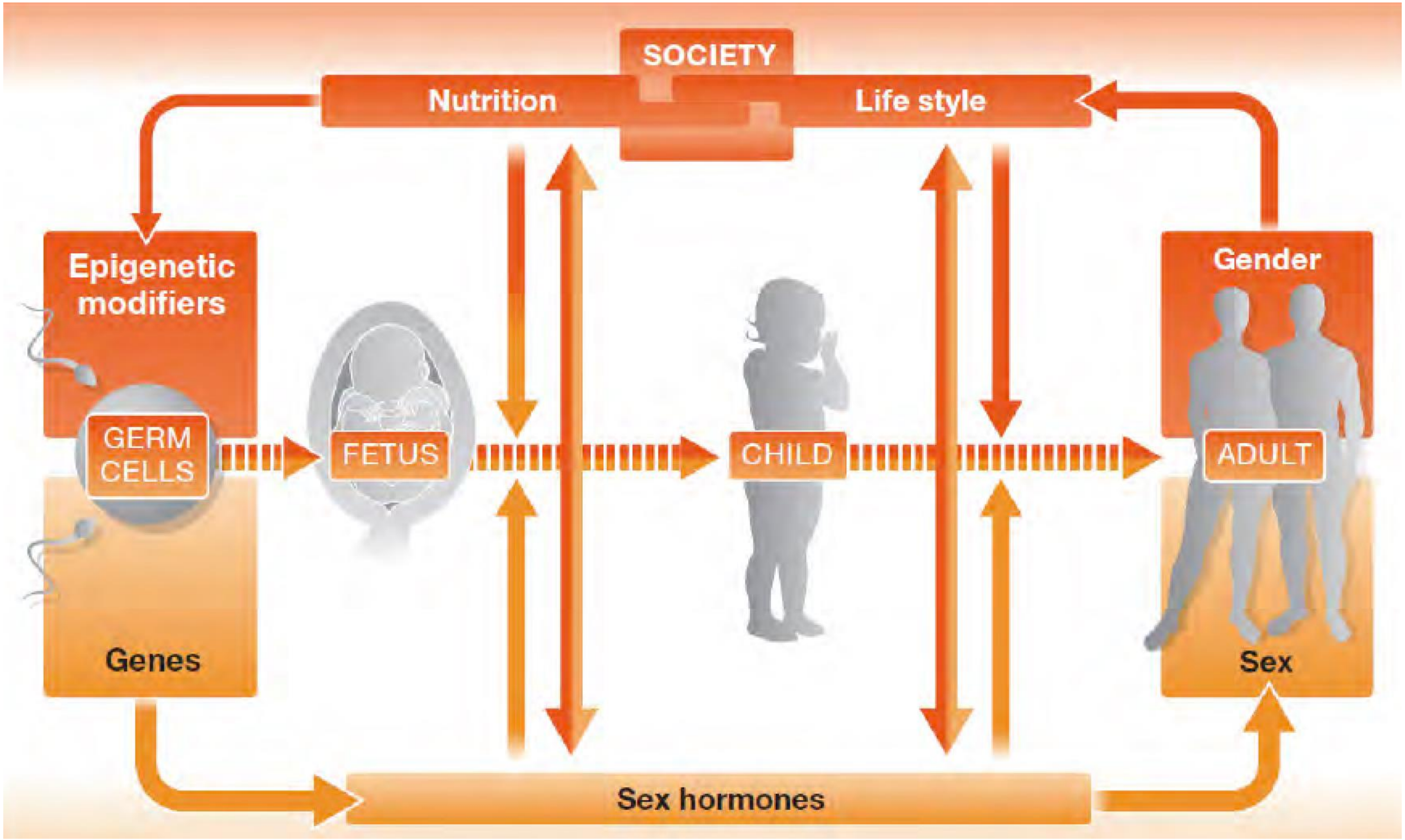
D. MARAZZITI, A. BALDINI, M. CARLINI ET AL. GIORN ITAL PSICOPAT 2007; 13: 69-75


Peso corporeo
Massa magra
Massa grassa
Velocità di svuotamento gastrico e secrezione
Motilità intestinale
Velocità di filtrazione glomerulare

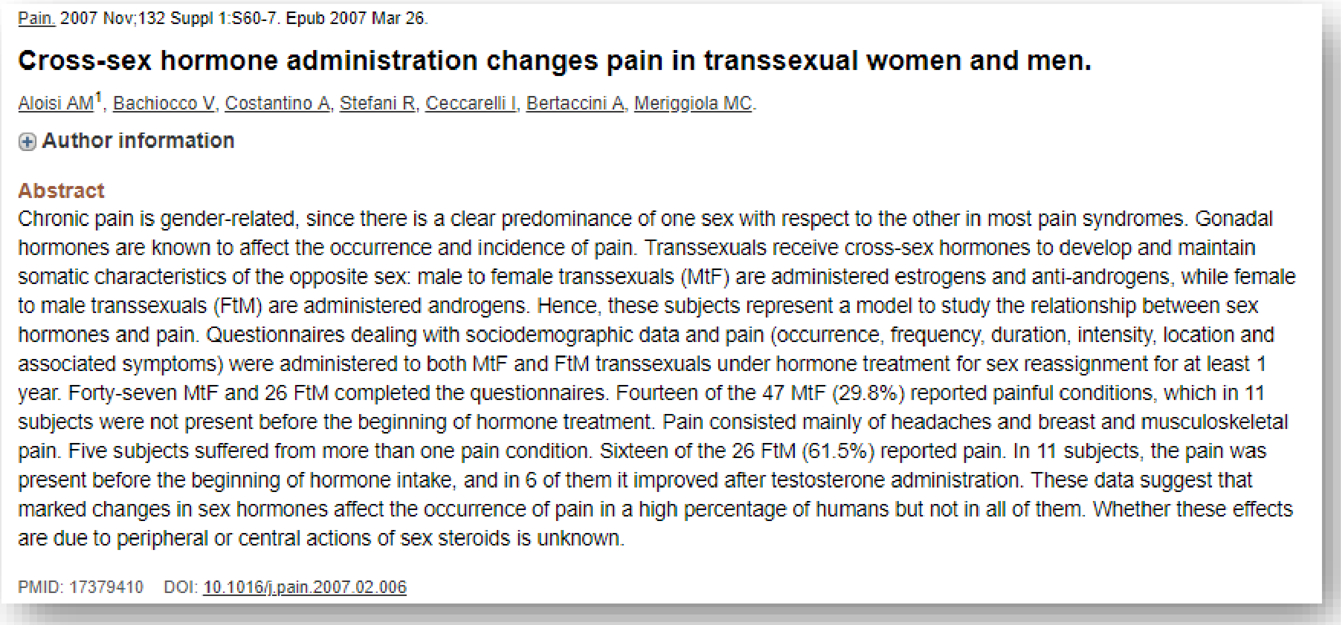
I FATTI

Molte malattie sono determinate da differenze biologiche legate al sesso:

- **Donne a maggior rischio di malattie autoimmuni**
- **Donne a maggior incidenza di fratture**
- **Donne a maggior rischio di depressione e demenza (AD), uomini a maggior rischio di Parkinson**
- **Uomini a maggior rischio di malattie cardiovascolari in età più giovane, dopo la menopausa aumento del rischio nelle donne**
- **Uomini a maggior rischio di mortalità per cancro**


SOCIETY
Nutrition
Life style
Epigenetic modifiers
Gender
GERM CELLS
FETUS
CHILD
ADULT
Genes
Sex
Sex hormones

Regitz-Zagrosek V, EMBO Rep. 2012;13:596-603



Pain. 2007 Nov;132 Suppl 1:S60-7. Epub 2007 Mar 26.

Cross-sex hormone administration changes pain in transsexual women and men.

Aloisi AM[1], Bachiocco V, Costantino A, Stefani R, Ceccarelli I, Bertaccini A, Meriggiola MC.

⊕ Author information

Abstract

Chronic pain is gender-related, since there is a clear predominance of one sex with respect to the other in most pain syndromes. Gonadal hormones are known to affect the occurrence and incidence of pain. Transsexuals receive cross-sex hormones to develop and maintain somatic characteristics of the opposite sex: male to female transsexuals (MtF) are administered estrogens and anti-androgens, while female to male transsexuals (FtM) are administered androgens. Hence, these subjects represent a model to study the relationship between sex hormones and pain. Questionnaires dealing with sociodemographic data and pain (occurrence, frequency, duration, intensity, location and associated symptoms) were administered to both MtF and FtM transsexuals under hormone treatment for sex reassignment for at least 1 year. Forty-seven MtF and 26 FtM completed the questionnaires. Fourteen of the 47 MtF (29.8%) reported painful conditions, which in 11 subjects were not present before the beginning of hormone treatment. Pain consisted mainly of headaches and breast and musculoskeletal pain. Five subjects suffered from more than one pain condition. Sixteen of the 26 FtM (61.5%) reported pain. In 11 subjects, the pain was present before the beginning of hormone intake, and in 6 of them it improved after testosterone administration. These data suggest that marked changes in sex hormones affect the occurrence of pain in a high percentage of humans but not in all of them. Whether these effects are due to peripheral or central actions of sex steroids is unknown.

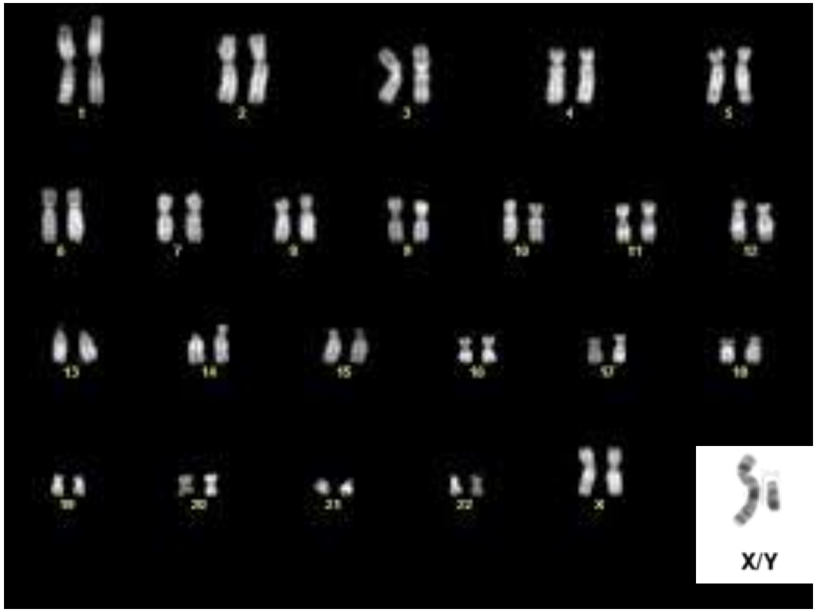
PMID: 17379410 DOI: 10.1016/j.pain.2007.02.006

Le donne sono a maggior rischio di dolore cronico

I transessuali che ricevono una terapia ormonale per sviluppare e mantenere caratteristiche somatiche del sesso opposto possono risultare più inclini o più protetti in base al trattamento ormonale:

- **un terzo dei maschi, transessuali femminili**, sviluppano dolore cronico in concomitanza con il trattamento a base di estrogeni/anti-androgeni e ha mostrato una maggiore sensibilità al dolore secondo il calendario di terapia ormonale
- **la metà delle femmine**, transessuali maschi, trattata con testosterone ha registrato un significativo miglioramento del dolore cronico (per esempio, mal di testa) già presente prima dell'inizio del trattamento e ha migliorato i profili di sensibilità al dolore in seguito alla terapia ormonale.

Genoma Umano


1
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17
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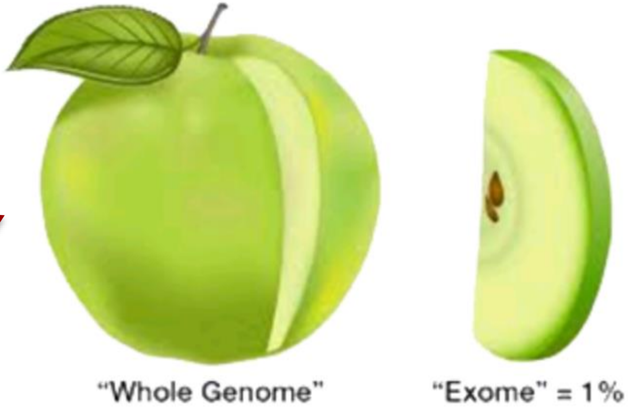
19
20
21
22
X
X/Y

Circca 3,2 miliardi di basi

20-25.000 geni

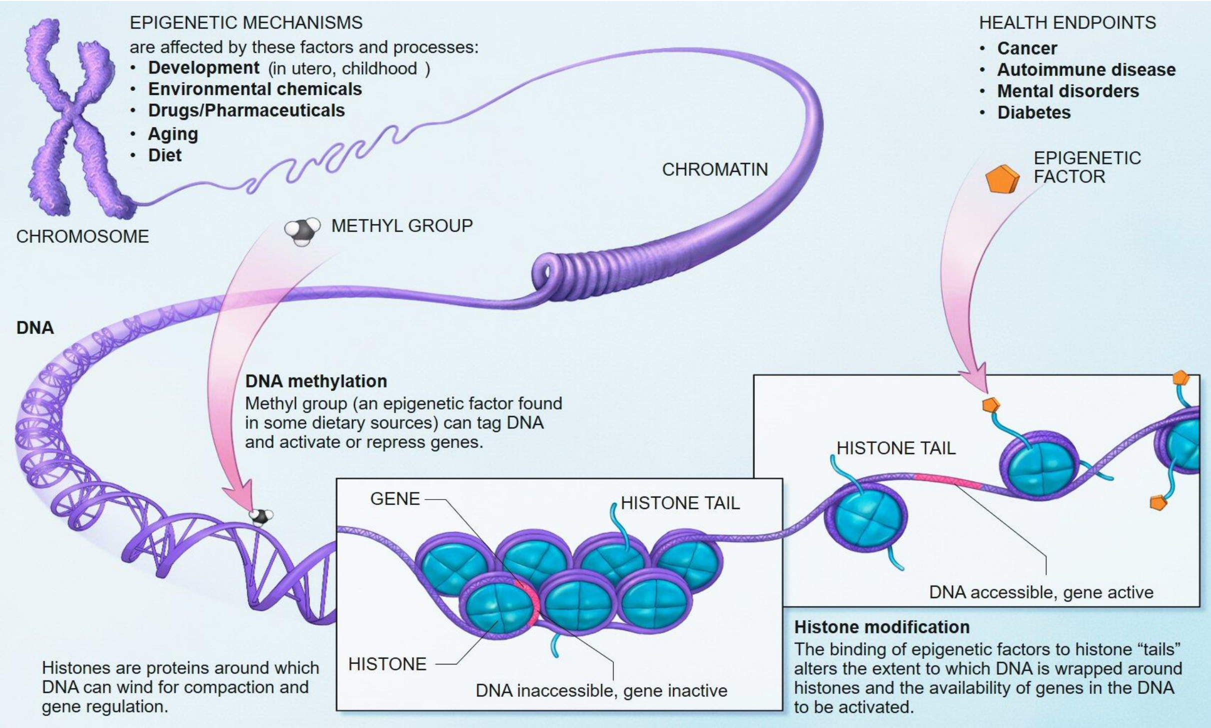

"Whole Genome"
"Exome" = 1%

Junk DNA: sequenze regolatorie, splicing alternativo, miRNA, ????

Sequenze codificanti proteine

EPIGENETICA: regola l’espressione genica senza alterare la sequenza del DNA

DAMN YOU, EPIGENOME.
BUTTER PECAN


CHROMOSOME
CHROMATIN
METHYL GROUP
DNA
EPIGENETIC FACTOR
GENE
HISTONE TAIL
HISTONE TAIL
HISTONE
DNA accessible, gene active
DNA inaccessible, gene inactive

EPIGENETIC MECHANISMS
are affected by these factors and processes:
- **Development** (in utero, childhood)
- **Environmental chemicals**
- **Drugs/Pharmaceuticals**
- **Aging**
- **Diet**

HEALTH ENDPOINTS
- **Cancer**
- **Autoimmune disease**
- **Mental disorders**
- **Diabetes**

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.

Histone modification
The binding of epigenetic factors to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Meccanismi epigenetici:

Modificazioni del DNA = metilazione della citosina da parte delle metiltrasferasi

Modificazione delle proteine = acetilazione, metilazione, ubiquitinazione, fosforilazione, sumoilazione

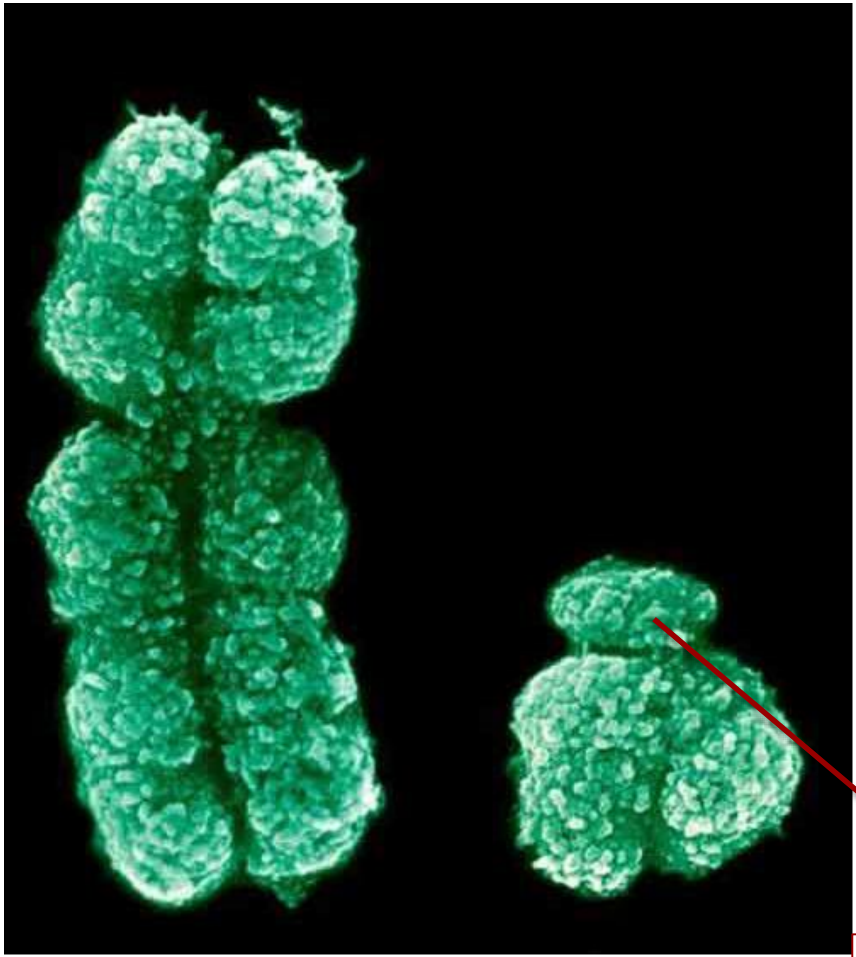
Silenziamento genico (lncRNAs, miRNAs)

Inattivazione del Cromosoma X

Imprinting genomico

Cromosoma X

5% del DNA totale
155 milioni di paia di basi
800 geni codificanti
600 geni non codificanti (10% dei miRNA genomici totali)

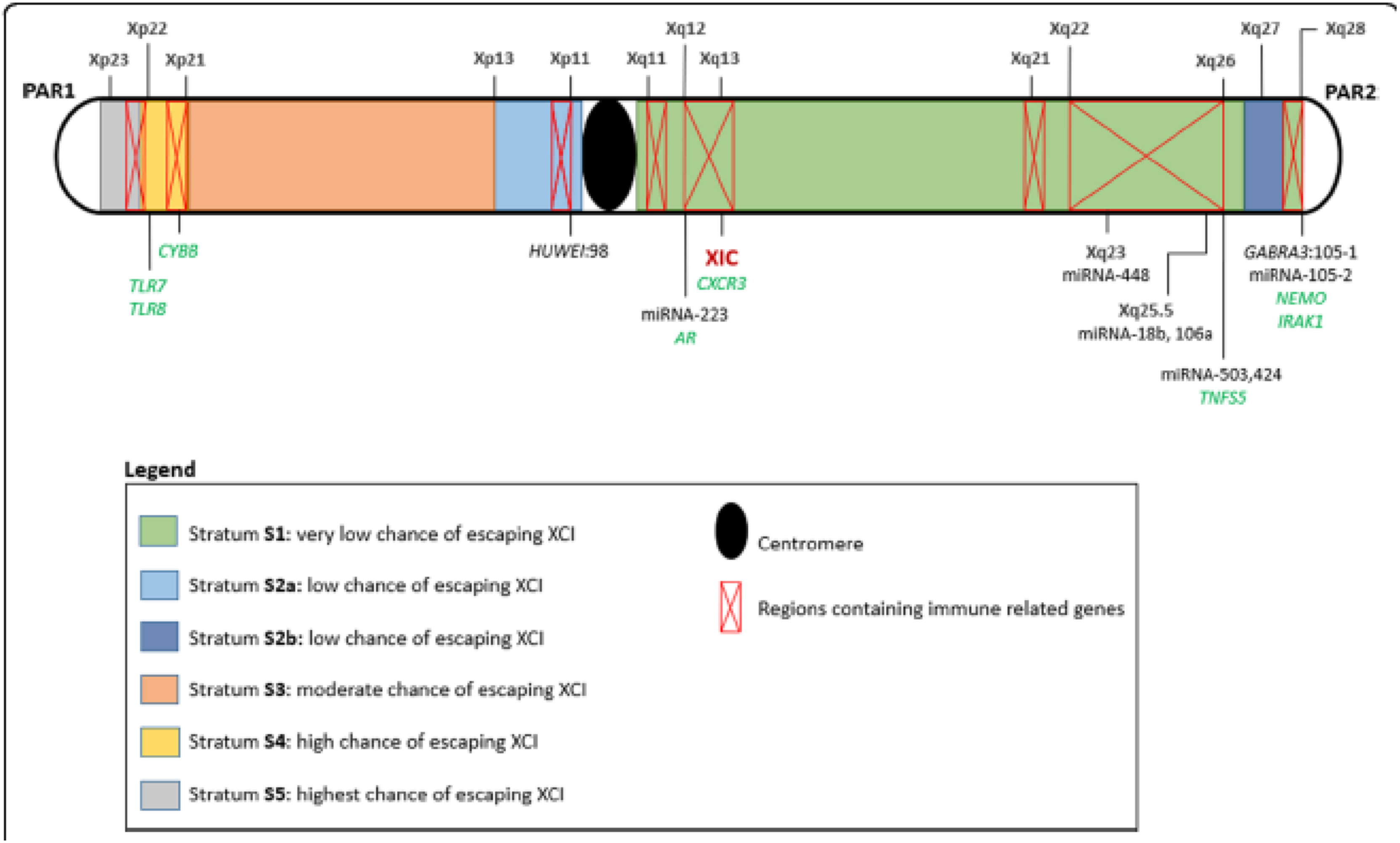


Cromosoma Y

2% del DNA totale
58 milioni di paia di basi
75 geni codificanti
125 geni non codificanti

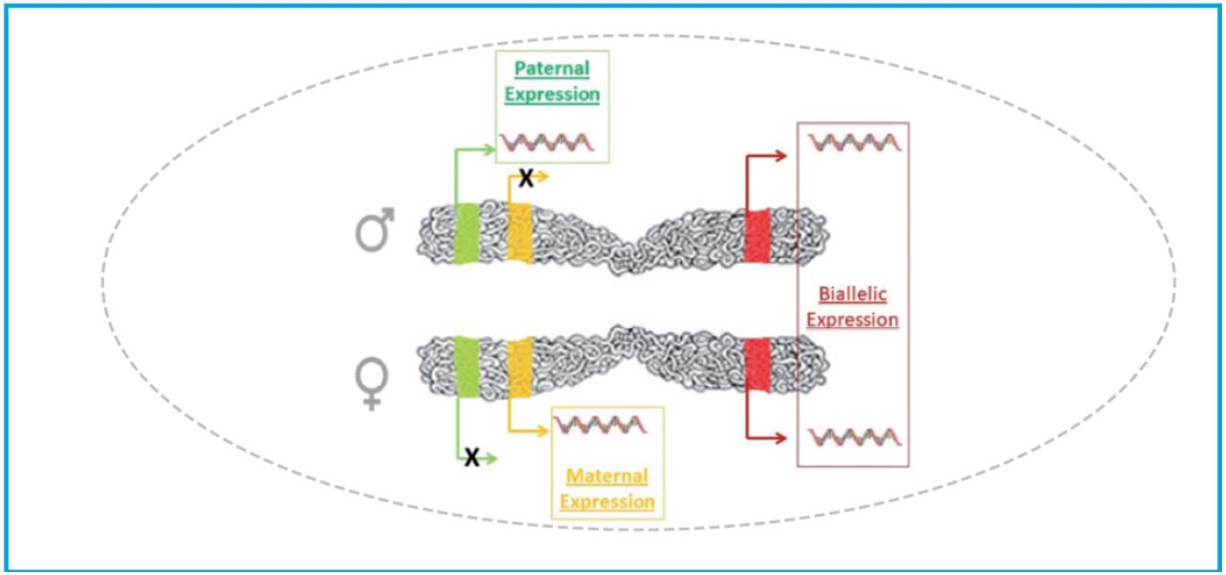
SRY: fattore di trascrizione che favorisce sviluppo dei testicoli. Regolatore espressione enzimi coinvolti metabolismo DA

Cromosoma X e risposta immunitaria


Xp22
Xp23
Xp21
Xp13
Xp11
Xq11
Xq12
Xq13
Xq21
Xq22
Xq26
Xq27
Xq28
PAR1
PAR2
CYBB
TLR7
TLR8
HUWE1:98
XIC
CXCR3
miRNA-223
AR
Xq23
miRNA-448
Xq25.5
miRNA-18b, 106a
miRNA-503,424
TNFS5
GABRA3:105-1
miRNA-105-2
NEMO
IRAK1
Legend
🟩 Stratum **S1**: very low chance of escaping XCI
🟦 Stratum **S2a**: low chance of escaping XCI
🟦 Stratum **S2b**: low chance of escaping XCI
🟧 Stratum **S3**: moderate chance of escaping XCI
🟨 Stratum **S4**: high chance of escaping XCI
⬜ Stratum **S5**: highest chance of escaping XCI
● Centromere
☒ Regions containing immune related genes

Schurz *et al. Human Genomics* (2019) 13:2

IMPRINTING GENOMICO



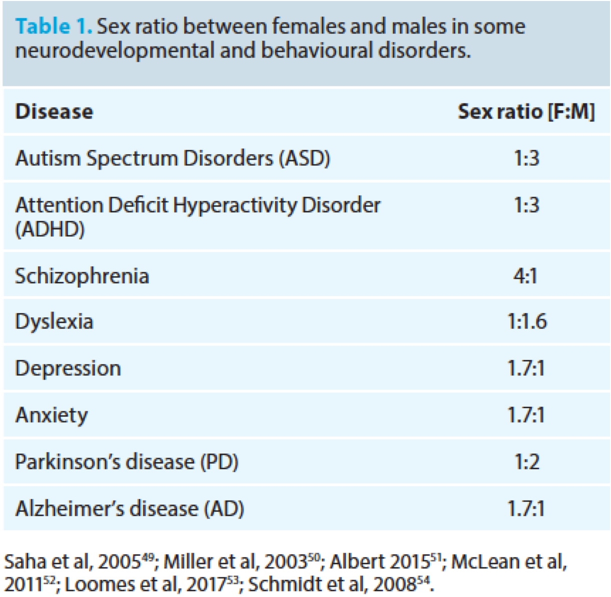


Table 1. Sex ratio between females and males in some neurodevelopmental and behavioural disorders.

Disease	Sex ratio [F:M]
Autism Spectrum Disorders (ASD)	1:3
Attention Deficit Hyperactivity Disorder (ADHD)	1:3
Schizophrenia	4:1
Dyslexia	1:1.6
Depression	1.7:1
Anxiety	1.7:1
Parkinson's disease (PD)	1:2
Alzheimer's disease (AD)	1.7:1

Saha et al, 2005[49]; Miller et al, 2003[50]; Albert 2015[51]; McLean et al, 2011[52]; Loomes et al, 2017[53]; Schmidt et al, 2008[54].

L'imprinting genomico consiste nell'espressione monoallelica (paterna o materna) di geni localizzati in regioni specifiche che vengono metilate

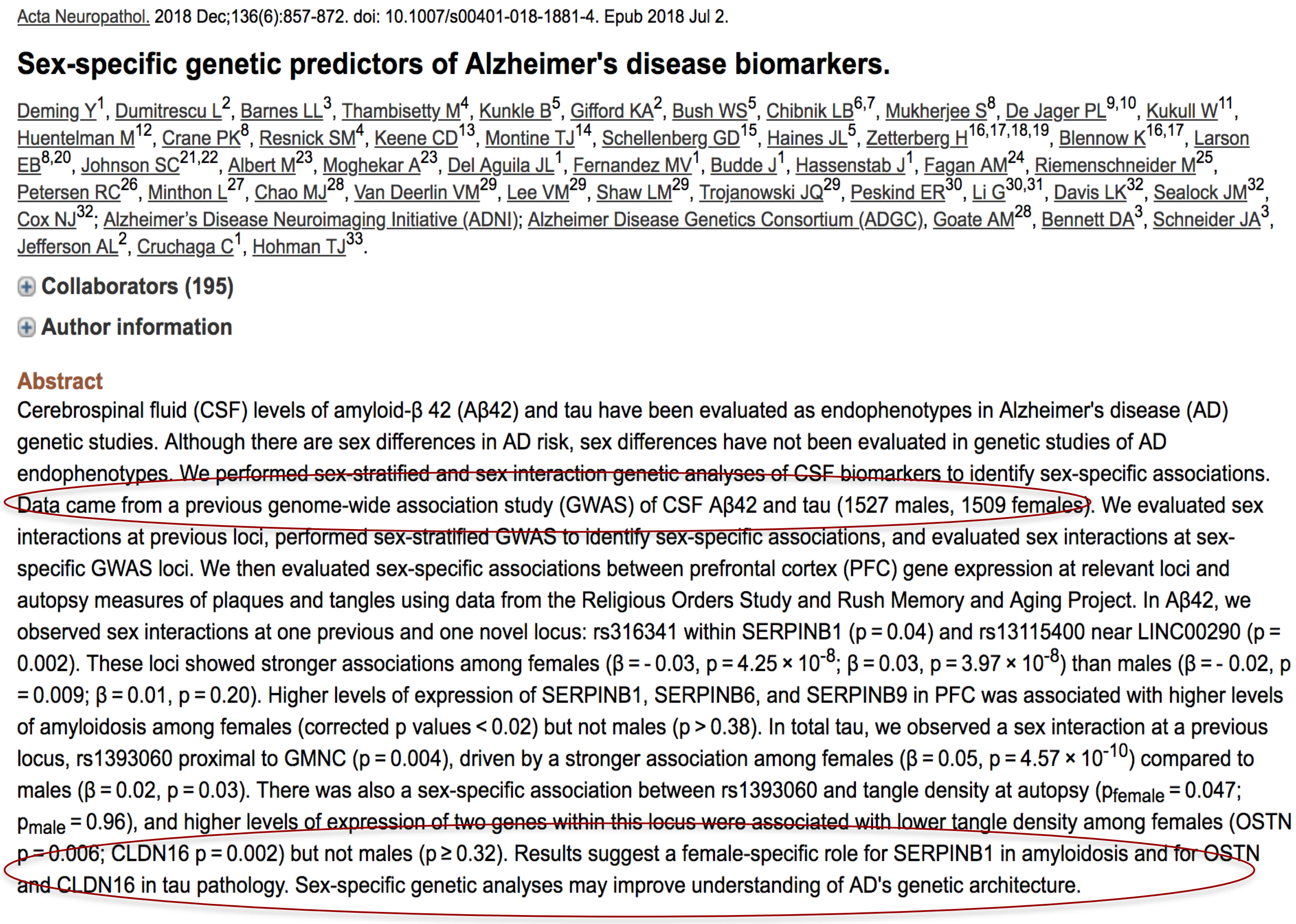
L'imprinting genomico avviene subito dopo la fecondazione ed ha un ruolo fondamentale nella crescita del feto e nello sviluppo della placenta

La perdita dell'imprinting causa patologie dello sviluppo fetale e disordini del comportamento (i.e. Angelman, Prader-Willi)

Il cervello contiene molte aree soggette ad imprinting

La maggior parte di patologie Mendeliane causate da mutazioni di proteine coinvolte nei processi epigenetici sono di natura neurologica (disabilità intellettiva, demenza)

Differenze di genere nella genetica della Demenza di Alzheimer



Acta Neuropathol. 2018 Dec;136(6):857-872. doi: 10.1007/s00401-018-1881-4. Epub 2018 Jul 2.

Sex-specific genetic predictors of Alzheimer's disease biomarkers.

Deming Y[1], Dumitrescu L[2], Barnes LL[3], Thambisetty M[4], Kunkle B[5], Gifford KA[2], Bush WS[5], Chibnik LB[6,7], Mukherjee S[8], De Jager PL[9,10], Kukull W[11], Huentelman M[12], Crane PK[8], Resnick SM[4], Keene CD[13], Montine TJ[14], Schellenberg GD[15], Haines JL[5], Zetterberg H[16,17,18,19], Blennow K[16,17], Larson EB[8,20], Johnson SC[21,22], Albert M[23], Moghekar A[23], Del Aguila JL[1], Fernandez MV[1], Budde J[1], Hassenstab J[1], Fagan AM[24], Riemenschneider M[25], Petersen RC[26], Minthon L[27], Chao MJ[28], Van Deerlin VM[29], Lee VM[29], Shaw LM[29], Trojanowski JQ[29], Peskind ER[30], Li G[30,31], Davis LK[32], Sealock JM[32], Cox NJ[32]; Alzheimer's Disease Neuroimaging Initiative (ADNI); Alzheimer Disease Genetics Consortium (ADGC), Goate AM[28], Bennett DA[3], Schneider JA[3], Jefferson AL[2], Cruchaga C[1], Hohman TJ[33].

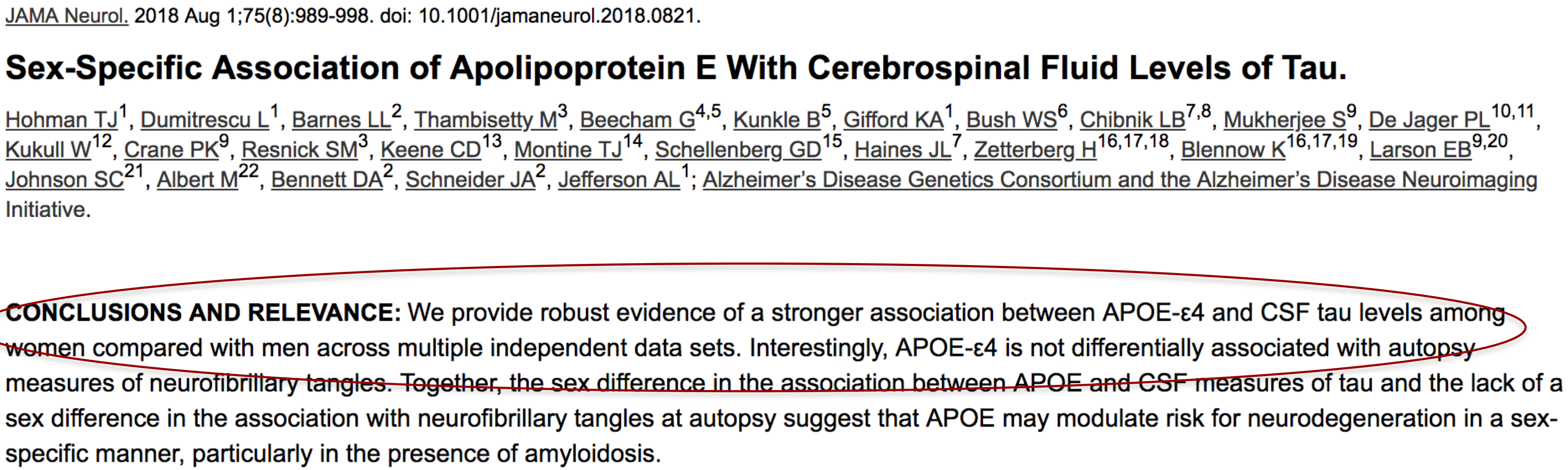
⊕ **Collaborators (195)**

⊕ **Author information**

Abstract

Cerebrospinal fluid (CSF) levels of amyloid-β 42 (Aβ42) and tau have been evaluated as endophenotypes in Alzheimer's disease (AD) genetic studies. Although there are sex differences in AD risk, sex differences have not been evaluated in genetic studies of AD endophenotypes. We performed sex-stratified and sex interaction genetic analyses of CSF biomarkers to identify sex-specific associations. Data came from a previous genome-wide association study (GWAS) of CSF Aβ42 and tau (1527 males, 1509 females). We evaluated sex interactions at previous loci, performed sex-stratified GWAS to identify sex-specific associations, and evaluated sex interactions at sex-specific GWAS loci. We then evaluated sex-specific associations between prefrontal cortex (PFC) gene expression at relevant loci and autopsy measures of plaques and tangles using data from the Religious Orders Study and Rush Memory and Aging Project. In Aβ42, we observed sex interactions at one previous and one novel locus: rs316341 within SERPINB1 ($p = 0.04$) and rs13115400 near LINC00290 ($p = 0.002$). These loci showed stronger associations among females ($\beta = -0.03$, $p = 4.25 \times 10^{-8}$; $\beta = 0.03$, $p = 3.97 \times 10^{-8}$) than males ($\beta = -0.02$, $p = 0.009$; $\beta = 0.01$, $p = 0.20$). Higher levels of expression of SERPINB1, SERPINB6, and SERPINB9 in PFC was associated with higher levels of amyloidosis among females (corrected p values < 0.02) but not males ($p > 0.38$). In total tau, we observed a sex interaction at a previous locus, rs1393060 proximal to GMNC ($p = 0.004$), driven by a stronger association among females ($\beta = 0.05$, $p = 4.57 \times 10^{-10}$) compared to males ($\beta = 0.02$, $p = 0.03$). There was also a sex-specific association between rs1393060 and tangle density at autopsy ($p_{female} = 0.047$; $p_{male} = 0.96$), and higher levels of expression of two genes within this locus were associated with lower tangle density among females (OSTN $p = 0.006$; CLDN16 $p = 0.002$) but not males ($p \geq 0.32$). Results suggest a female-specific role for SERPINB1 in amyloidosis and for OSTN and CLDN16 in tau pathology. Sex-specific genetic analyses may improve understanding of AD's genetic architecture.

Differenze di genere nella genetica della Demenza di Alzheimer



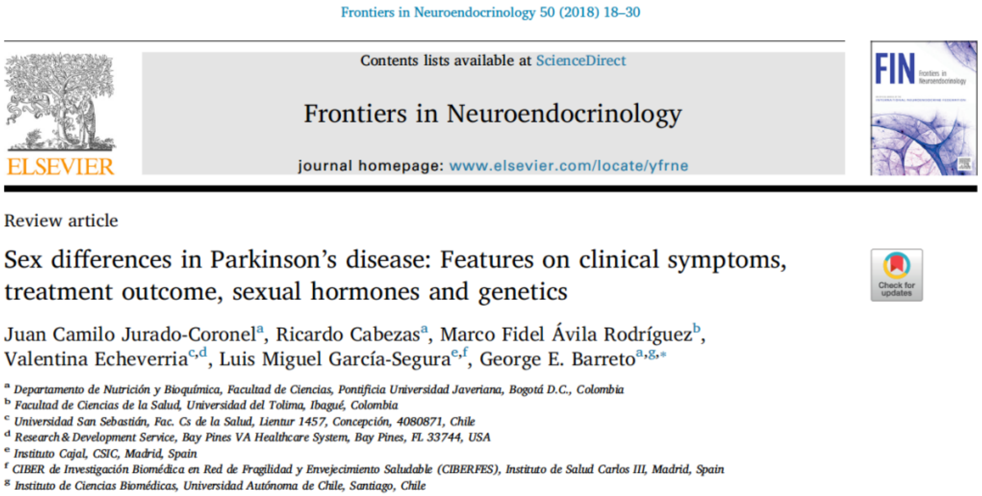
JAMA Neurol. 2018 Aug 1;75(8):989-998. doi: 10.1001/jamaneurol.2018.0821.

Sex-Specific Association of Apolipoprotein E With Cerebrospinal Fluid Levels of Tau.

Hohman TJ[1], Dumitrescu L[1], Barnes LL[2], Thambisetty M[3], Beecham G[4,5], Kunkle B[5], Gifford KA[1], Bush WS[6], Chibnik LB[7,8], Mukherjee S[9], De Jager PL[10,11], Kukull W[12], Crane PK[9], Resnick SM[3], Keene CD[13], Montine TJ[14], Schellenberg GD[15], Haines JL[7], Zetterberg H[16,17,18], Blennow K[16,17,19], Larson EB[9,20], Johnson SC[21], Albert M[22], Bennett DA[2], Schneider JA[2], Jefferson AL[1]; Alzheimer's Disease Genetics Consortium and the Alzheimer's Disease Neuroimaging Initiative.

CONCLUSIONS AND RELEVANCE: We provide robust evidence of a stronger association between APOE-ε4 and CSF tau levels among women compared with men across multiple independent data sets. Interestingly, APOE-ε4 is not differentially associated with autopsy measures of neurofibrillary tangles. Together, the sex difference in the association between APOE and CSF measures of tau and the lack of a sex difference in the association with neurofibrillary tangles at autopsy suggest that APOE may modulate risk for neurodegeneration in a sex-specific manner, particularly in the presence of amyloidosis.

Differenze di genere nella genetica del Parkinson



Frontiers in Neuroendocrinology 50 (2018) 18–30

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Review article

Sex differences in Parkinson's disease: Features on clinical symptoms, treatment outcome, sexual hormones and genetics

Juan Camilo Jurado-Coronel[a], Ricardo Cabezas[a], Marco Fidel Ávila Rodríguez[b], Valentina Echeverria[c,d], Luis Miguel García-Segura[e,f], George E. Barreto[a,g,*]

[a] Departamento de Nutrición y Bioquímica, Facultad de Ciencias, Pontificia Universidad Javeriana, Bogotá D.C., Colombia
[b] Facultad de Ciencias de la Salud, Universidad del Tolima, Ibagué, Colombia
[c] Universidad San Sebastián, Fac. Cs de la Salud, Lientur 1457, Concepción, 4080871, Chile
[d] Research & Development Service, Bay Pines VA Healthcare System, Bay Pines, FL 33744, USA
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[g] Instituto de Ciencias Biomédicas, Universidad Autónoma de Chile, Santiago, Chile

Cervello:

SNCA e PINK1 up-regolati nell'uomo.

Geni coinvolti maturazione neuronale up-regolati nella donna.

Parkinsonism and Related Disorders 20 (2014) 911–914

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Short communication

LRRK2 mutations in Parkinson's disease: Confirmation of a gender effect in the Italian population

Roberto Cilia[a], Chiara Siri[a], Damiana Rusconi[b], Roberta Allegra[a], Andrea Ghiglietti[c], Giorgio Sacilotto[a], Michela Zini[a], Anna L. Zecchinelli[a], Rosanna Asselta[d], Stefano Duga[d], Anna M. Paganoni[c], Gianni Pezzoli[a], Manuela Seia[b], Stefano Goldwurm[a,*]

[a] Parkinson Institute, Istituti Clinici di Perfezionamento, via Bignami 1, 20126 Milan, Italy
[b] Medical Genetics Laboratory, Foundation IRCCS "Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena", Milan, Italy
[c] MOX, Dipartimento di Matematica, Politecnico di Milano, Italy
[d] Dipartimento di Biotecnologie Mediche e Medicina Traslazionale, Università degli Studi di Milano, Italy

THE LANCET

Volume 393 · Number 10171 · Pages 493-610 · February 9-15, 2019 www.thelancet.com

Advancing women in science, medicine, and global health

Editorial
Feminism is for everybody
See page 493

Articles
Are gender gaps due to evaluations of the applicant or the science?
See page 531

Articles
Sex-related reporting in medical research
See page 550

Review
Organisational best practices towards gender equality in science and medicine
See page 587

Health Policy
More talk than action: gender and ethnic diversity in universities
See page 594

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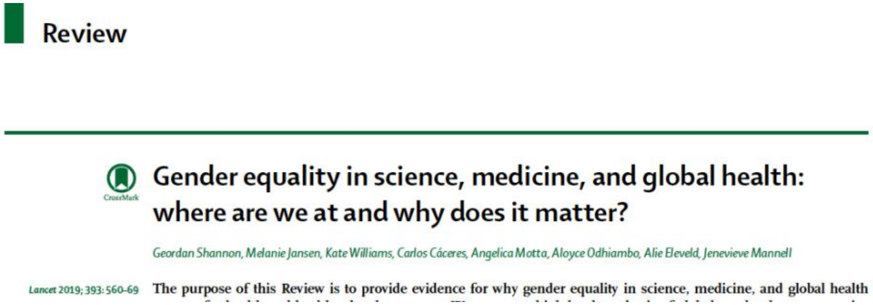


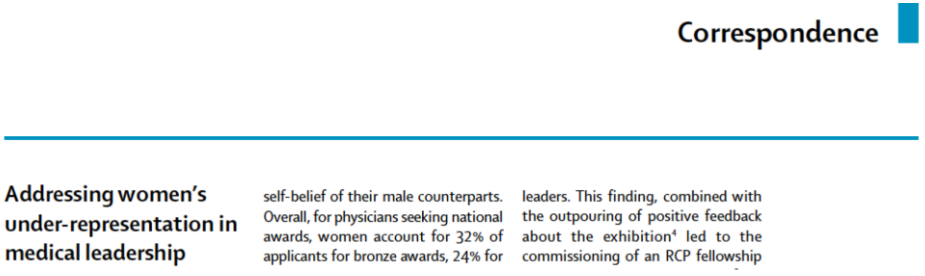
Review

Gender equality in science, medicine, and global health: where are we at and why does it matter?

Geordan Shannon, Melanie Jansen, Kate Williams, Carlos Cáceres, Angelica Motta, Aloyce Odhiambo, Alie Eleveld, Jenevieve Mannell

Lancet 2019; 393: 560-69

The purpose of this Review is to provide evidence for why gender equality in science, medicine, and global health

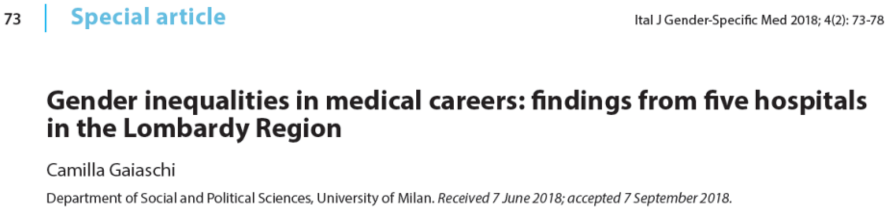


Correspondence

Addressing women's under-representation in medical leadership

self-belief of their male counterparts. Overall, for physicians seeking national awards, women account for 32% of applicants for bronze awards, 24% for

leaders. This finding, combined with the outpouring of positive feedback about the exhibition[4] led to the commissioning of an RCP fellowship



73 | **Special article** Ital J Gender-Specific Med 2018; 4(2): 73-78

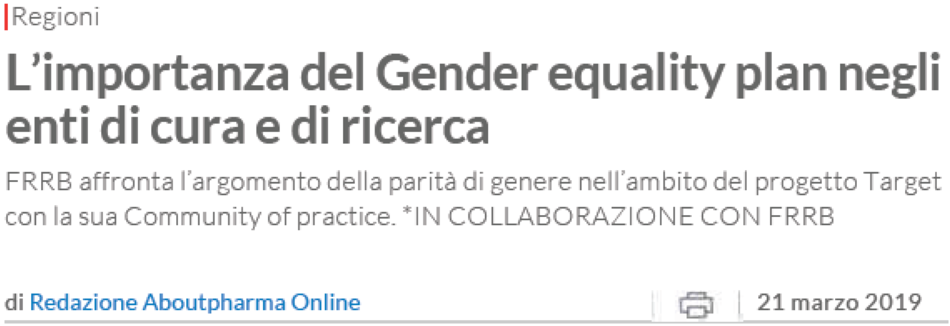
Gender inequalities in medical careers: findings from five hospitals in the Lombardy Region

Camilla Gaiaschi

Department of Social and Political Sciences, University of Milan. *Received 7 June 2018; accepted 7 September 2018.*

EIGE
Istituto europeo
per l'uguaglianza di genere

GUIDA AI CAMBIAMENTI STRUTTURALI
NEL MONDO ACCADEMICO
E NELLE ORGANIZZAZIONI DI RICERCA
PASSO DOPO PASSO

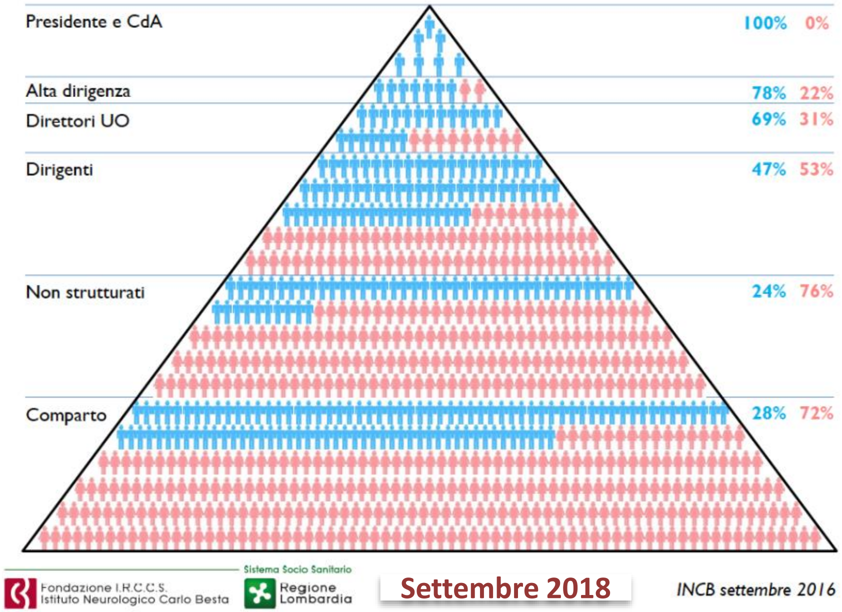


Regioni

L'importanza del Gender equality plan negli enti di cura e di ricerca

FRRB affronta l'argomento della parità di genere nell'ambito del progetto Target con la sua Community of practice. *IN COLLABORAZIONE CON FRRB

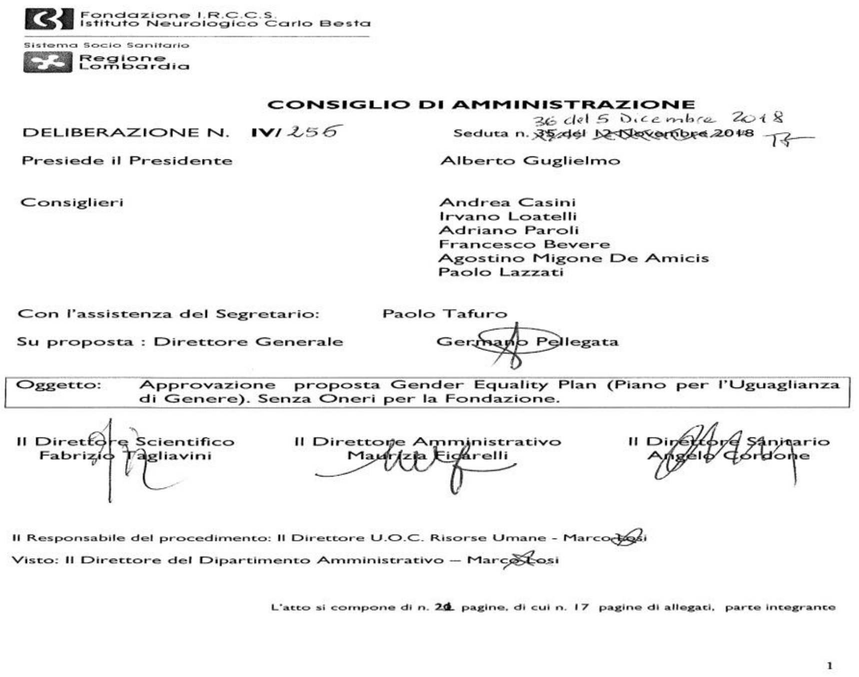
di Redazione Aboutpharma Online | 21 marzo 2019



Settembre 2018

INCB settembre 2016

Con il termine "parità di genere" non si intende che uomini e donne debbano essere uguali o in ugual numero, ma che abbiano pari accesso alle stesse opportunità, pur conservando le loro peculiarità



Fondazione I.R.C.C.S.
Istituto Neurologico Carlo Besta

Sistema Socio Sanitario
Regione Lombardia

CONSIGLIO DI AMMINISTRAZIONE

DELIBERAZIONE N. **IV/** 256 — Seduta n. 36 del 5 Dicembre 2018 ~~35 del 12 Novembre~~ 2018 TF

Presiede il Presidente — Alberto Guglielmo

Consiglieri
Andrea Casini
Irvano Loatelli
Adriano Paroli
Francesco Bevere
Agostino Migone De Amicis
Paolo Lazzati

Con l'assistenza del Segretario: Paolo Tafuro

Su proposta : Direttore Generale — Germano Pellegata

Oggetto:	Approvazione proposta Gender Equality Plan (Piano per l'Uguaglianza di Genere). Senza Oneri per la Fondazione.

Il Direttore Scientifico
Fabrizio Tagliavini

Il Direttore Amministrativo
Maurizia Ficarelli

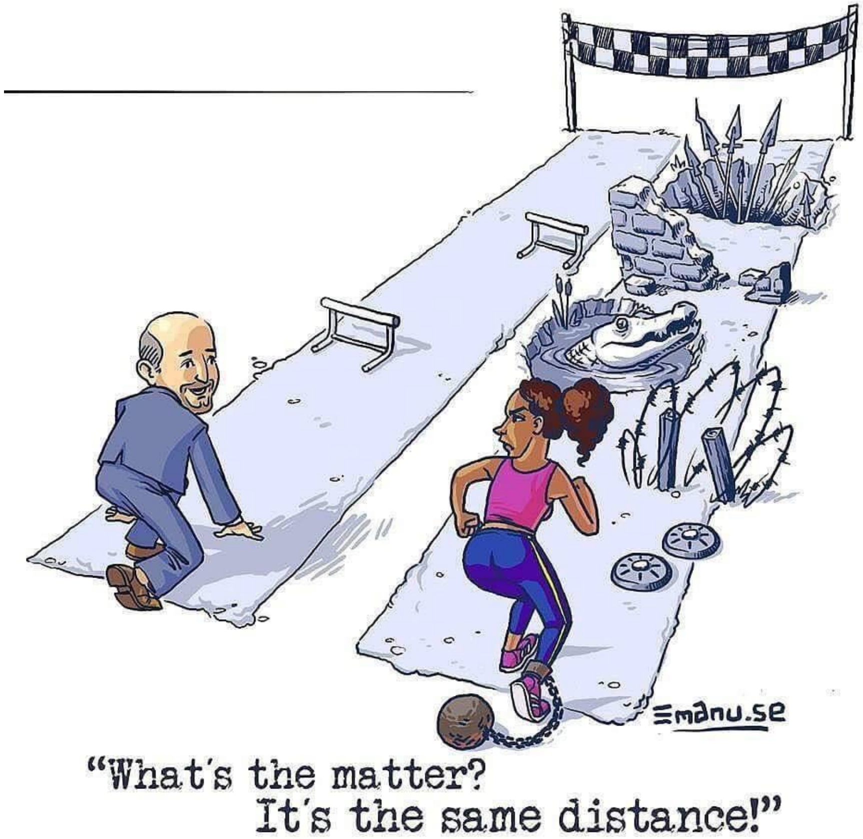
Il Direttore Sanitario
Angelo Cordone

Il Responsabile del procedimento: Il Direttore U.O.C. Risorse Umane - Marco Losi

Visto: Il Direttore del Dipartimento Amministrativo – Marco Losi

L'atto si compone di n. 21 pagine, di cui n. 17 pagine di allegati, parte integrante

1


Emanu.se
"What's the matter?
It's the same distance!"

Grazie per l'attenzione