L’inattivazione del cromosoma X

Female cells have double the number of X chromosomes as male cells. Therefore, female cells should express twice the amount of X chromosome genes (n=1300!) than male cells. BUT - they DON'T.

Male and female cells express X chromosome genes approximately at similar level.

XX XY

Brain-specific genes on Chromosome X

In addition to genes that are important in reproduction, the mammalian X chromosome is also enriched in genes related to neurological function.

Overall, X-linked genes are highly expressed in the brain, and the proportion of X-linked genes expressed in the brain is significantly higher than that in other somatic tissues

Many of genes expressed in the testes are also expressed in the brain

Brain-specific genes on Chromosome X Intellectual Disability

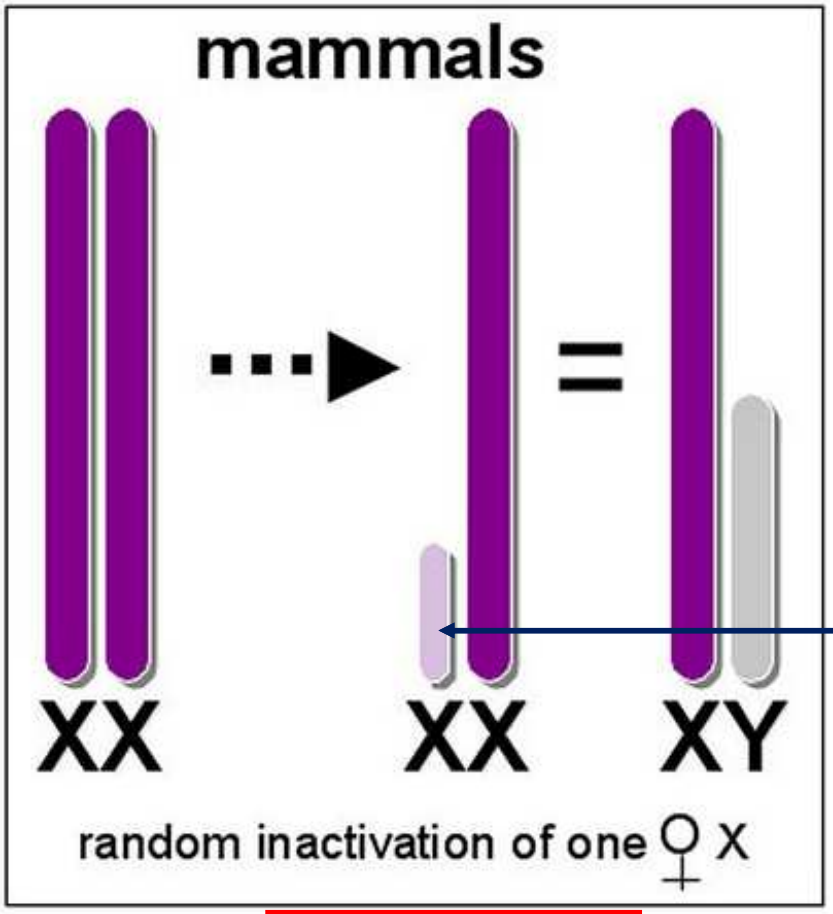
X-linked forms of intellectual disability are 3.5 times more common than autosomal forms,

Nearly 100 human X-linked genes have mutations in individuals with intellectual disability.

The effects of mutations in human X-linked genes associated with intellectual disability are variable in females (XCI skewing or escape from XCI).

XCI= X Chromosome Inactivation

Mechanisms of X chromosome dosage compensation: downregulation

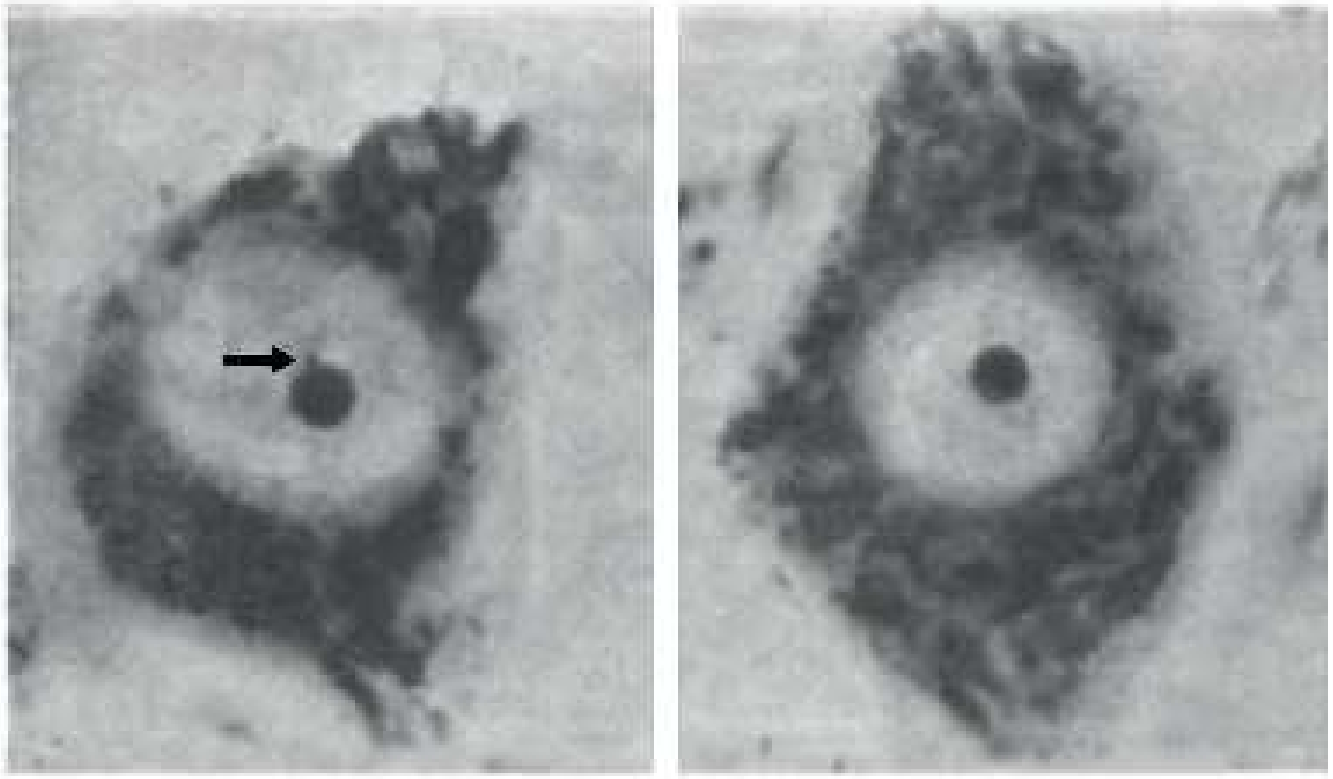


wormbook.org

L’inattivazione del cromosoma X

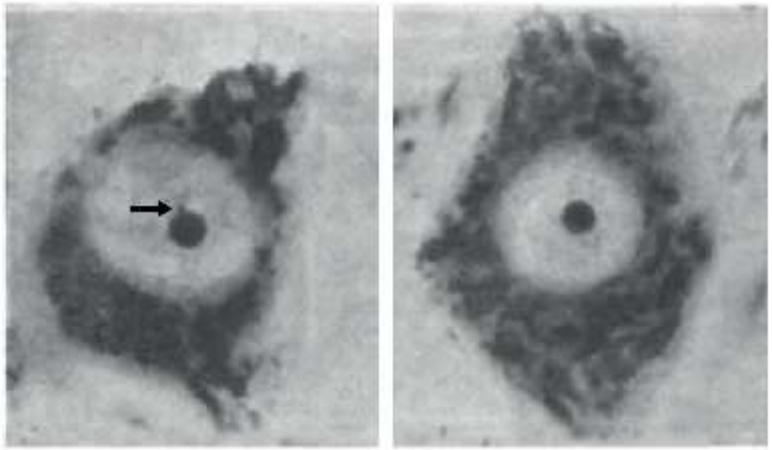
Il problema di inattivare solo uno
di due cromosomi molto simili

a The "nucleolar satellite" (1949)

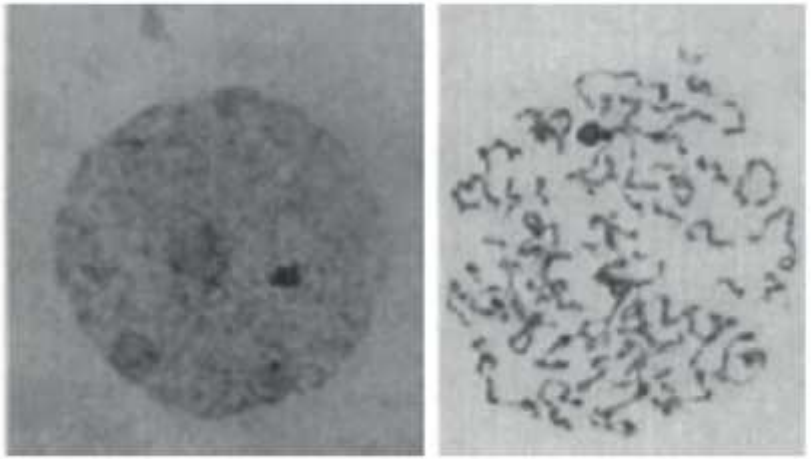


Annual Reviews 2018

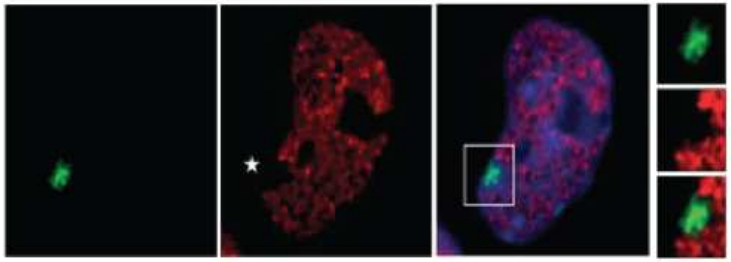
a The "nucleolar satellite" (1949)



b One heteropycnotic X chromosome (1959)

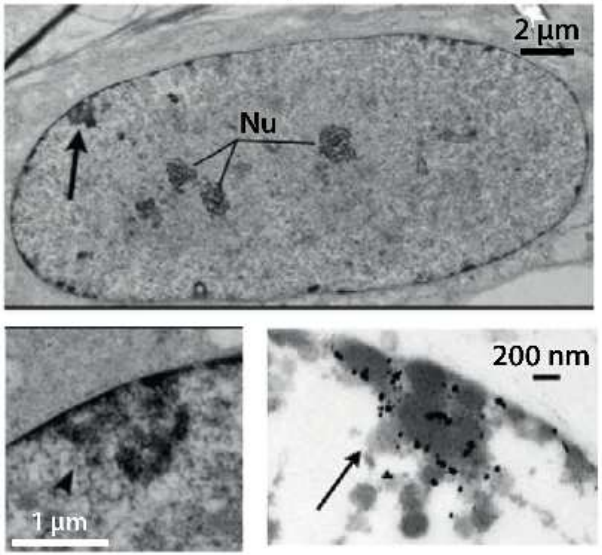


f Xist RNA silent nuclear compartment (2006)

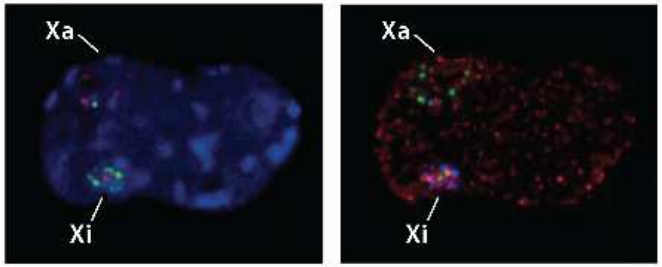


Xist RNA | RNA Pol II | Merge with DAPI

g Electron microscopy of the Barr body (2008)



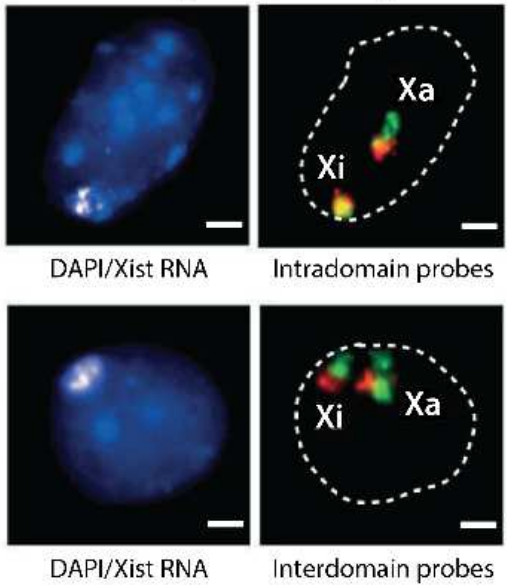
h Organization of repeats and genes (2010)



Xist RNA (*green*)
X-linked gene loci (*red*)

Xist RNA (*blue*)
X-linked gene loci (*green*)
Repetitive LINE-1 DNA (*red*)

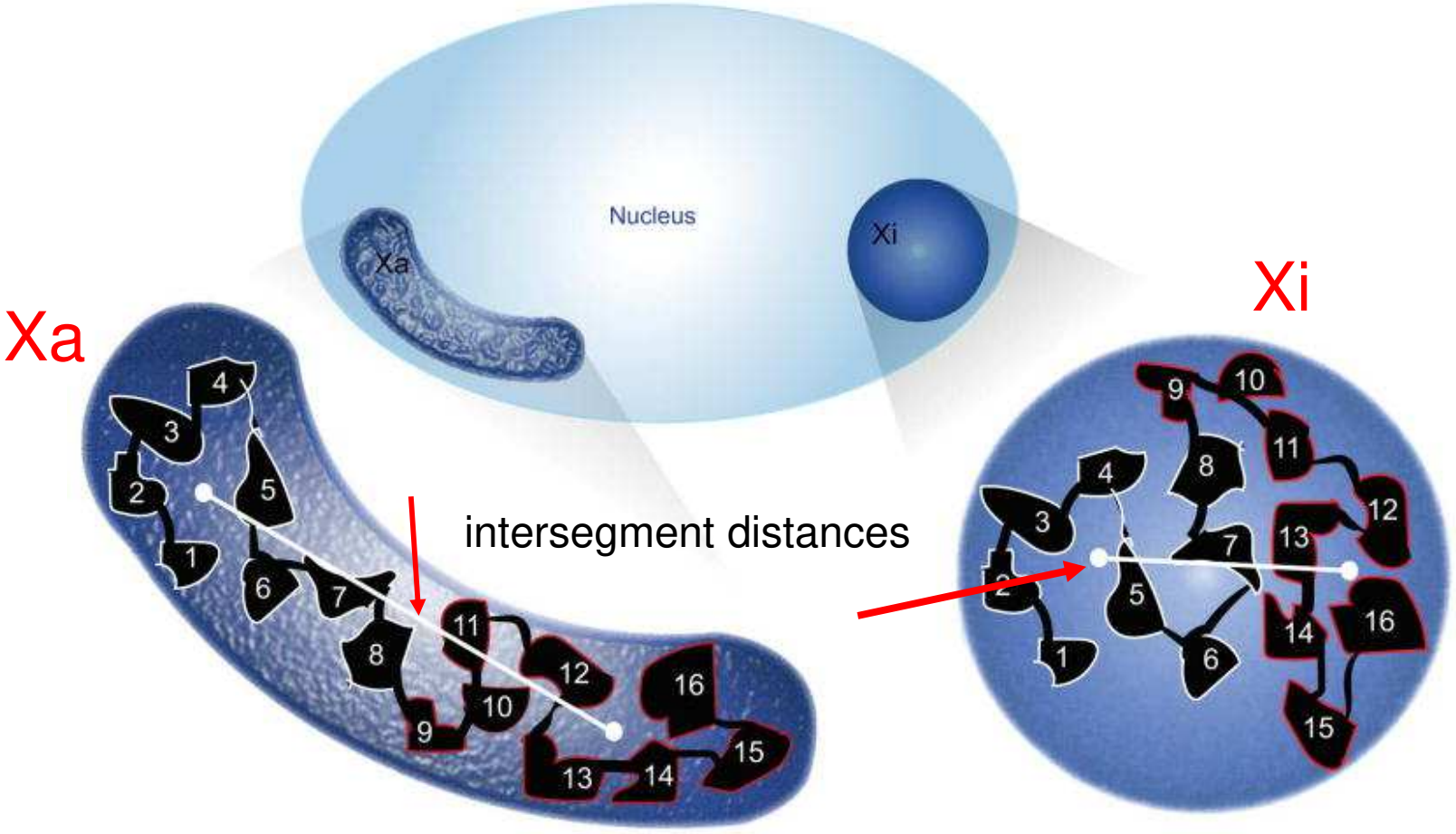
i The Xi is organized into mega-domains (2016)



DAPI/Xist RNA | Intradomain probes

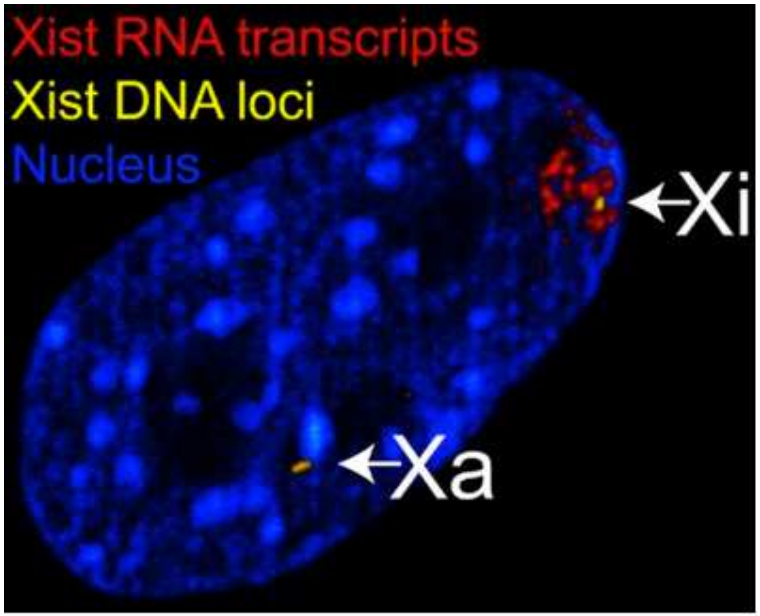
DAPI/Xist RNA | Interdomain probes

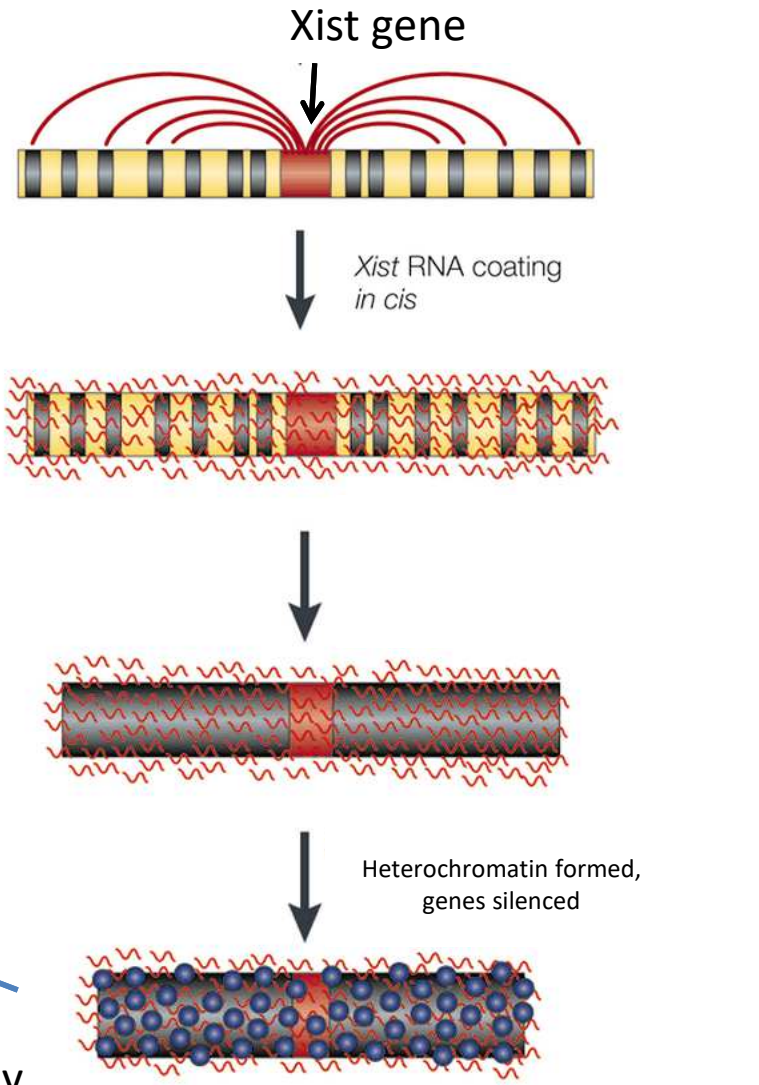
The shape and chromatin organization of the Xi is distinct from that of the Xa



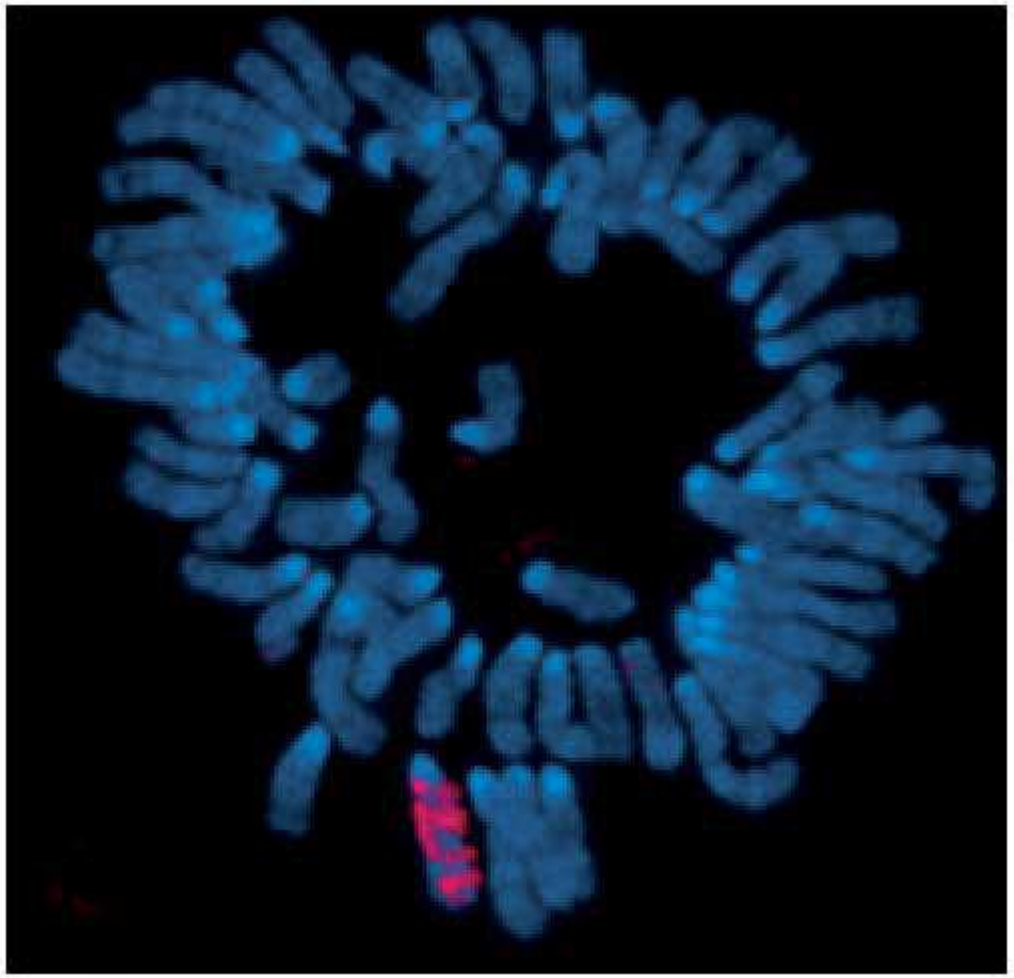
two large chromosomal segments (red and white regions) that differ in their relative arrangement but not in their compaction

X Chromosome Inactivation



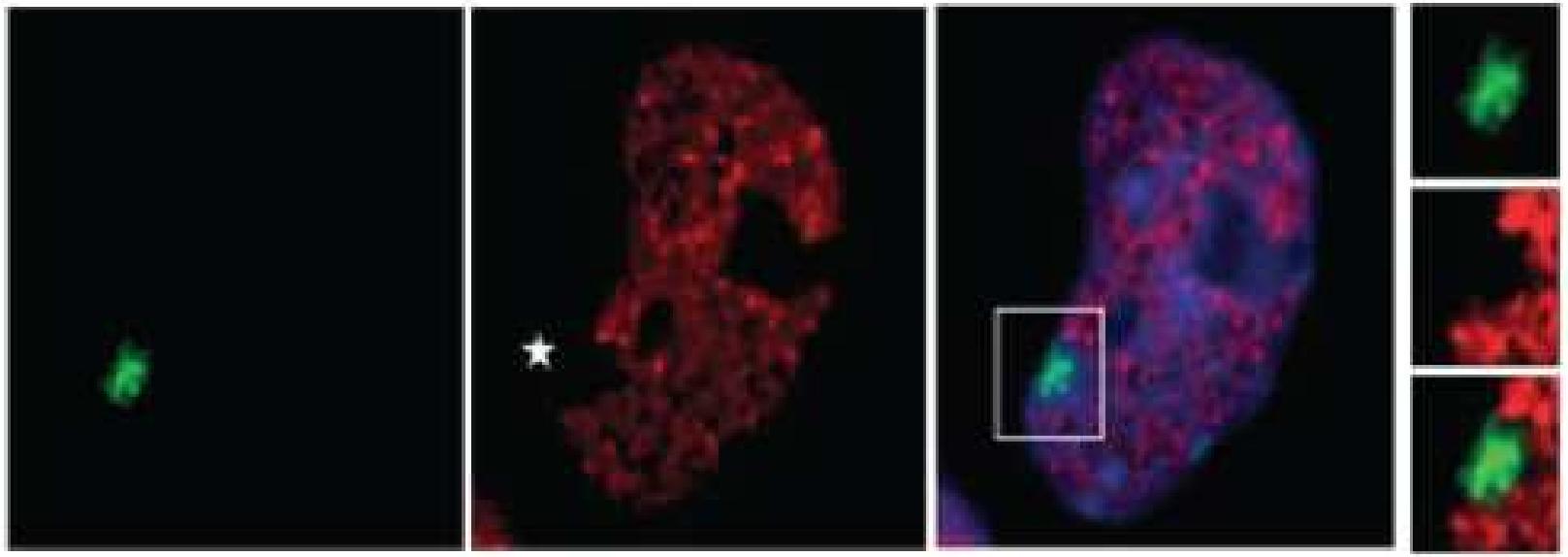


http://embryology.med.unsw.edu.au/embryology/images/thumb/3/3f/X_inactivation_Xist.jpg/400px-X_inactivation_Xist.jpg



EMBO Rep. 2007 January; 8(1): 34–39.
doi: 10.1038/sj.embor.7400871.

f Xist RNA silent nuclear compartment (2006)



Xist RNA RNA Pol II Merge with DAPI

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X Chromosome Inactivation

- Mechanism of X Chromosome inactivation
- XIC – X chromosome Inactivation Center
  - XIC controls expression of the *XIST* gene
  - *XIST*: X-inactive-specific transcript
  - *XIST* produces a non-coding 17 kb RNA molecule
  - "Coats" the entire *local* X-chromosome – *cis*-acting

Xist induction and maturation

- Nascent Xist RNA is processed to ~17 kb-length RNA by splicing, and different polyadenylation sites and alternative splicing patterns contribute to the generation of multiple isoforms of Xist RNA

The Xist RNA cloud is composed of discrete RNA foci distributed throughout the Xi territory

RNA FISH signal (green) DNA probes against the full length Xist RNA

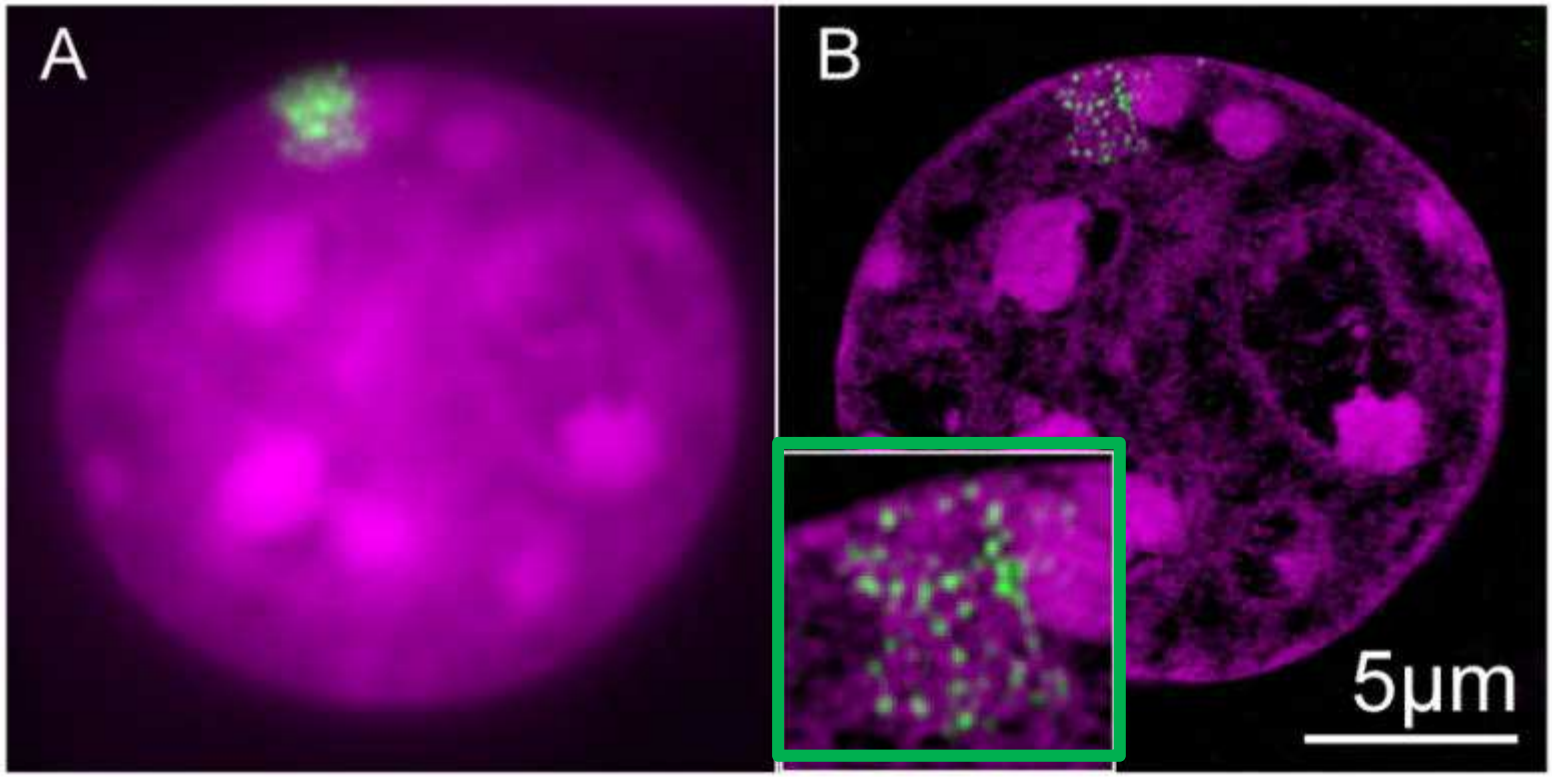
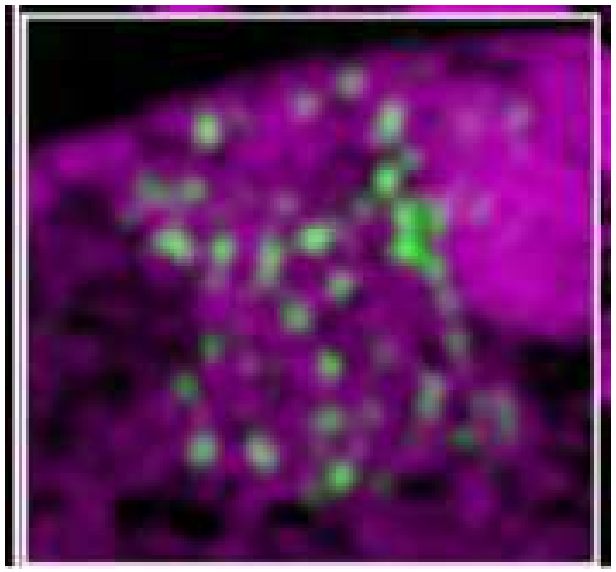


Image courtesy of Dr. Yolanda Markaki

DNA probes against the full length Xist RNA

The Xist RNA cloud is composed of discrete RNA foci distributed throughout the Xi territory

RNA FISH signal (green) DNA probes against the full length Xist RNA



DNA probes against the full length Xist RNA

X inactive-specific transcript (Xist)

X inactive-specific transcript (Xist) is a long noncoding RNA that plays an essential role in X chromosome inactivation.

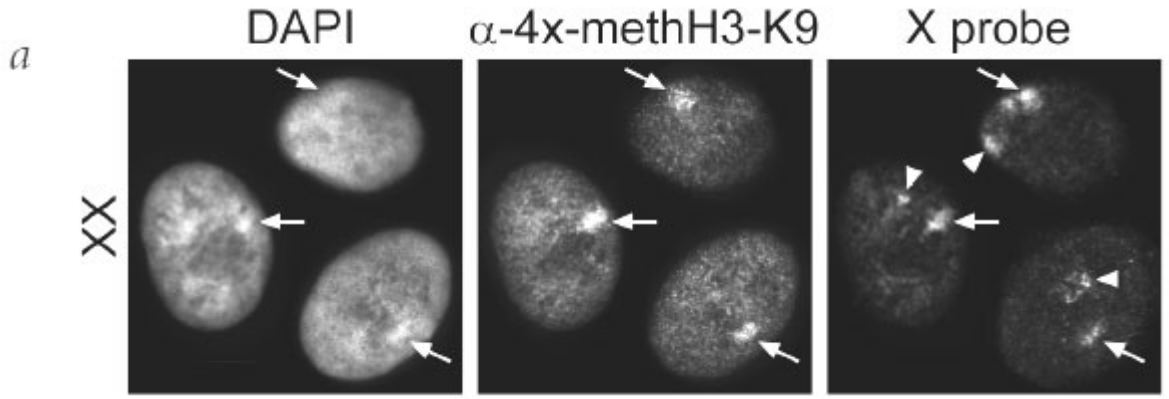
Xist RNA, like protein-coding mRNAs, is transcribed by RNA polymerase II, spliced and polyadenylated

Xist RNA is retained in the nucleus and associates with the X chromosome it originates from (Cis).

One of the major proteins constituting the nuclear matrix, hnRNP U is required for the association of Xist RNA with the inactive X chromosome (Xi).

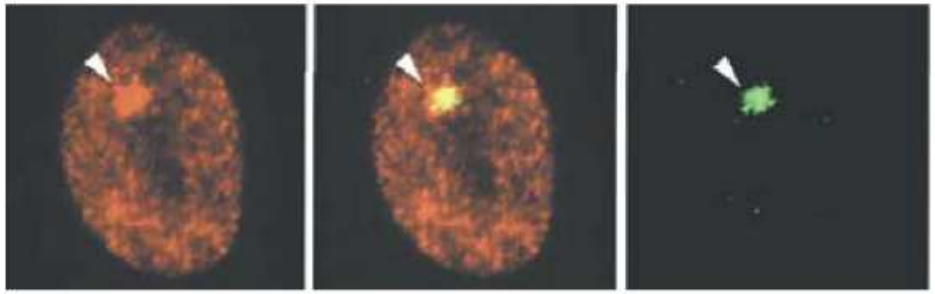
Xist RNA recruits proteins involved in epigenetic modifications and chromatin compaction to the X chromosome.

X Chromosome Inactivation: Chromatin



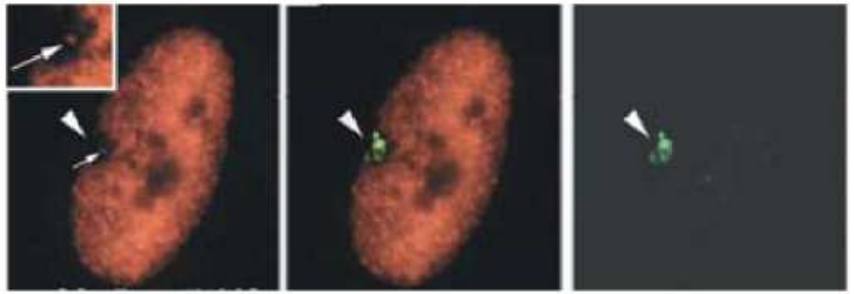
Peters *et al.* *Nature Genetics* **30**, 77 – 80 (2002)

d Enrichment of repressive chromatin mark on the Xi (2002)



H3K9me2 Merge Xist RNA

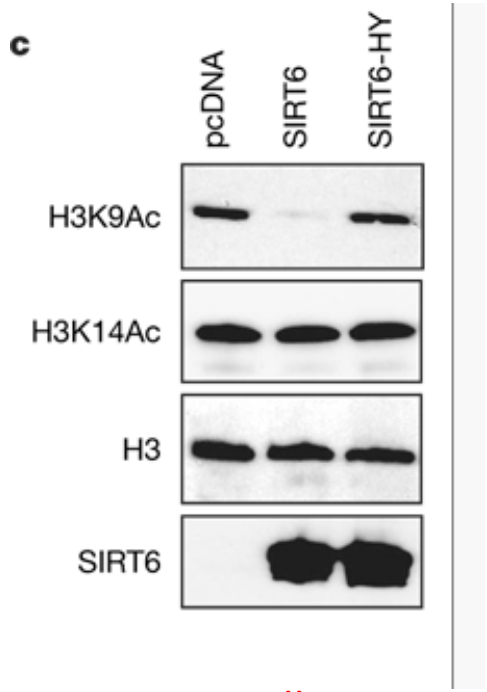
e Depletion of active chromatin mark on the Xi (2002)



H3K4me Merge Xist RNA

CONFRONTO!

SIRT6 (sir 2) deacetylates lysine 9 of histone H3 at telomeric chromatin



293Tcells
overexpressing SIRT6

SIRT6-HY: *catalytic H133Y SIRT6 mutant protein*

L’inattivazione del cromosoma X

Il problema del dosaggio «ridotto»

Mechanisms of X chromosome dosage compensation: upregulation to compensate for autosomal biallelic expression

1) Active mouse X-linked promoters are enriched in

the initiation form of RNA polymerase II (Pol II-S5p)

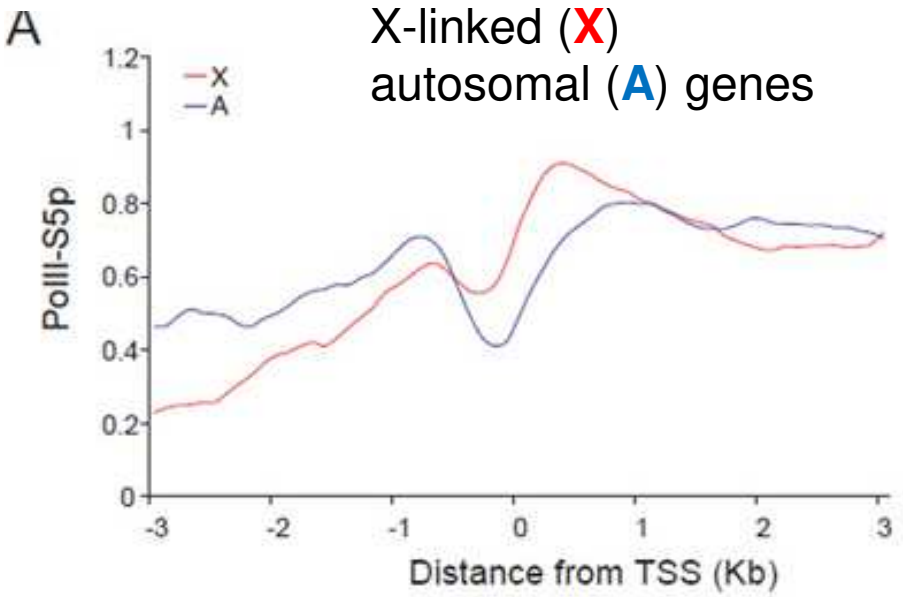
forms of RNA polymerase II

PolII-S5p (phosphorylated at serine 5) initiation

and PolII-S2p (phosphorylated at serine 2), elongation

PolII-S5p occupancy is enhanced at expressed X-linked genes in female ES cells

analyses of
355 X-linked and
387 chr19-linked expressed genes



X-linked (**X**)
autosomal (**A**) genes

3kb up- and downstream of the TSS
(transcriptional start site)

ChIP-chip analyses using genome tiling arrays

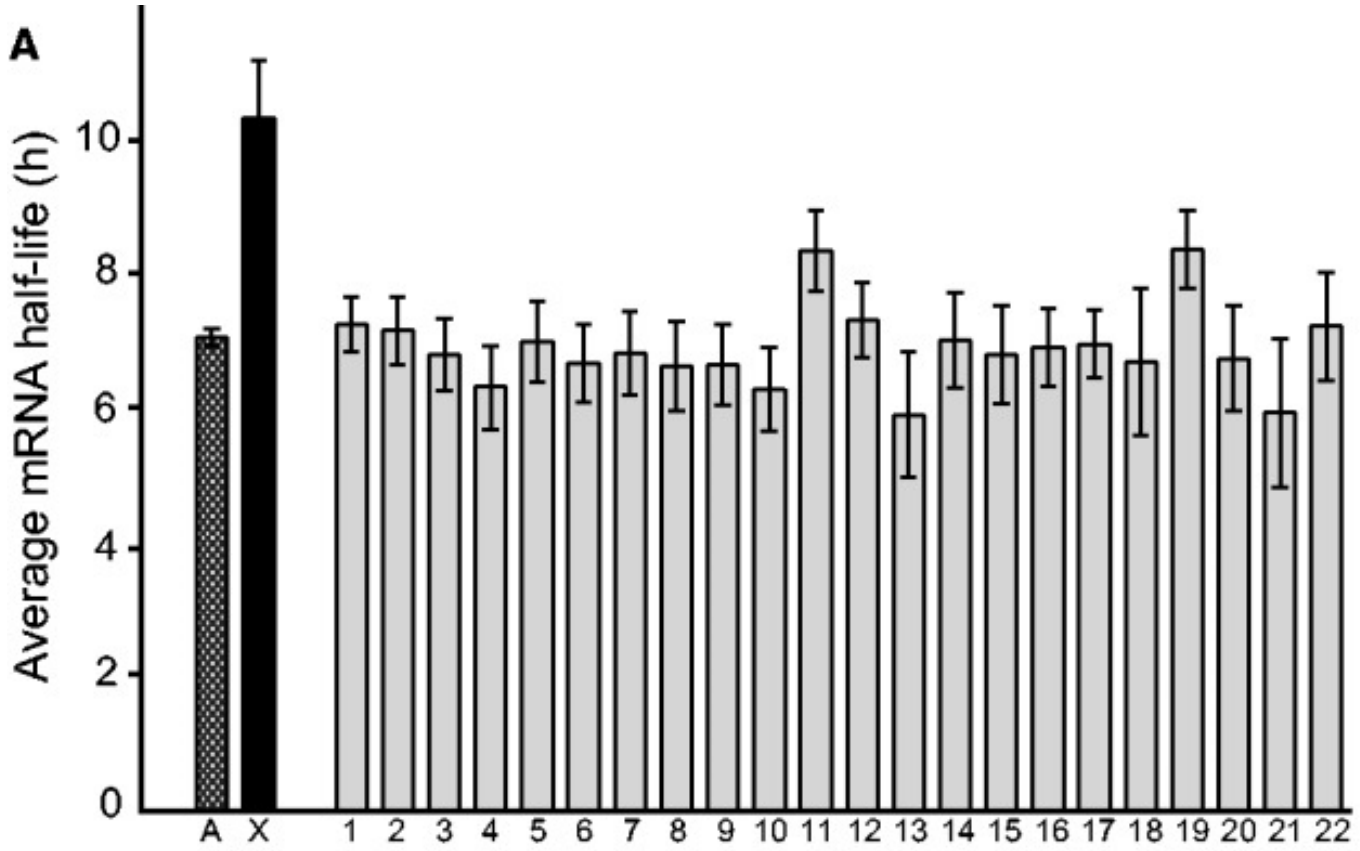
compensate for autosomal biallelic expression

Active mouse X-linked promoters are enriched in

the initiation form of RNA polymerase II (Pol II-S5p)

in specific histone marks, including histone H4 acetylated at lysine 16 (H4K16ac)

RNA half-life data show increased stability of mammalian X-linked transcripts


A
Average mRNA half-life (h)
0
2
4
6
8
10
A X 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

Mechanisms of X chromosome dosage compensation: upregulation to compensate for autosomal biallelic expression

3) RNA half-life data show increased stability of mammalian X-linked transcripts