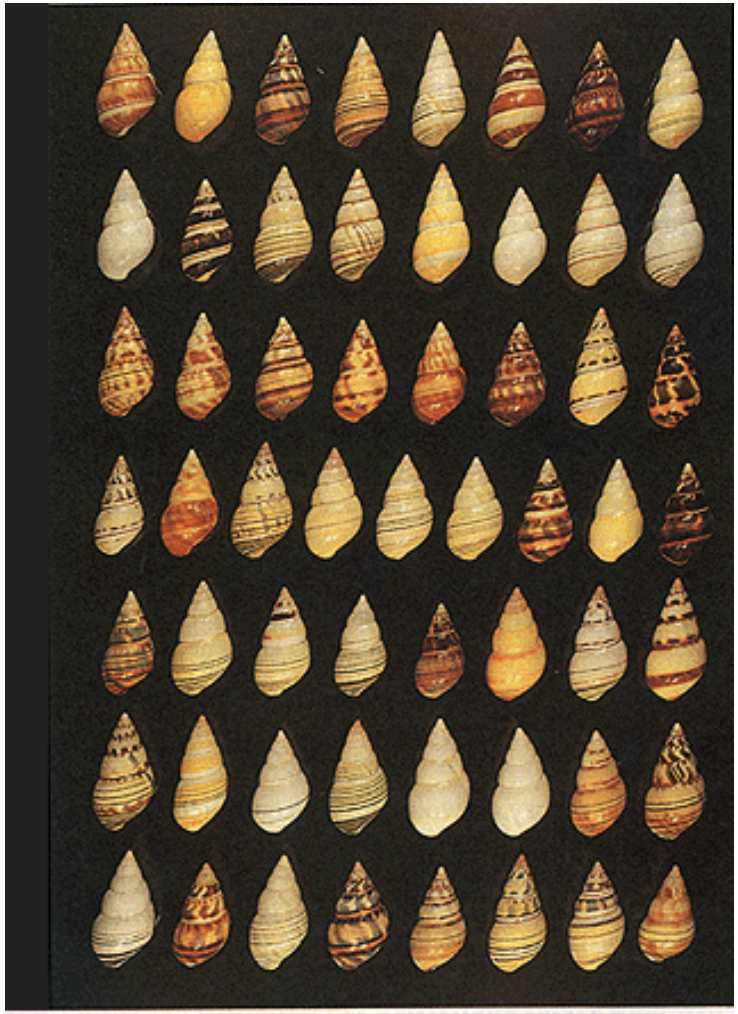
Genèse des mutations germinales chez l'Homme

Molly Przeworski

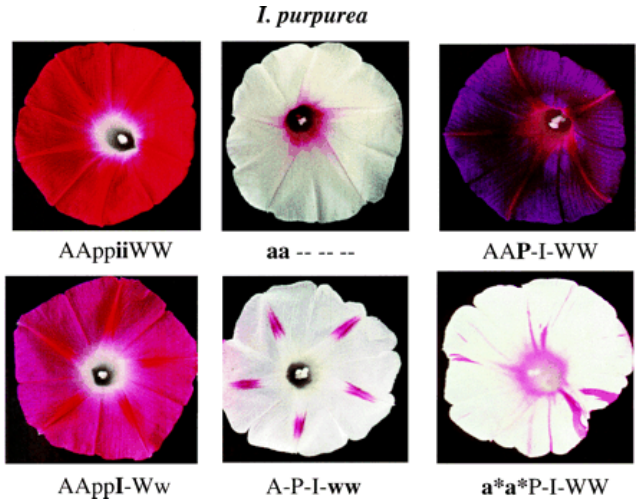
Cours #1



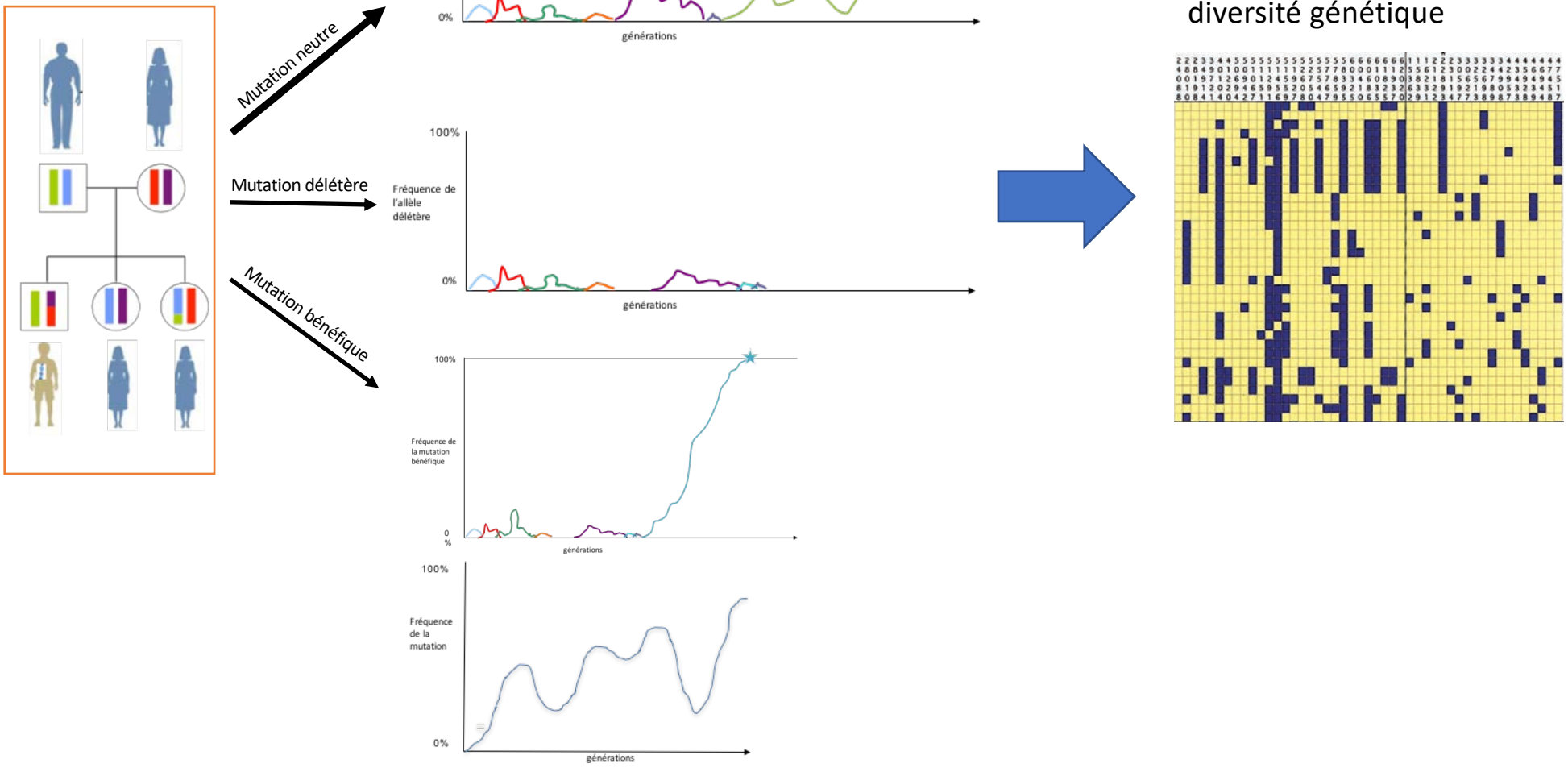
Shell color polymorphism in *Liguus fascitus*. (From David Hillis, *Journal of Heredity*, July – August 1991.)

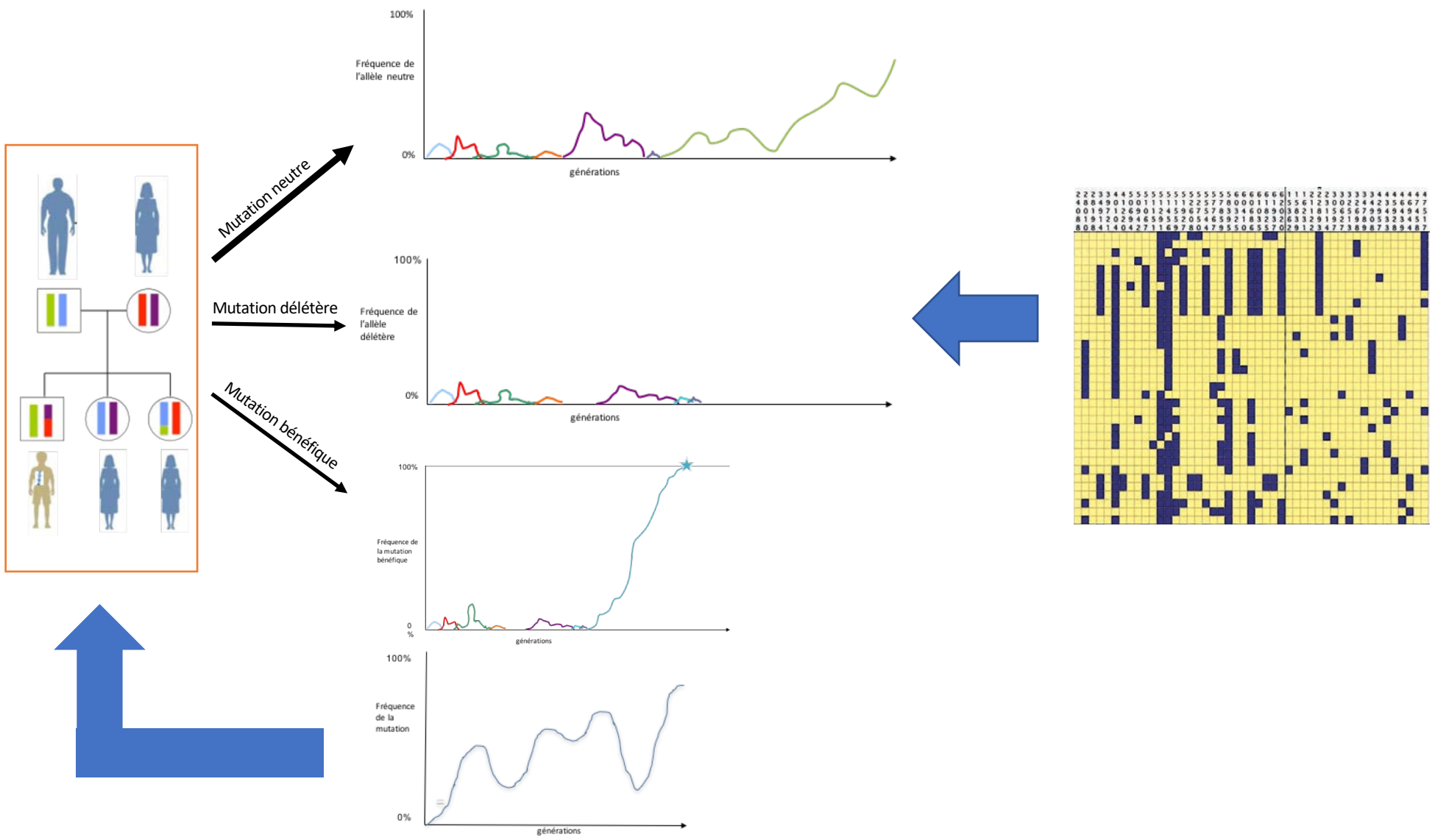
http://www.sbs.utexas.edu/levin/bio213/popgen/popgen.html

https://www.rdmag.com/news/2017/02/understanding-genetics-human-height



http://www.pnas.org/content/97/13/7016


Mutation neutre
Mutation délétère
Mutation bénéfique
100%
Fréquence de l'allèle neutre
0%
générations
100%
Fréquence de l'allèle délétère
0%
générations
100%
Fréquence de la mutation bénéfique
0 %
générations
100%
Fréquence de la mutation
0%
générations
diversité génétique


Mutation neutre
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100%
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0%
générations
100%
Fréquence de la mutation bénéfique
0 %
générations
100%
Fréquence de la mutation
0%
générations

9 novembre 2018
Cours: « Genèse des mutations germinales chez l'Homme »
Séminaire de Michel Georges (Liège): « Le processus de mutagenèse germinale revisité chez le bovin»

16 novembre 2018
Cours: « Evolution des mutations germinales chez les primates et datation de la spéciation humaine »
Séminaire de Michel Brunet (Collège de France, émérite) ; « « Paléontologie et phylogénie moléculaire... Réflexions autour de Toumai et la dichotomie Chimpanzés - Famille humaine »

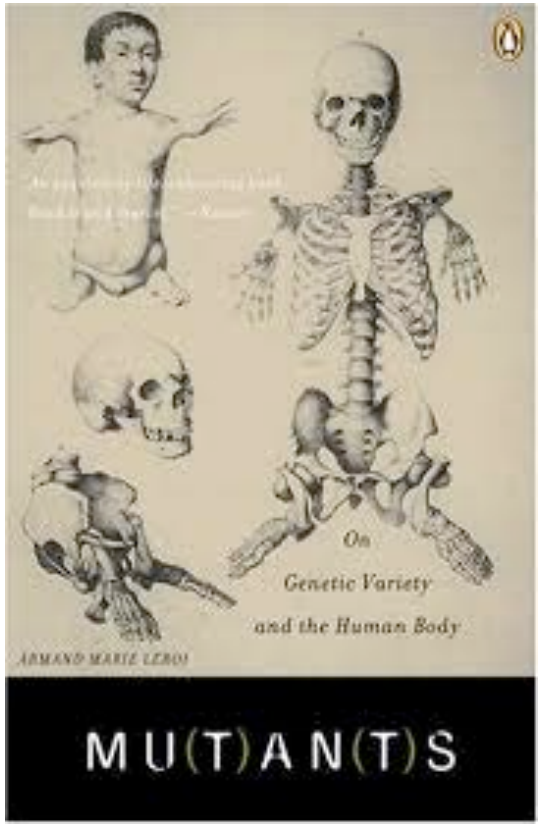
23 novembre 2018
Cours: « Mutation, sélection naturelle et fréquences des allèles pathologiques chez l'Homme »
Séminaire en anglais de Guy Sella (Columbia/Pasteur): «A population genetic interpretation of complex trait architecture in humans»

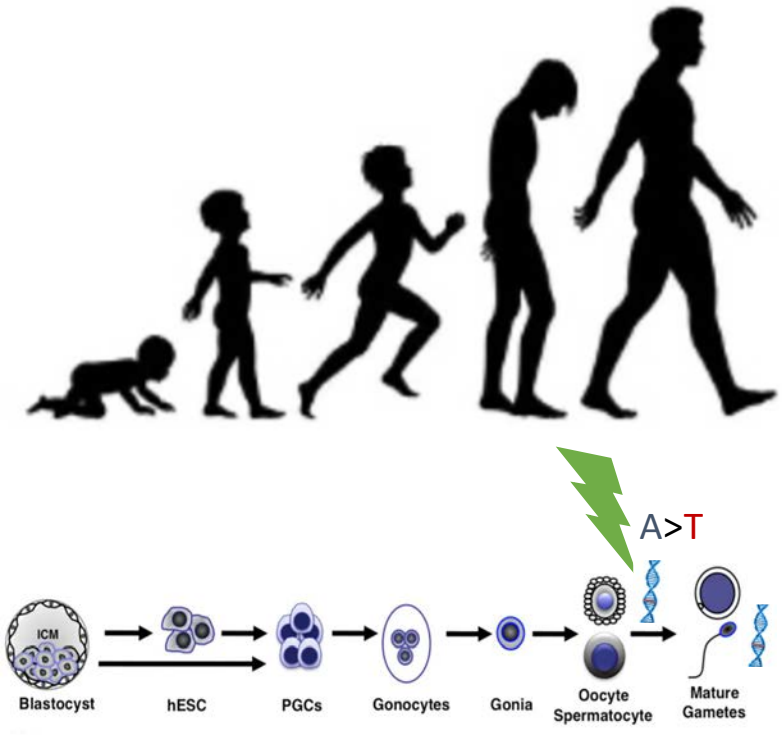
20 mars 2019
Cours: « Causes de la variation du taux de recombinaison chez les vertébrés »
Séminaire de Bernard de Massy (Montpellier): « Le contrôle de la distribution de la recombinaison par Prdm9, une intrigante stratégie moléculaire»

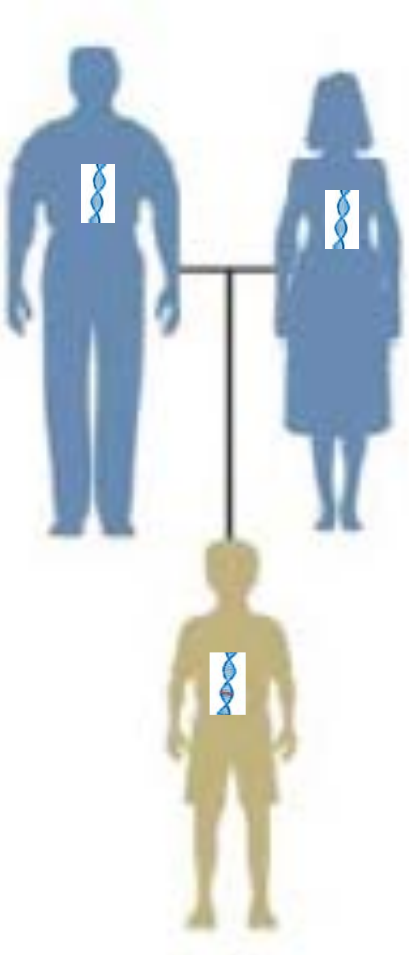
27 mars 2019
Cours: « Conséquences de la variation du taux de recombinaison chez les vertébrés »
Séminaire de Laurent Duret (Lyon) : « Conversion génique biaisée: la face cachée de la recombinaison »

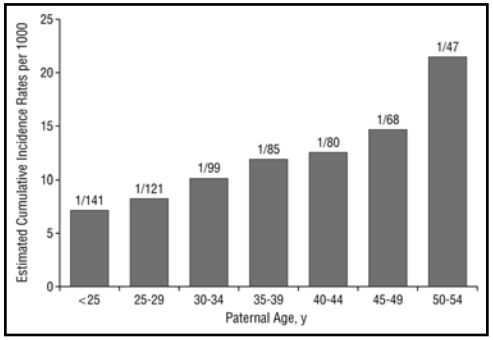
3 avril 2019
Cours: « À la recherche de la base moléculaire des adaptations »
Séminaire en anglais de David Reich (Harvard): “Learning about human adaptation from ancient DNA”

10 avril 2019
Cours: « Empreintes de l'adaptation dans le génome humain »
Séminaire de Laure Ségurel (Musée de l’Homme): « Adaptation à la consommation de lait chez l'Homme: un cas d'école pourtant encore bien mystérieux »


On
Genetic Variety
and the Human Body
ARMAND MARIE LEROI
MU(T)AN(T)S

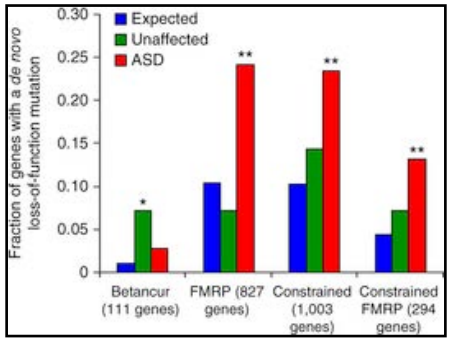

A>T
ICM
Blastocyst
hESC
PGCs
Gonocytes
Gonia
Oocyte
Spermatocyte
Mature
Gametes





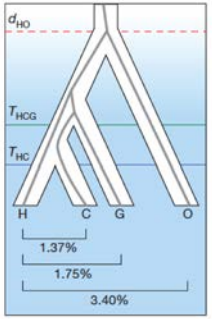
Malaspina et al. 2001 Arch Gen Psychiatry

Comprendre l'effet de l'âge des parents sur le risque de certaines maladies héréditaires



Samocha et al. 2014 Nat Gen

Cartographier les mutations qui conduisent à des maladies graves



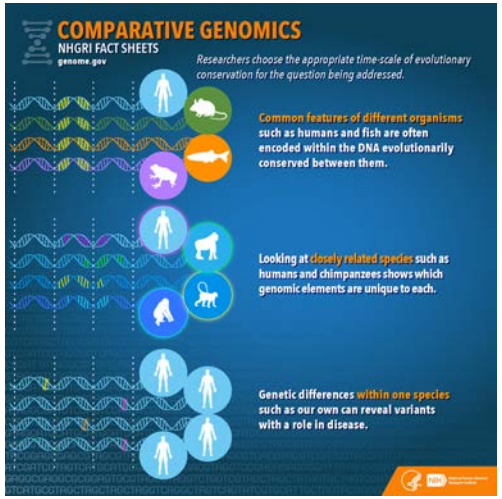
Scally et al. 2012 Nature

Dater les événements dans l'évolution humaine

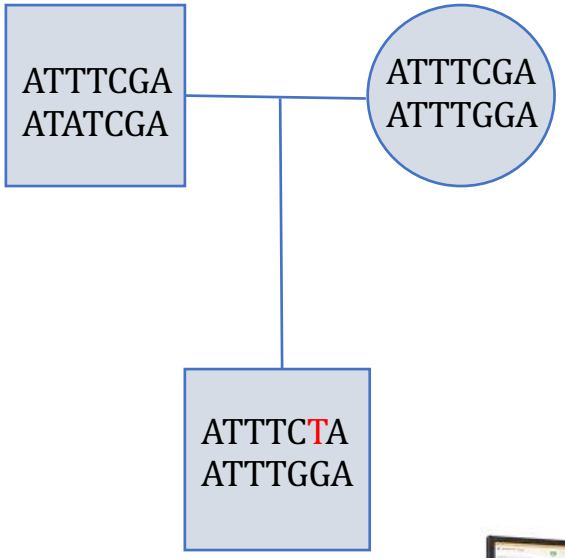
VOLUME XXXI. OCTOBER, 1935 No. 3

THE RATE OF SPONTANEOUS MUTATION OF A HUMAN GENE.

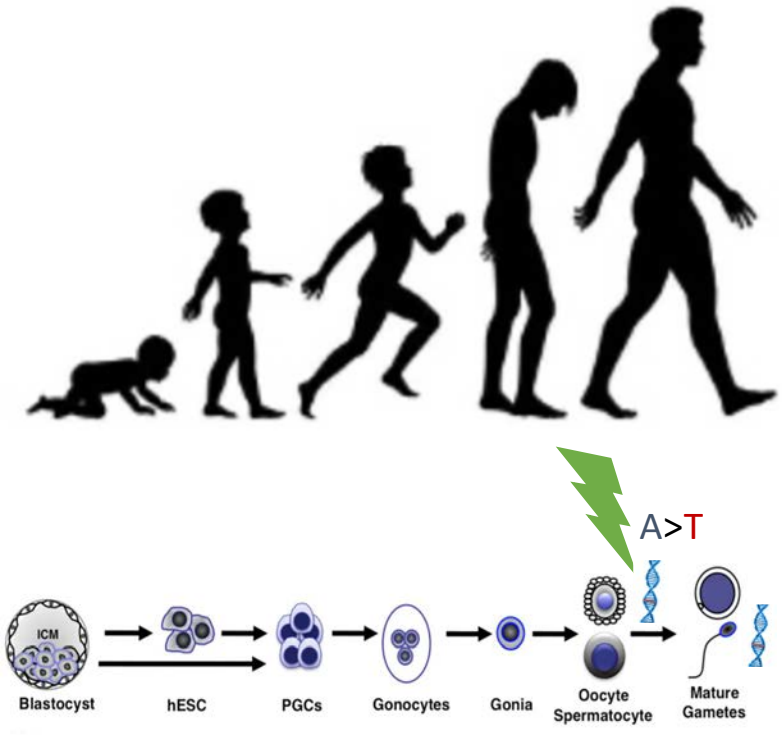
By J. B. S. HALDANE.



https://www.genome.gov/images/content/comparative_genomics_factsheet.jpg



Roach et al. 2010 Science


A>T
ICM
Blastocyst
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PGCs
Gonocytes
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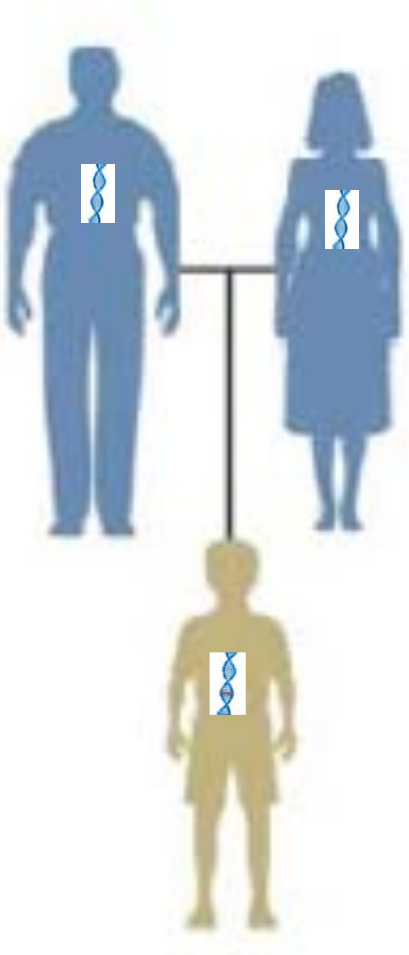
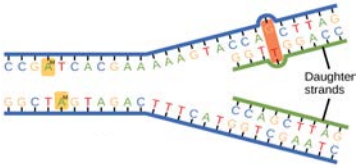
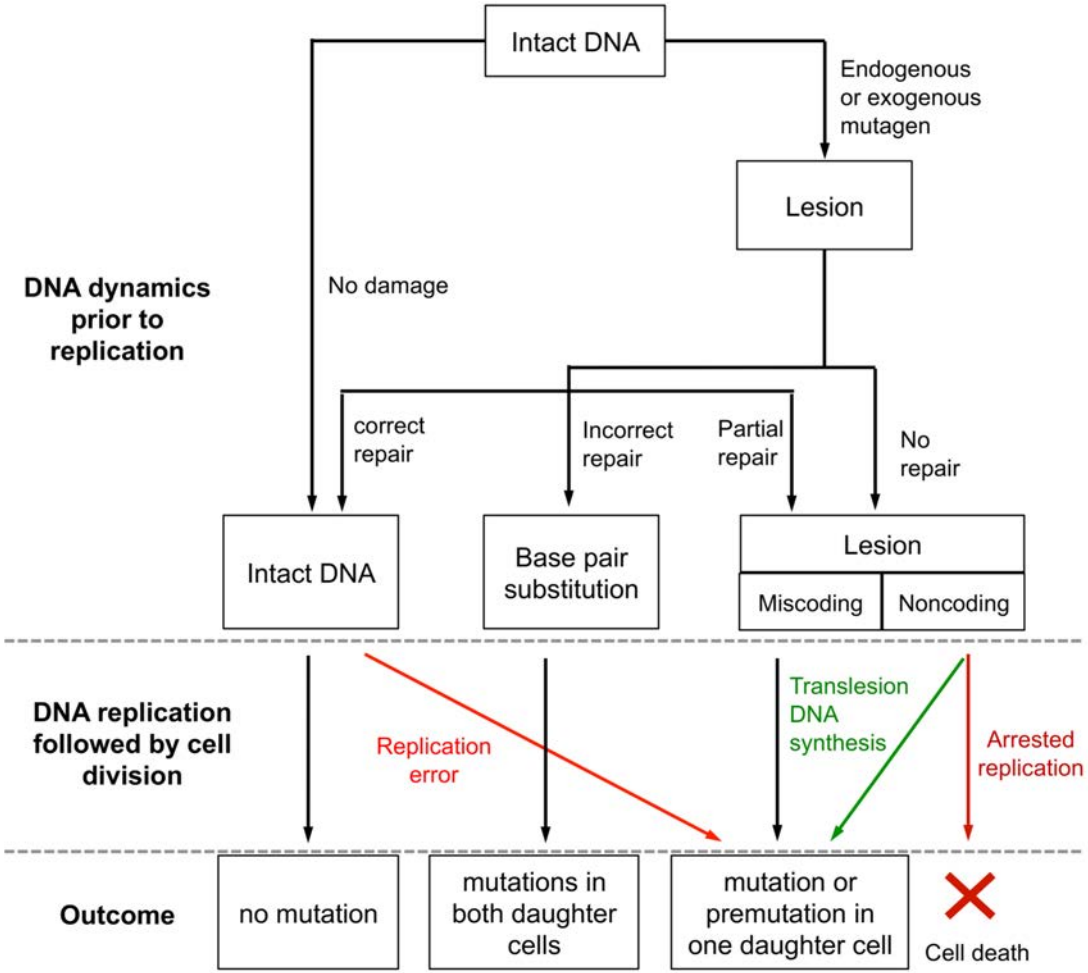
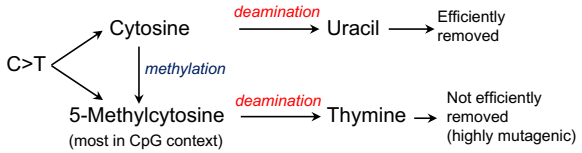
Mature
Gametes





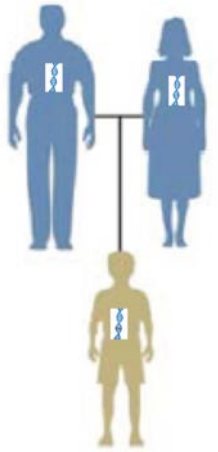


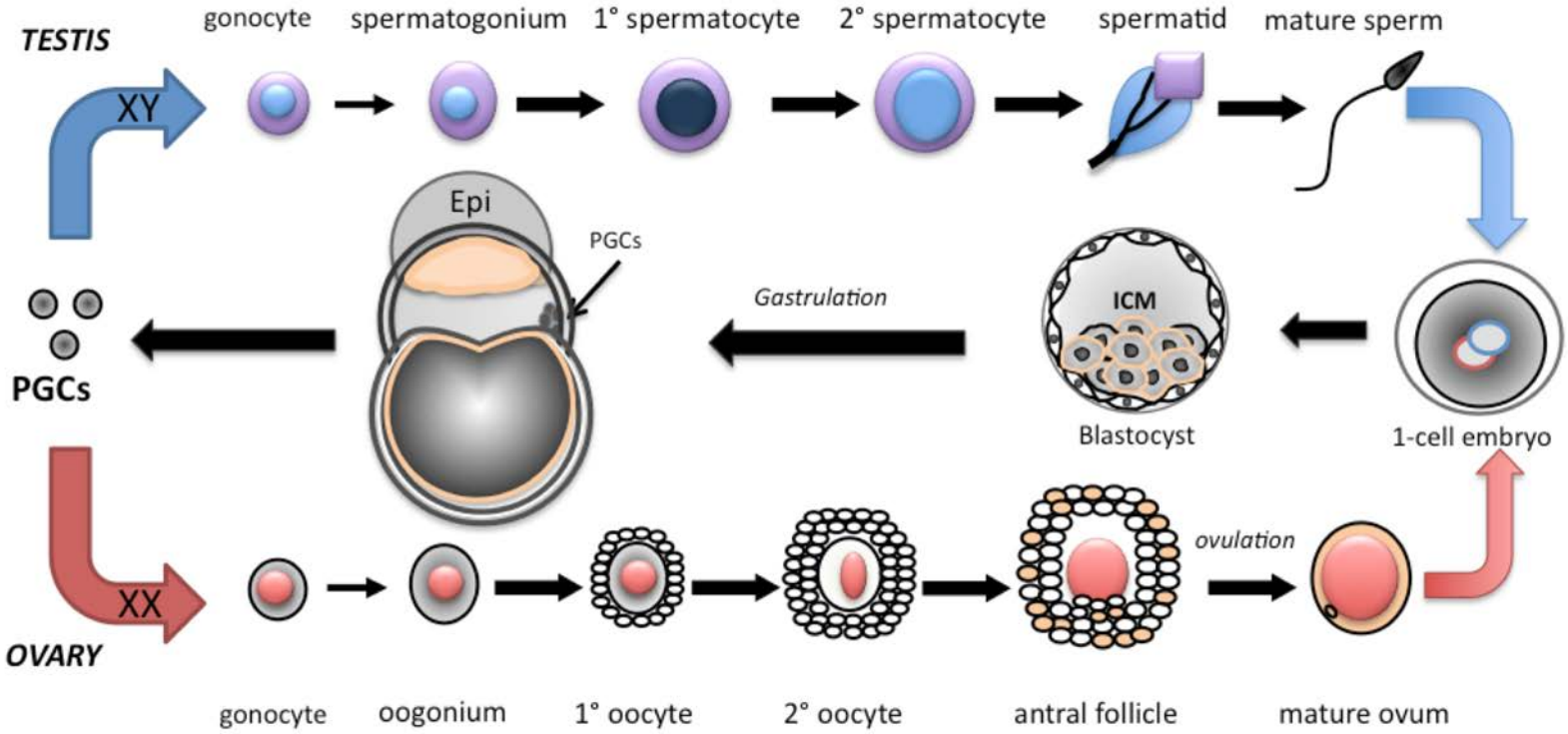
5' methylated cytosine



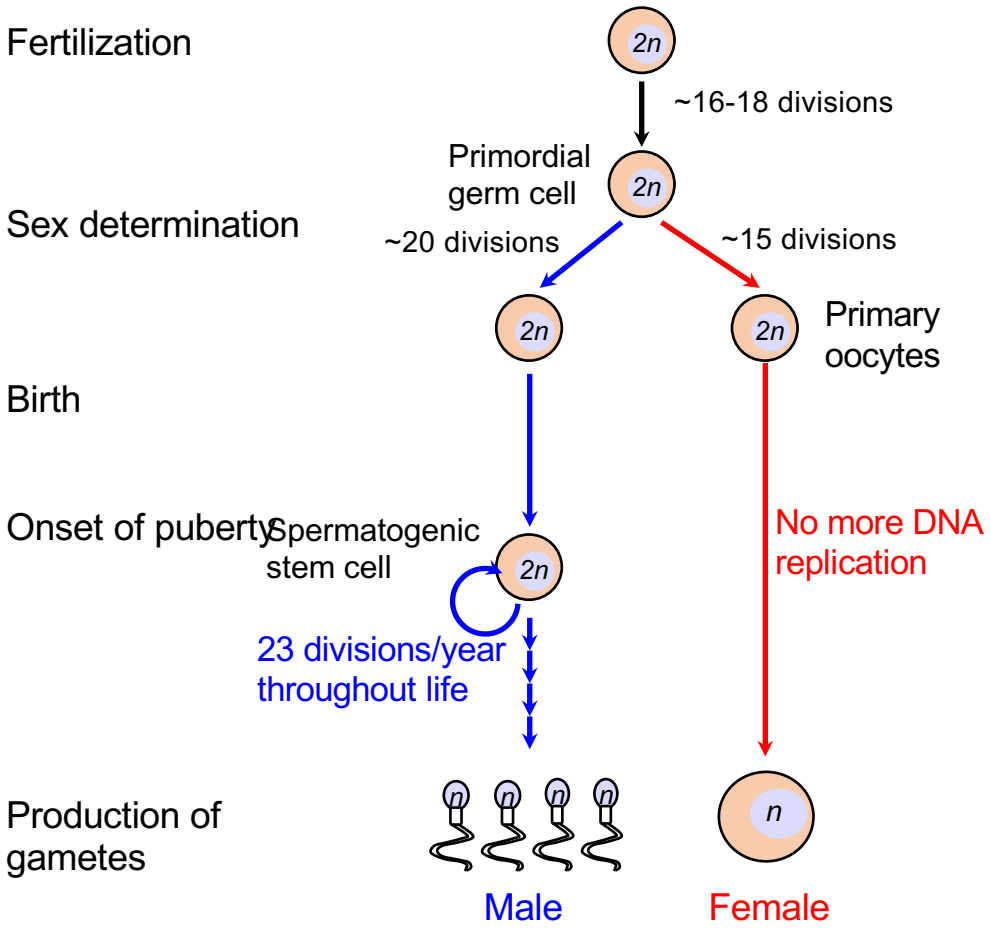
From Gao et al. 2016 PLoS Biology

Spermatogenesis ongoing after onset of puberty

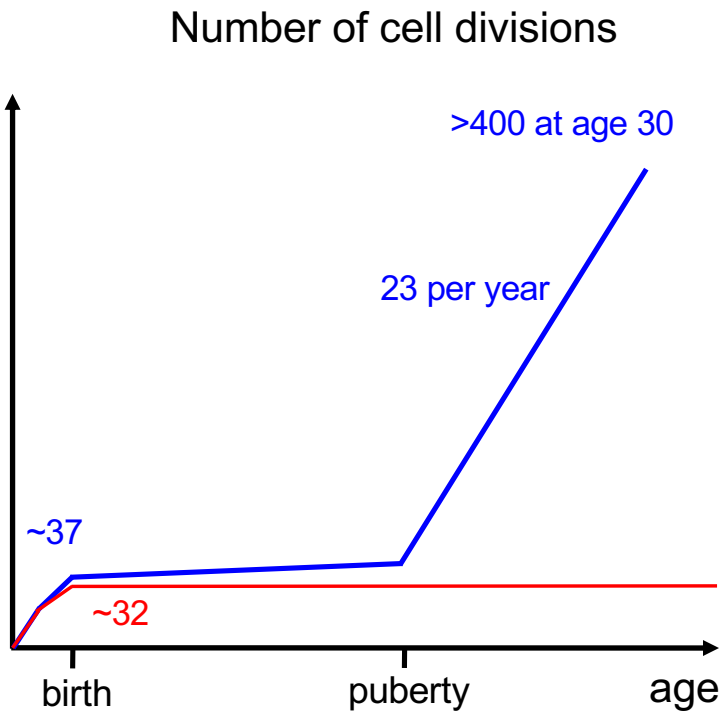




Oocytogenesis completed by birth

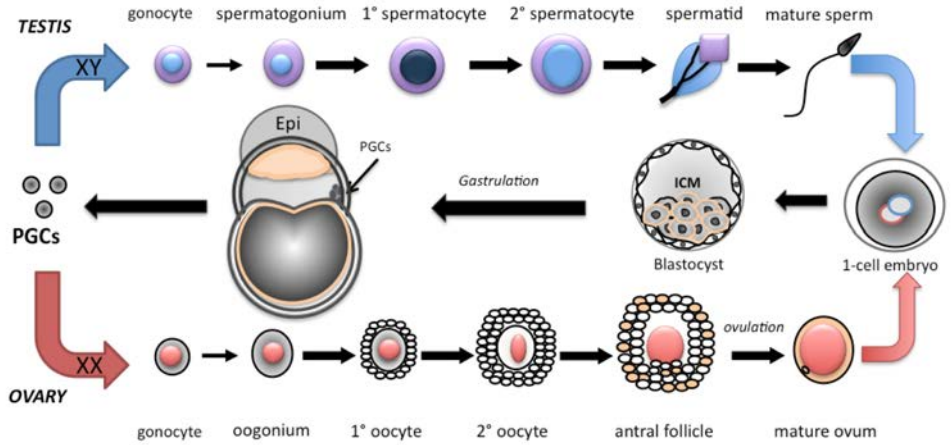


Based on Drost and Lee, (1995)

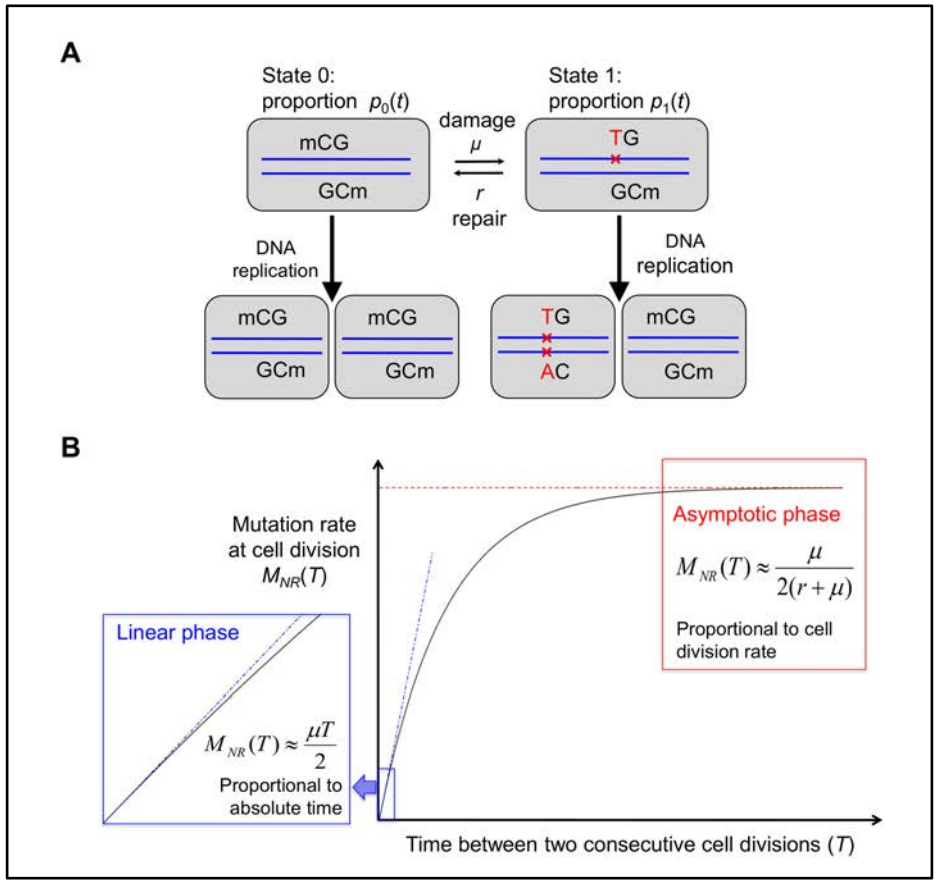


Slide courtesy of Ziyue Gao (Stanford)

Mutations not due to replication errors?

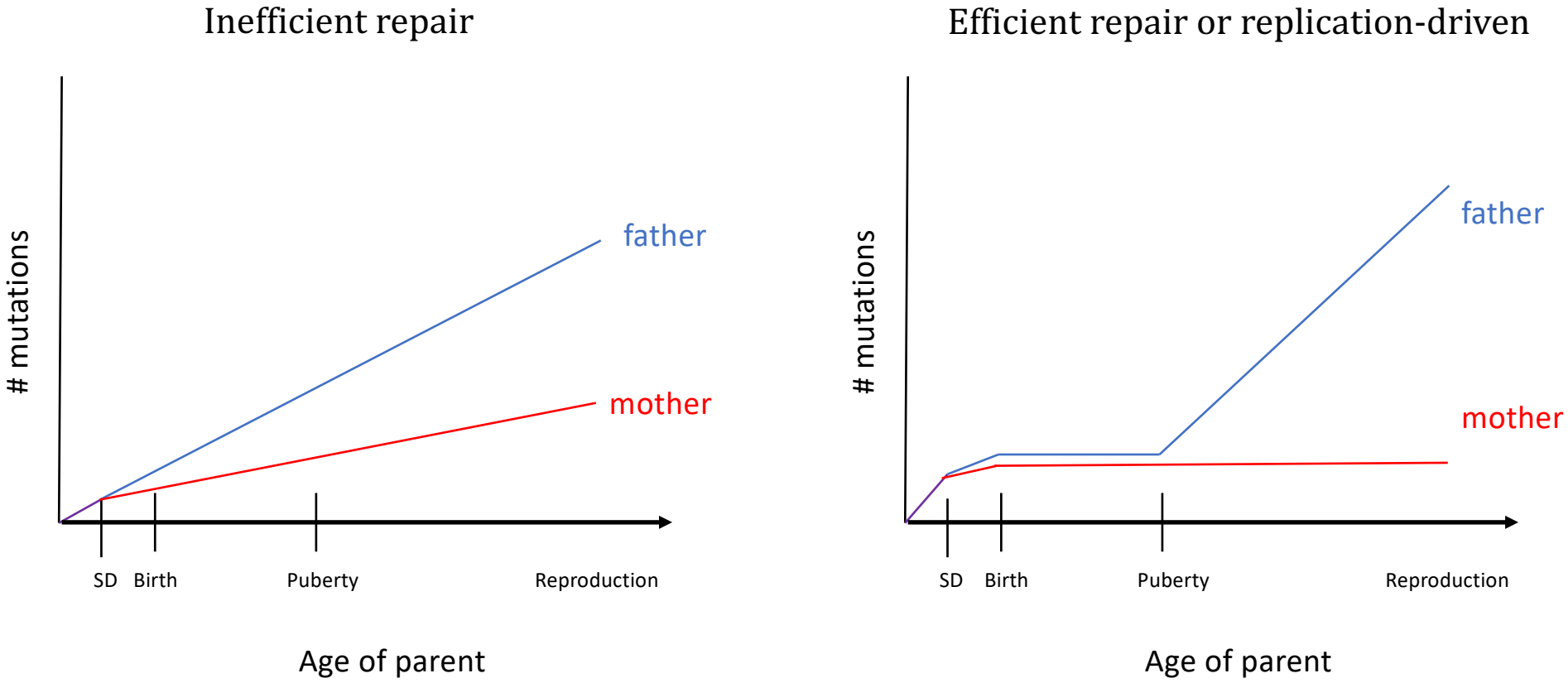


Ziyue Gao



Gao et al. 2016 PLoS Biology

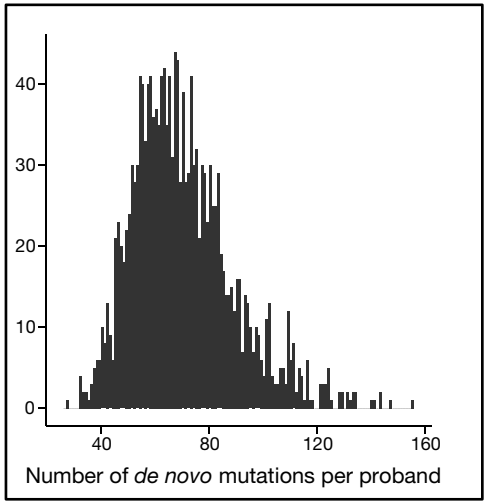
Dependencies on age & sex

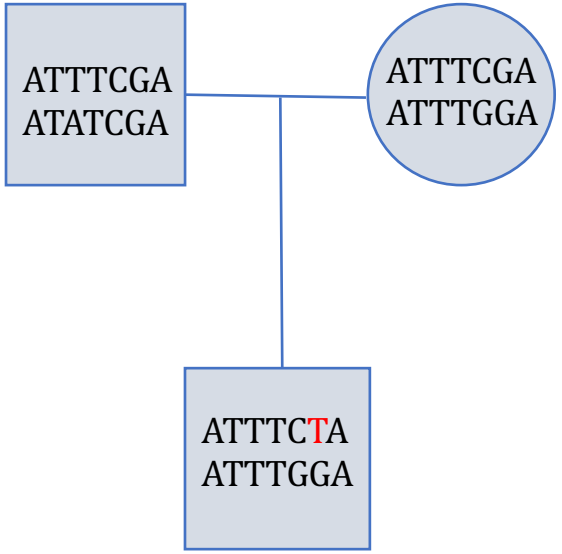


Gao et al. 2016 PLoS Biology

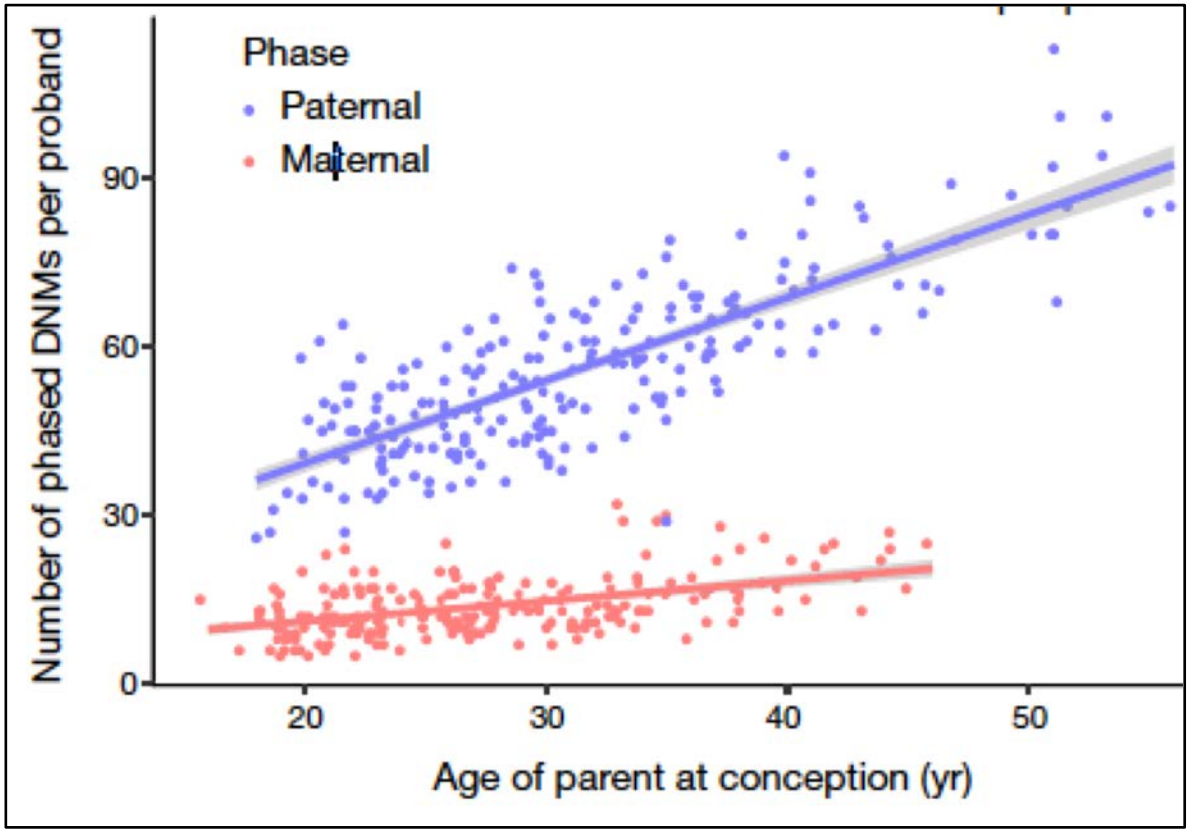
Parental influence on human germline *de novo* mutations in 1,548 trios from Iceland 2017

Hákon Jónsson[1], Patrick Sulem[1], Birte Kehr[1], Snaedis Kristmundsdottir[1], Florian Zink[1], Eirikur Hjartarson[1], Marteinn T. Hardarson[1], Kristjan E. Hjorleifsson[1], Hannes P. Eggertsson[1], Sigurjon Axel Gudjonsson[1], Lucas D. Ward[1], Gudny A. Arnadottir[1], Einar A. Helgason[1], Hannes Helgason[1], Arnaldur Gylfason[1], Adalbjorg Jonasdottir[1], Aslaug Jonasdottir[1], Thorunn Rafnar[1], Mike Frigge[1], Simon N. Stacey[1], Olafur Th. Magnusson[1], Unnur Thorsteinsdottir[1,2], Gisli Masson[1], Augustine Kong[1,3], Bjarni V. Halldorsson[1,4], Agnar Helgason[1,5], Daniel F. Gudbjartsson[1,3] & Kari Stefansson[1,2]





Roach et al. 2010 Science



Borrowed from Jónsson et al. 2017 Nature

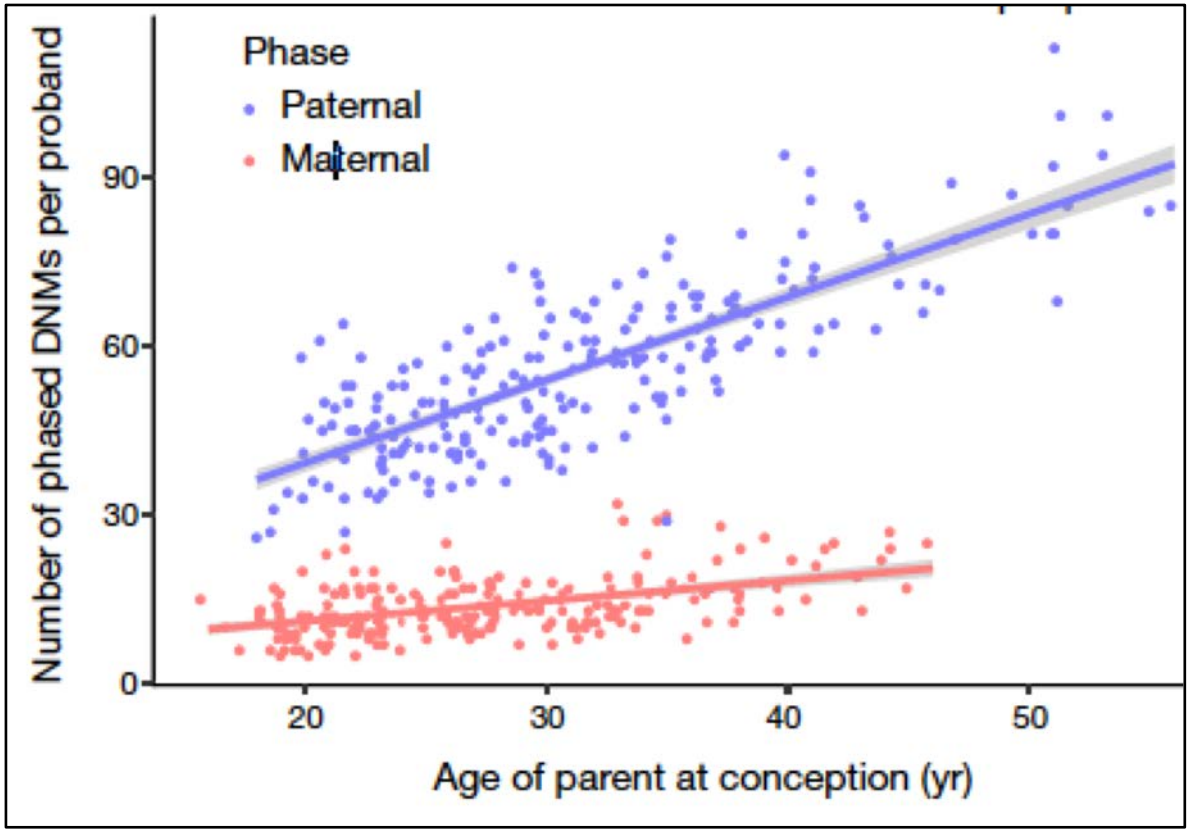
Linear increase with paternal age

~¾ of mutations inherited from father.

~1.5 mutations per year

Must be spontaneous damage that is inefficiently repaired

~0.4 mutations per year

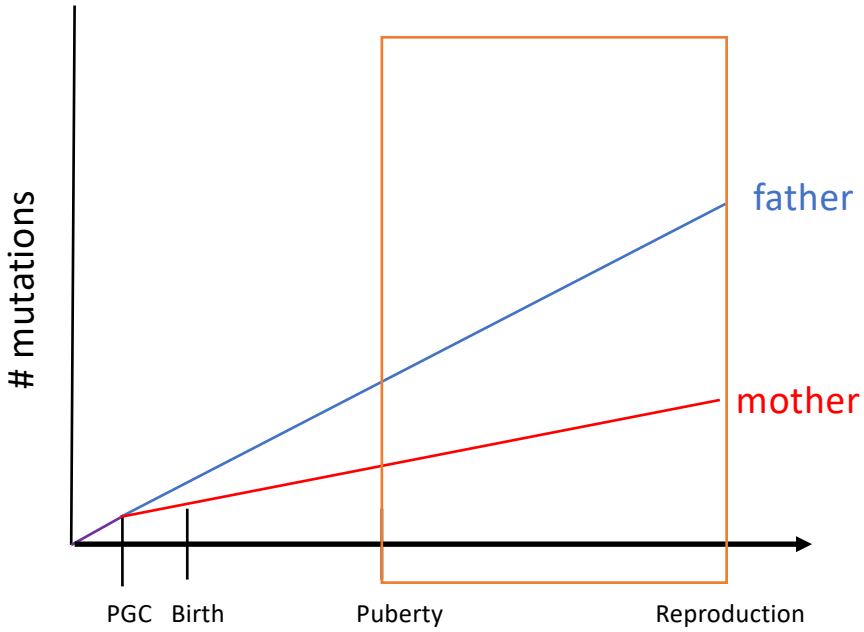


"One plausible explanation for the drastic age-related sex differences in transmitted DNMs is the relative lack of mitosis in ageing oocytes compared with spermatogonia, which may enrich for damage-induced DNMs."

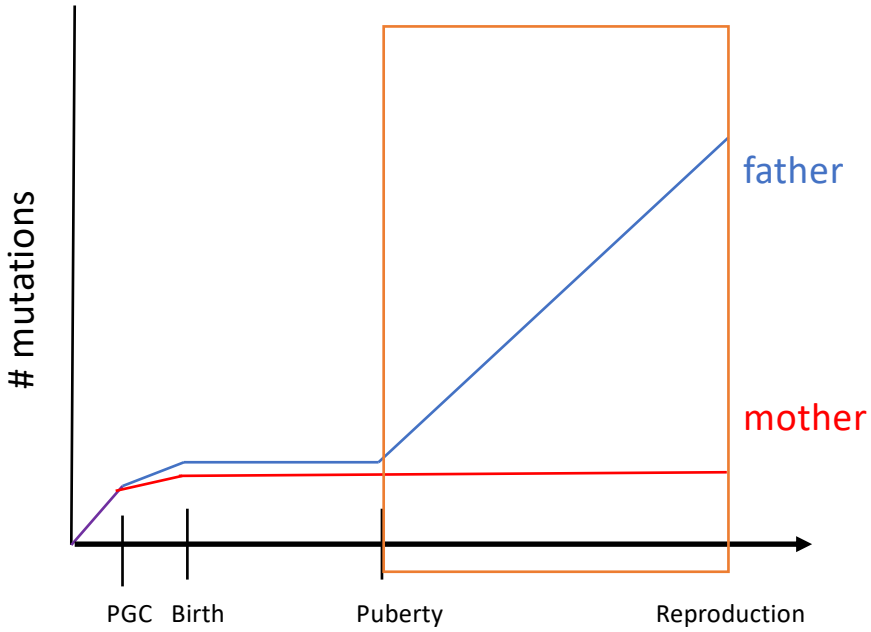
Jónsson et al. 2017 Nature

Ratio father: mother
= « alpha »

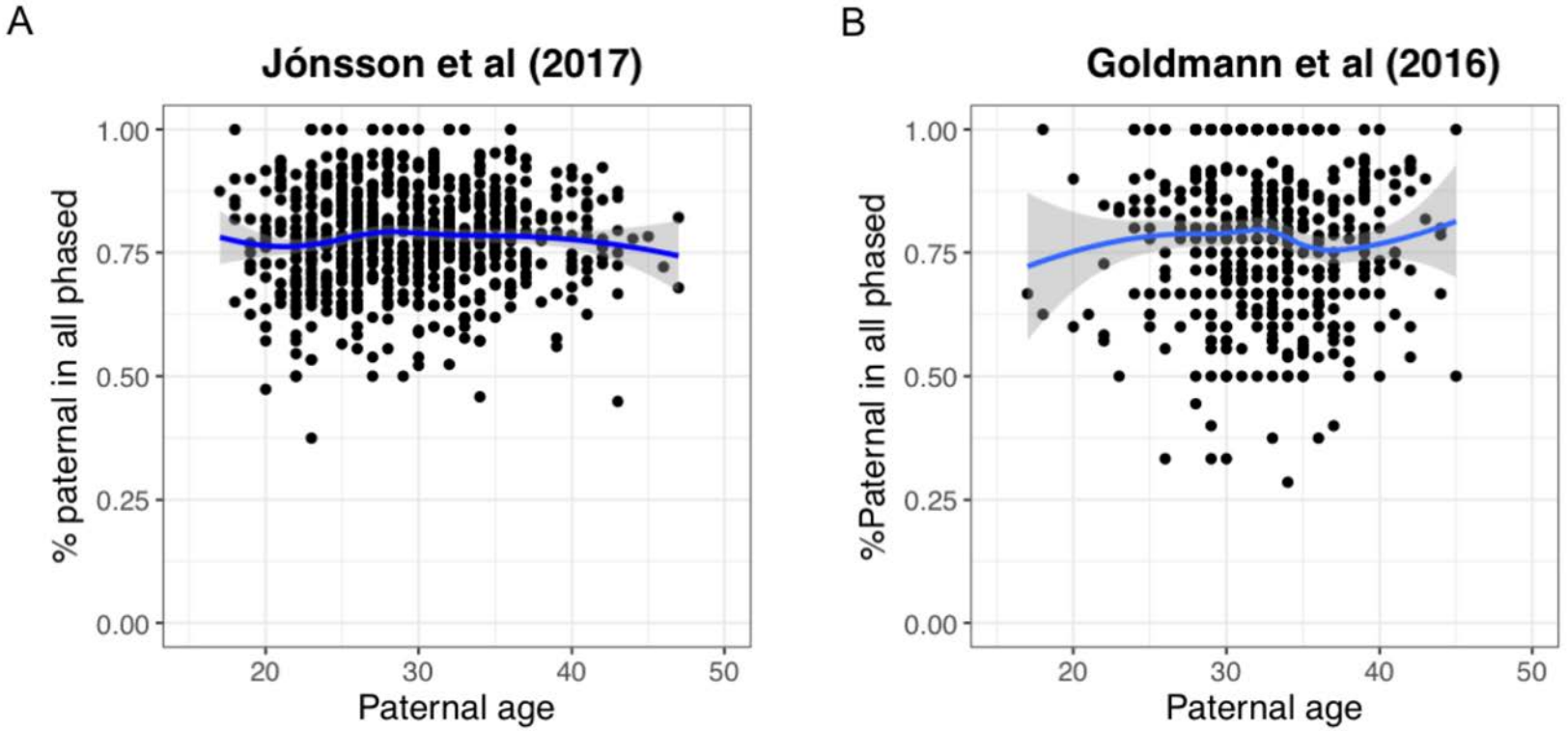
Inefficient repair



Efficient repair or due to replication

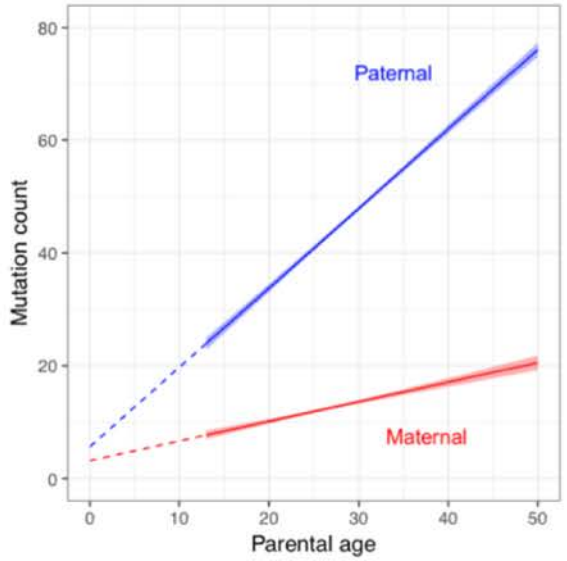


Gao et al. 2016 PLoS Biology



Gao et al., 2018 BioRxiv

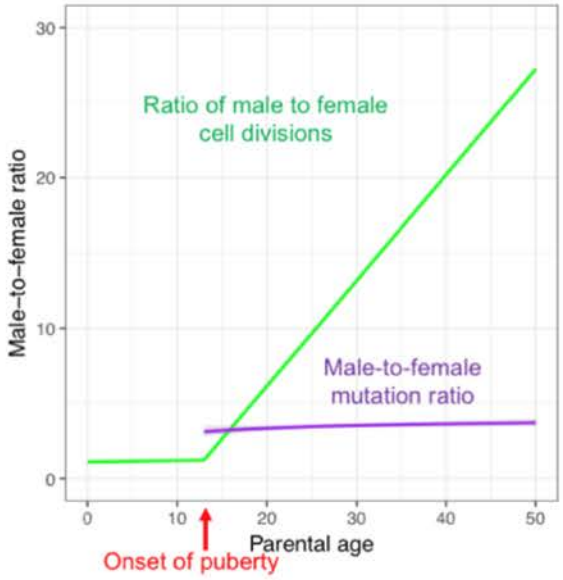
A.



1) le nombre de divisions de cellules germinales mâles de la détermination du sexe à la puberté a été considérablement sous-estimé
2) après la détermination du sexe, les divisions des cellules germinales sont beaucoup plus mutagènes chez les hommes que chez les femmes;

3) Les dommages contribuent de manière substantielle aux mutations de la lignée germinale mâle pendant la puberté.

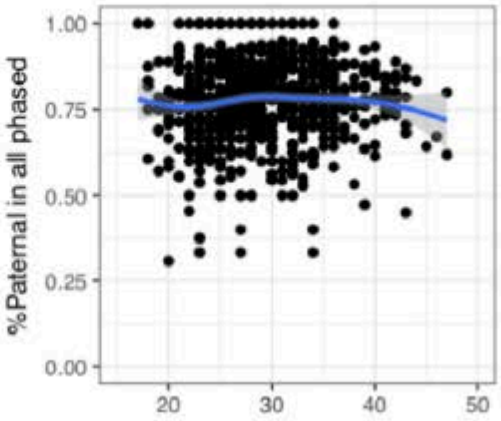
C.



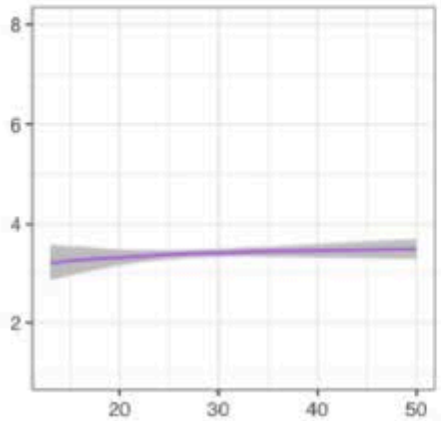
Gao et al., 2018 BioRxiv

All point mutations excluding C>G and CpG>TpG

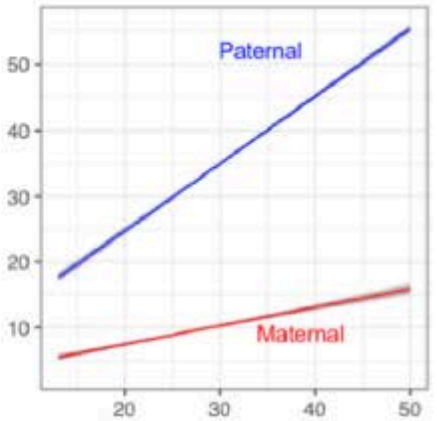
Fraction of paternal mutations



Ratio of male to female mutations



Predicted parental age effects



Direct estimates of alpha, ratio of male to female mutations in mammals

~3

Lindsay et al. BioRxiv

2.6

Lindsay et al. BioRxiv

2.6

Harland et al. BioRxiv (Michel Georges)

2.1

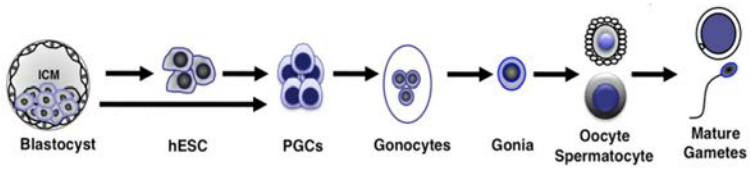
Thomas et al. 2018 Current Biology

Recap

The number of mutations inherited by a child increases with paternal and maternal age.

In a typical sample of humans, ¾ of mutations are of paternal origin. This number shows little dependence on parental ages.

Some fraction of mutations and possibly most mutations are non-replicative in origin and poorly repaired.


ICM
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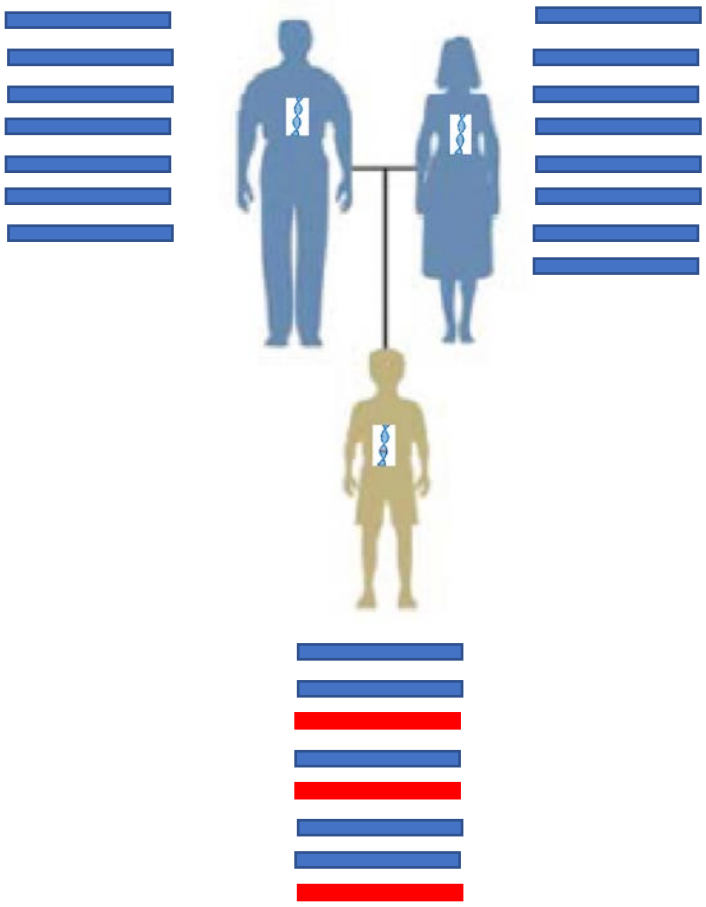
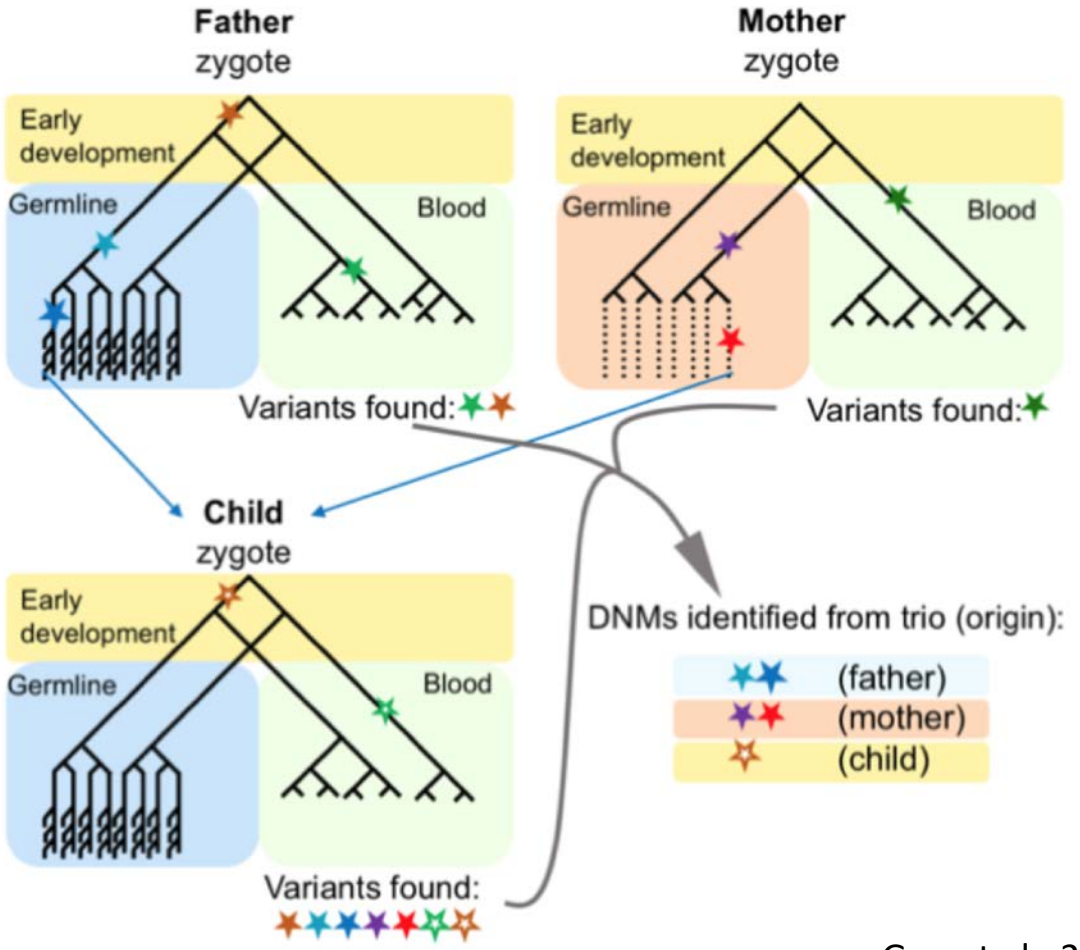
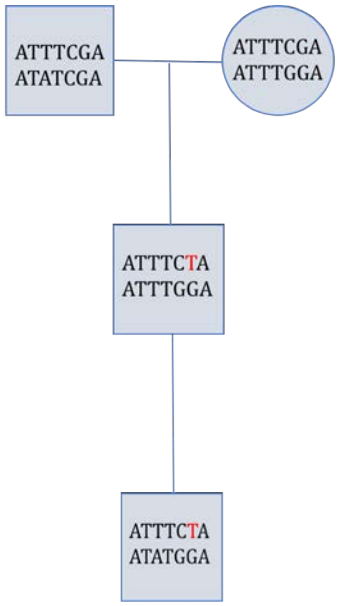
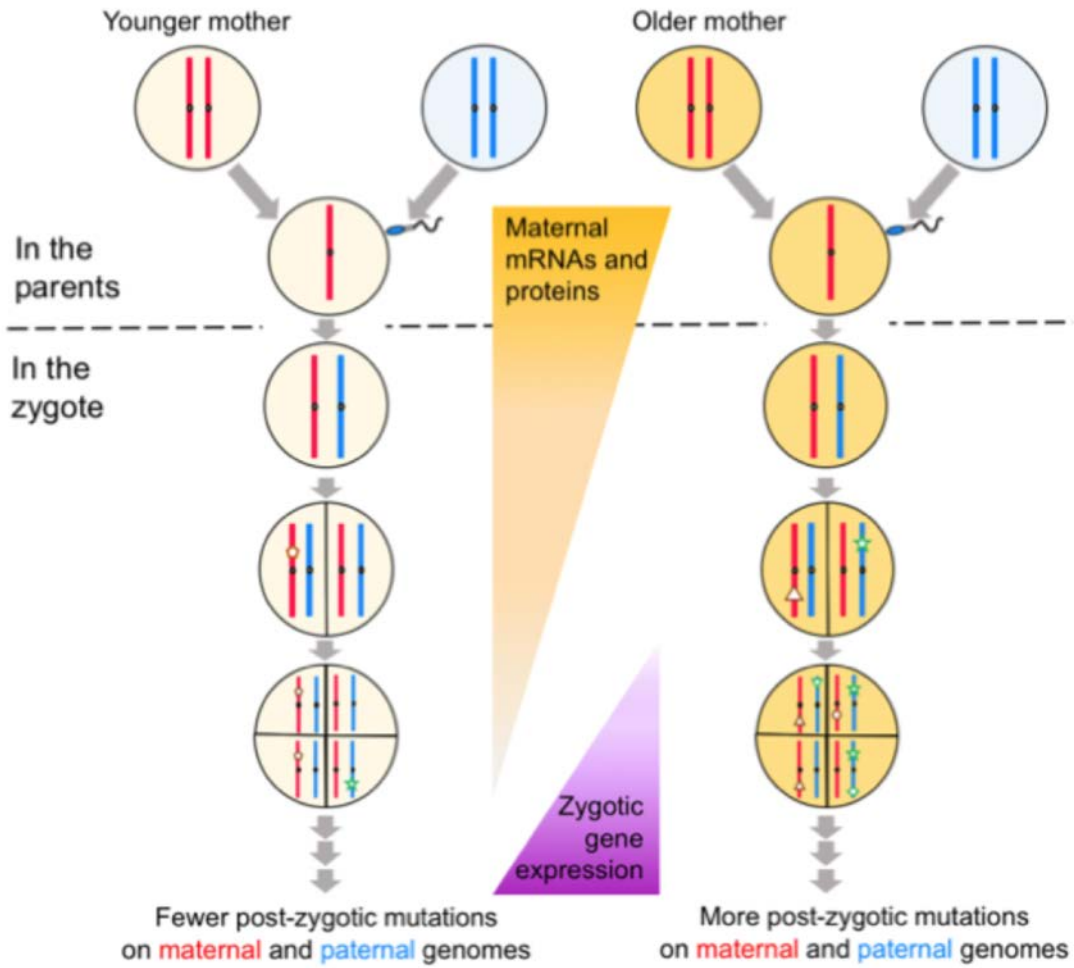




Gao et al., 2018 BioRxiv



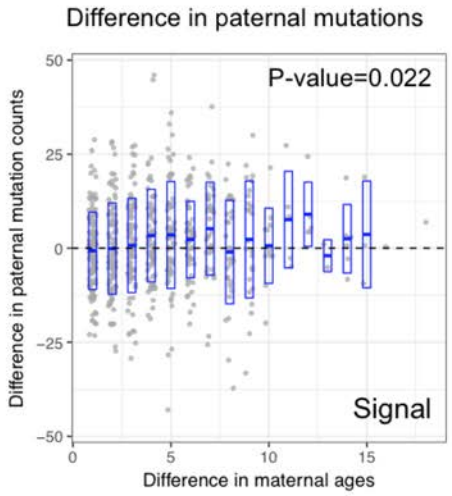


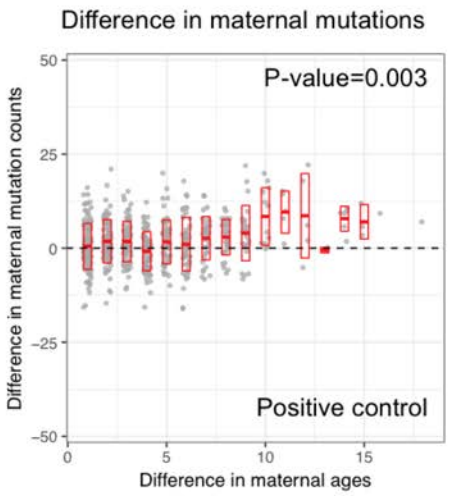
Gao et al., 2018 BioRxiv

génome paternel

génome maternel

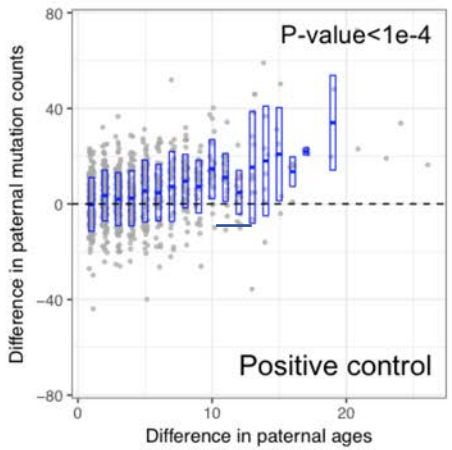
Same paternal age, different maternal ages

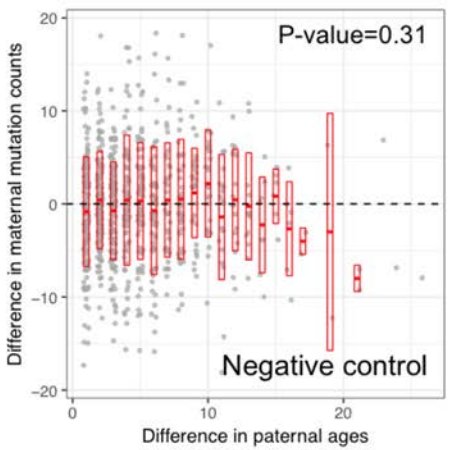




effet de la mère

Same maternal age, different paternal ages





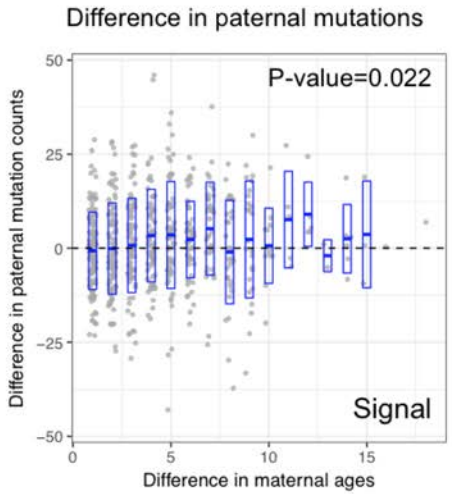
effet du père

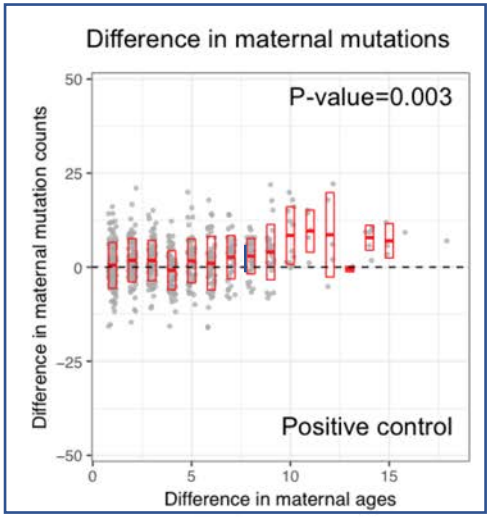
Gao et al., 2018 BioRxiv

génome paternel

génome maternel

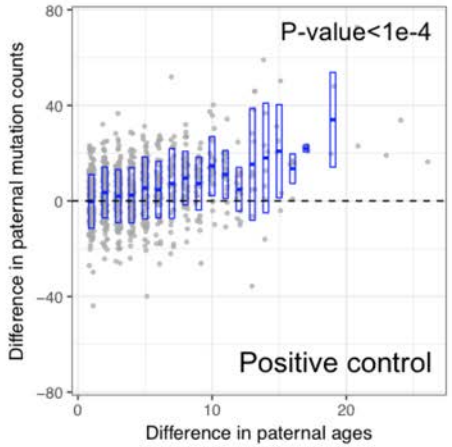
Same paternal age, different maternal ages

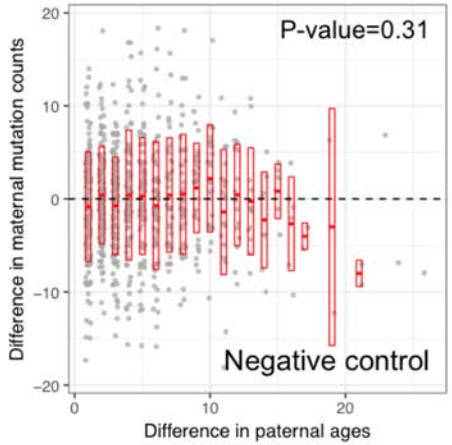




effet de la mère

Same maternal age, different paternal ages





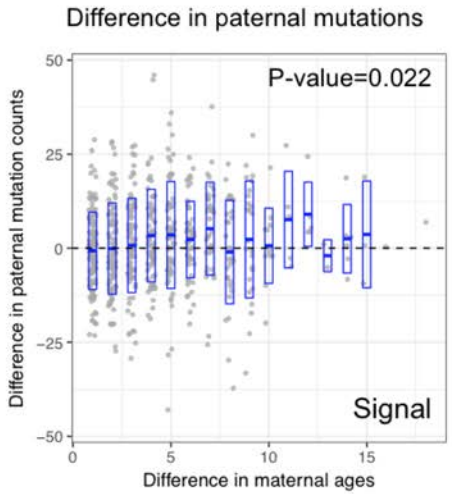
effet du père

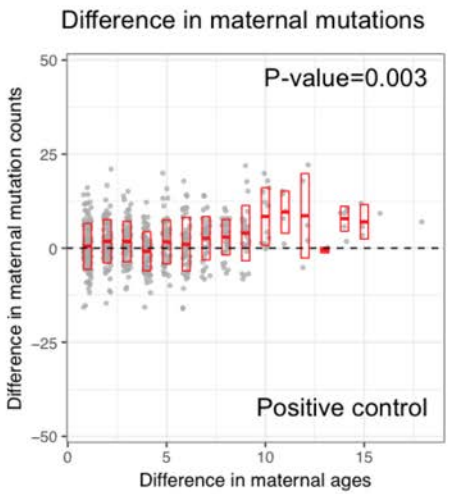
Gao et al., 2018 BioRxiv

génome paternel

génome maternel

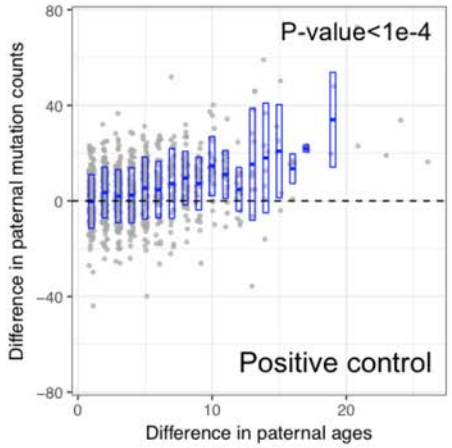
Same paternal age, different maternal ages

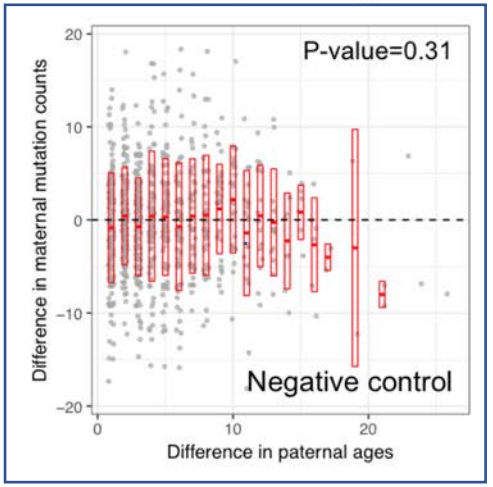




effet de la mère

Same maternal age, different paternal ages





effet du père

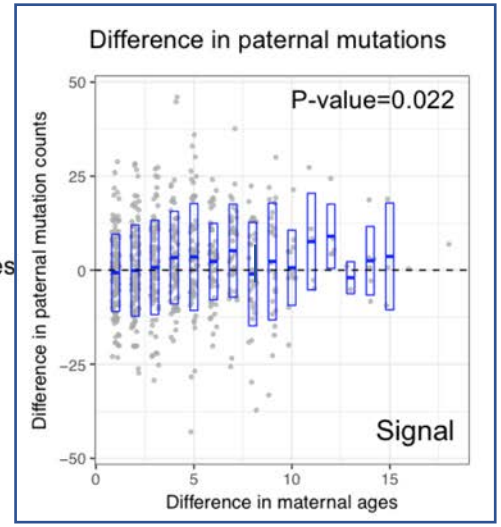
Gao et al., 2018 BioRxiv

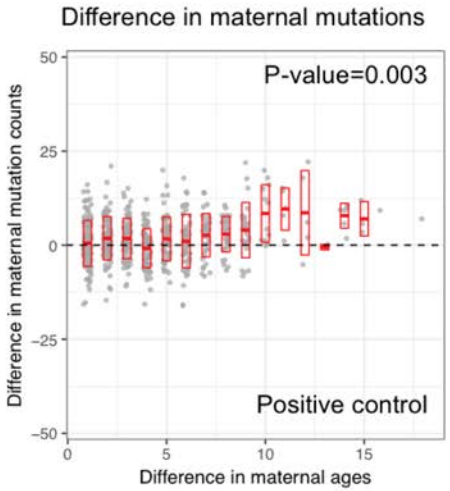
Stronger signal for C>A mutations

génome paternel

génome maternel

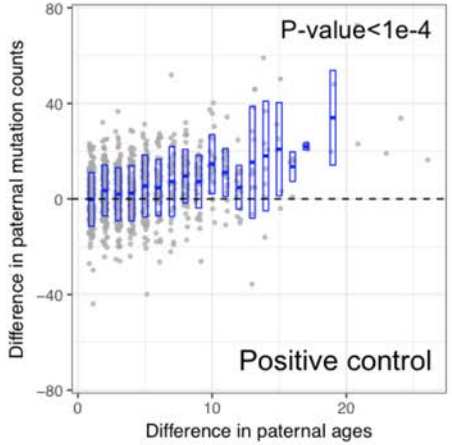
Same paternal age, different maternal ages

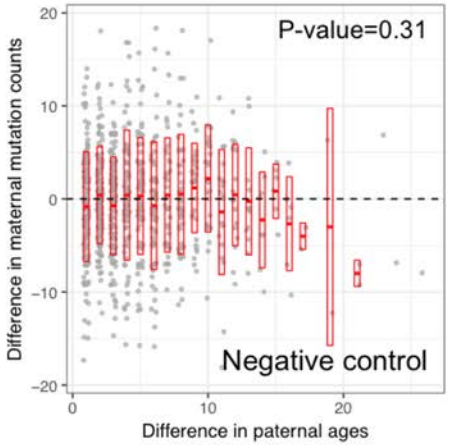




effet de la mère

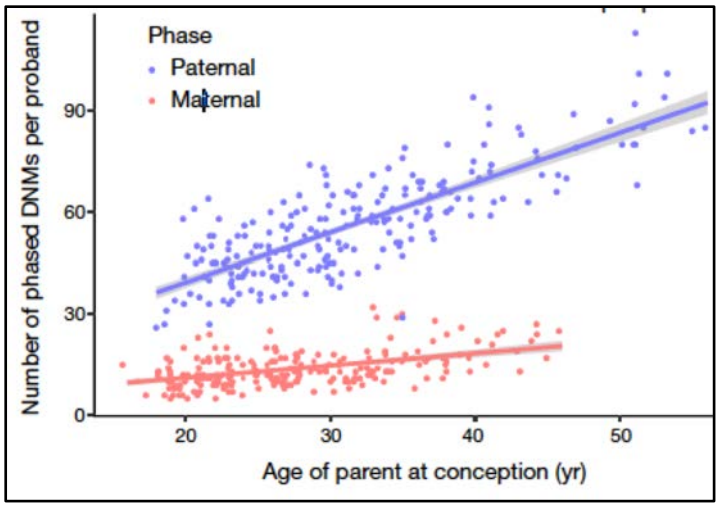
Same maternal age, different paternal ages



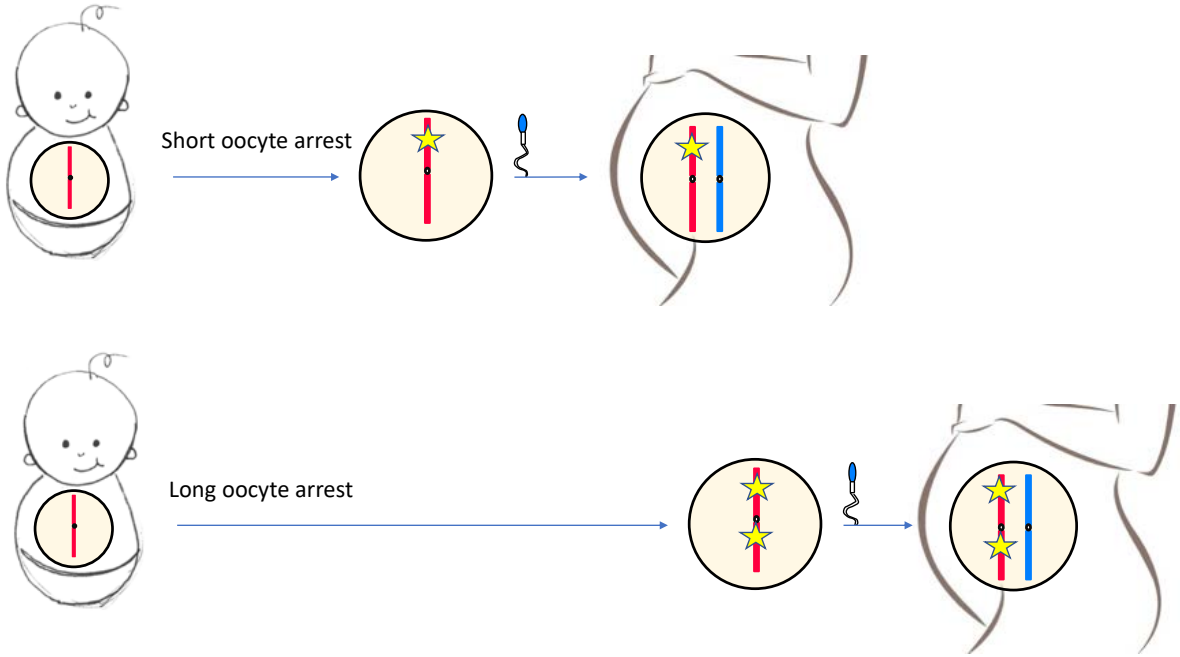


effet du père

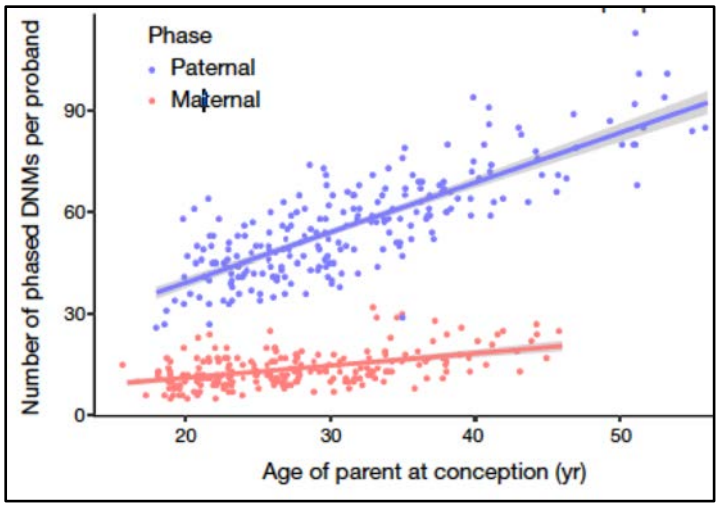
Gao et al., 2018 BioRxiv



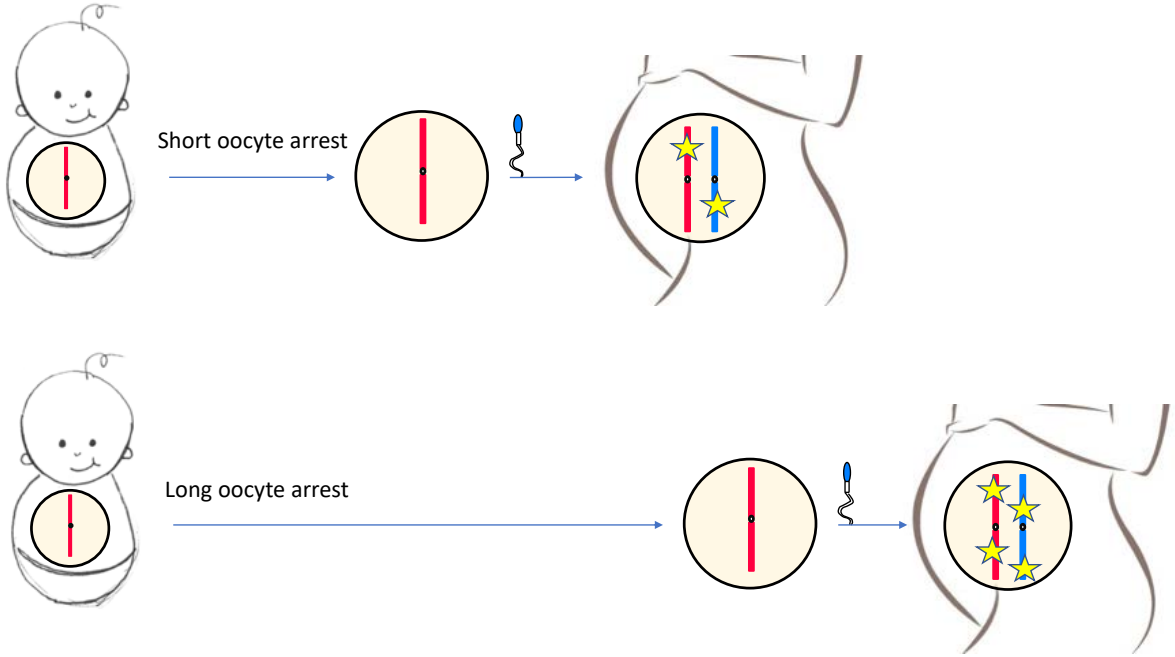
Borrowed from Jónsson et al. 2017 Nature



Slide courtesy of Guy Amster



Borrowed from Jónsson et al. 2017 Nature



Slide courtesy of Guy Amster

Summary

The number of mutations inherited by a child increases with paternal and maternal age.

In a typical sample of humans, ¾ of mutations are of paternal origin. This number shows little dependence on parental ages.

Some fraction of mutations and possibly most mutations are non-replicative in origin and poorly repaired.

Mutations arise at all stages of development, from zygote to sperm/egg. What fraction arise at each stage is still unknown in any mammals, and likely differs among species.