coreBio II - genetics: Wed 11 April 2018

sex linked + anticipation+ somatic

We will start first draft video presentations next week on Wednesday / Friday

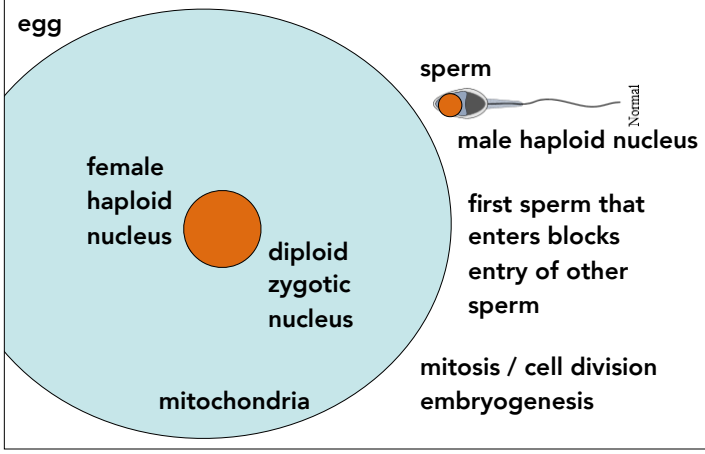
SEND ME BY EMAIL:

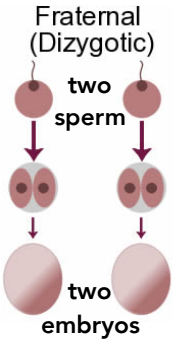
1). your title
2). which day you would prefer to present

At the start of class NEXT Wednesday - hand in question cards for course up to this point (things you are not sure you can answer)

questions about exam questions / answers? : answer key

Embryogenesis





Value of identical twins - very similar genomes (compared to fraternal twins or non-twin siblings

Non-Mendelian patterns of inheritance (part 2)

- sex-linked traits
- genetic anticipation
- somatic mutations and selection

Q: Under what conditions can an allele appear to act as both a Mendelian recessive and dominant

Sex-linked diseases

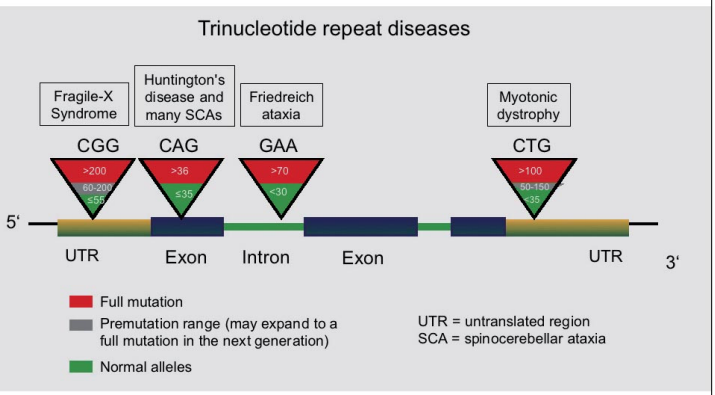
- **Typically recessive alleles in genes on the X chromosome**
- **Appear dominant in males - why?**
- **There fewer such disease associated alleles on the Y chromosome - why?**

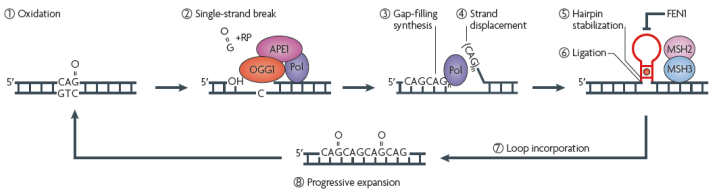
Sex-Linked Inheritance

who carries the disease allele?

Inheritance of Red-Green Blindness: an X-linked Recessive Trait

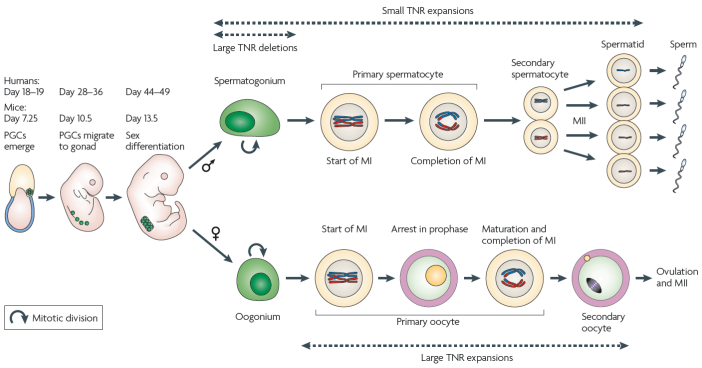
repeat diseases (genetic anticipation)- increasing severity





repeat diseases

- pre-mutation - below threshold - no phenotype
- intermediate - expansion
- pathogenic - severity linked to extent of expansion
- some (fragile X - repeats in non-coding region of FMR1 gene) due to get worse (longer) in maternal lineage
- mother's children more likely to display phenotype
- males do not transmit (contraction of repeat region)
- others (Huntington's disease - Htt gene) get worse paternal lineage; father's children more likely to display phenotype
- stable/contracts in maternal lineage.
- mechanisms uncertain



Chromosomal instability during neurogenesis in Huntington's disease

Albert Ruzo[1,*], Gist F. Croft[1,*], Jakob J. Metzger[1,2,*], Szilvia Galgoczi[1], Lauren J. Gerber[1], Cecilia Pellegrini[1], Hanbin Wang, Jr[1], Maria Fenner[1], Stephanie Tse[1], Adam Marks[1], Corbyn Nchako[1] and Ali H. Brivanlou[1,‡] 2018

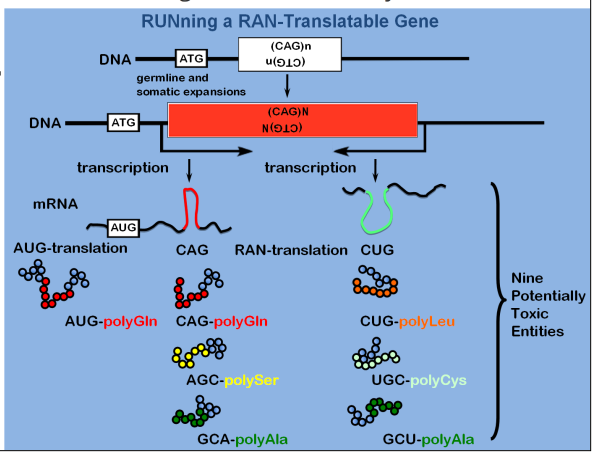
Surprisingly, the same phenotype emerged in $HTT^{-/-}$ but not $HTT^{+/-}$ lines. We conclude that HD is a developmental disorder characterized by chromosomal instability that impairs neurogenesis, and that HD represents a genetic dominant-negative loss of function, contrary to the prevalent gain-of-toxic-function hypothesis. The consequences of developmental alterations should be considered as a new target for HD therapies.

Considering the complexity of mutations (final)

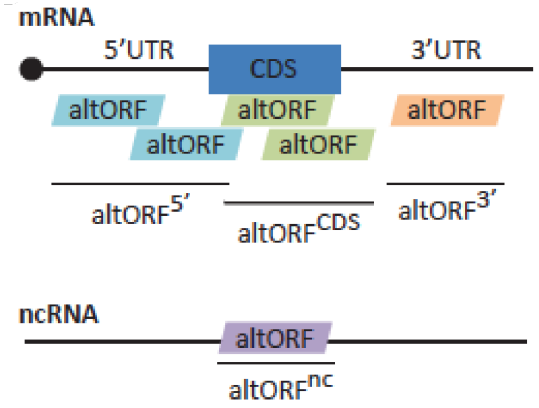
Repeat Associated Non-ATG Translation Initiation: One DNA, Two Transcripts, Seven Reading Frames, Potentially Nine Toxic Entities!

Christopher E. Pearson

Published: March 10, 2011



Considering the complexity of mutations (final)



modified from Samandi et al., 2017. Deep transcriptome annotation enables the discovery and functional characterization of cryptic small proteins

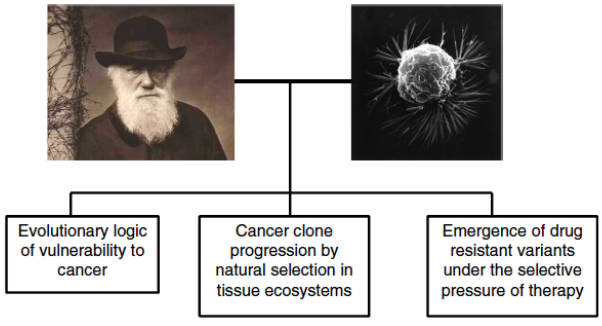
Greaves *BMC Biology* (2018) 16:22
DOI 10.1186/s12915-018-0493-8

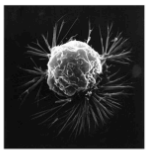
BMC Biology

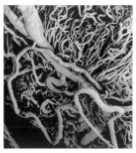
REVIEW Open Access

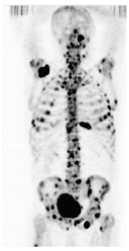
Nothing in cancer makes sense except…

Mel Greaves









Metastases
Drug resistant

1 mutant cell ⟶ ~10^{11}

Time: ——— months / decades ⟶

——— covert ----------

Charles Darwin, 1837, Notebook B