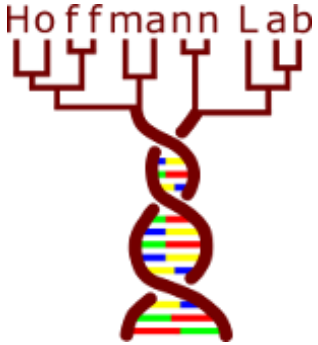
Evolución de familias multigénicas 2020

Evolución por variación en el número de copias génicas

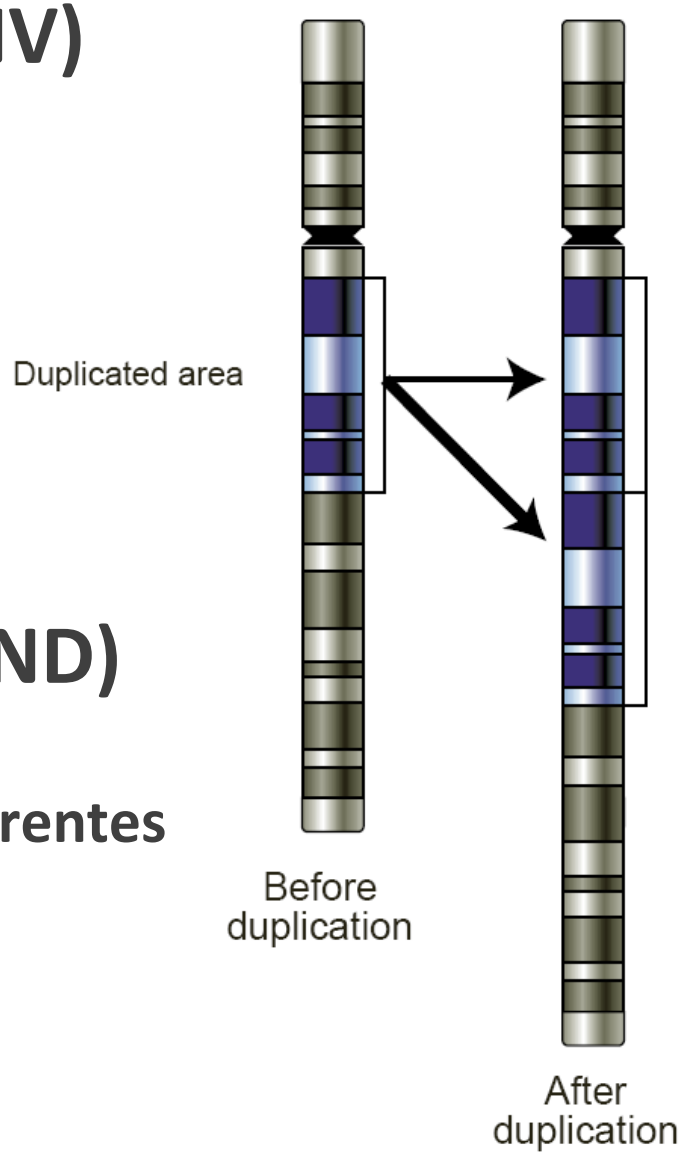


Variación en el número de copias de un gen (CNV)

Pérdida o ganancia de material genético entre individuos de la misma especie

Diferencias en el número de copias de un gen (CND)

Pérdida o ganancia de material genético entre individuos de diferentes especies



https://upload.wikimedia.org/wikipedia/commons/7/72/Gene-duplication.png

Variación en el número de copias de un gen (CNV)

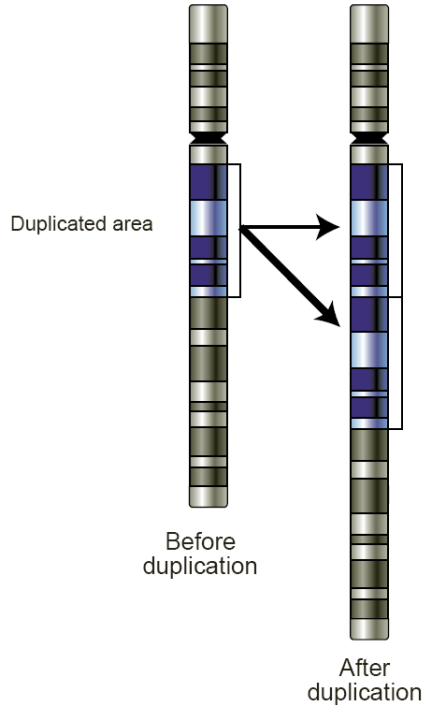
- **Clasificadas principalmente en dos categorías:**

- Secuencias repetidas cortas. Di- o tri-nucleótios, incluso combinaciones de ambos.

  - Polimorfismos en el número de copias (CNPs), menores a 10kb. Comunes en genes del sistema inmune, vías de detoxificación.

- Secuencias repetidas largas, que pueden representar hasta un gen completo.

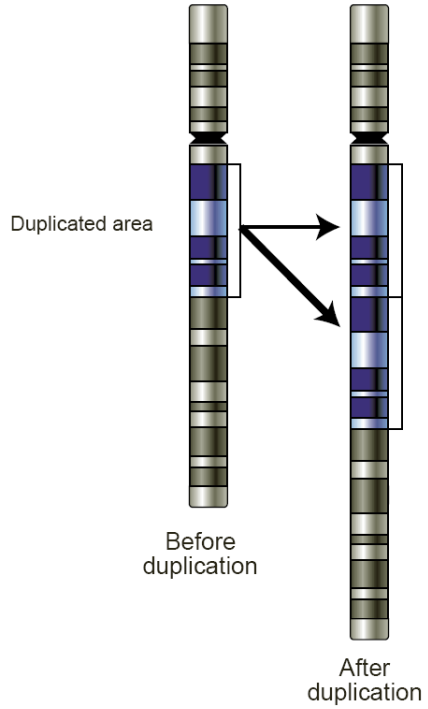
- Límite difuso entre ambas categorías.



Variación en el número de copias de un gen (CNV)

- **Secuencias repetidas largas, que pueden representar hasta un gen completo.**

- Causante de variación en el genoma.
- Ampliamente distribuidas a nivel poblacional.
- Rango de extensión $1x10^3$ a $5x10^6$ pb.
- Clasificadas como variaciones estructurales.
- Afectan el fenotipo.

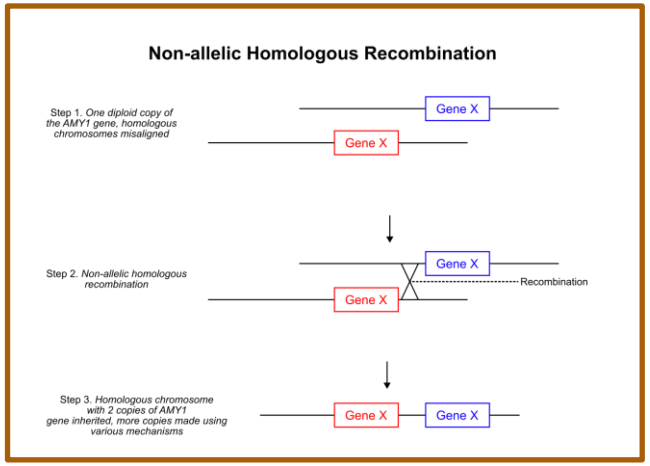


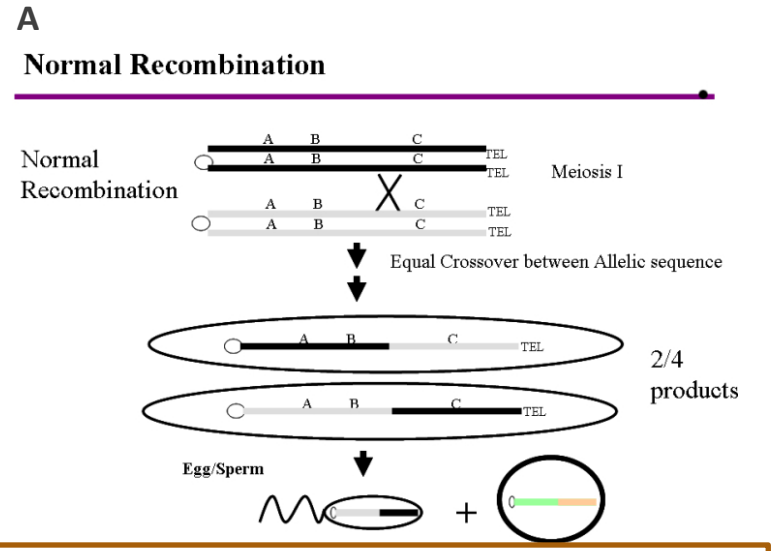
Variación en el número de copias de un gen (CNV)

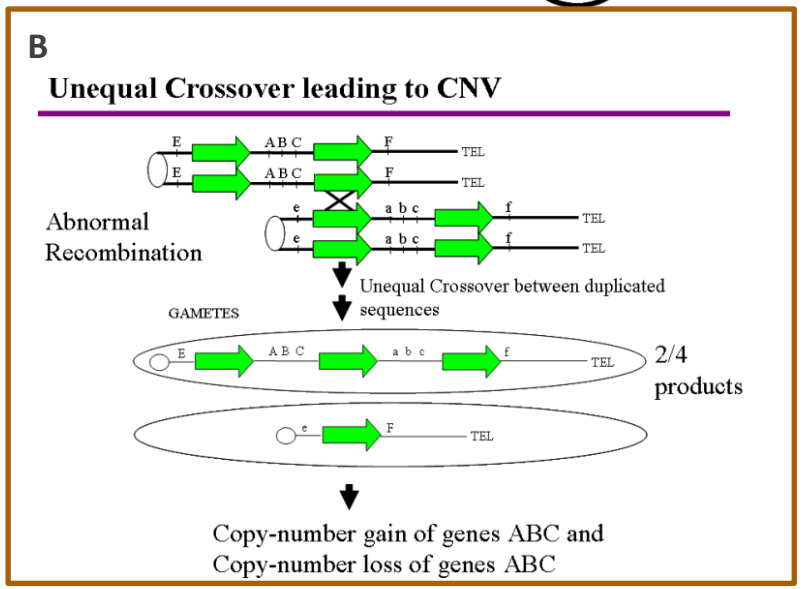
- ¿Cómo se generan?

- Recombinación homóloga no-alélica (B).

- Recombinación no homóloga, o de homología en muy pocas bases.



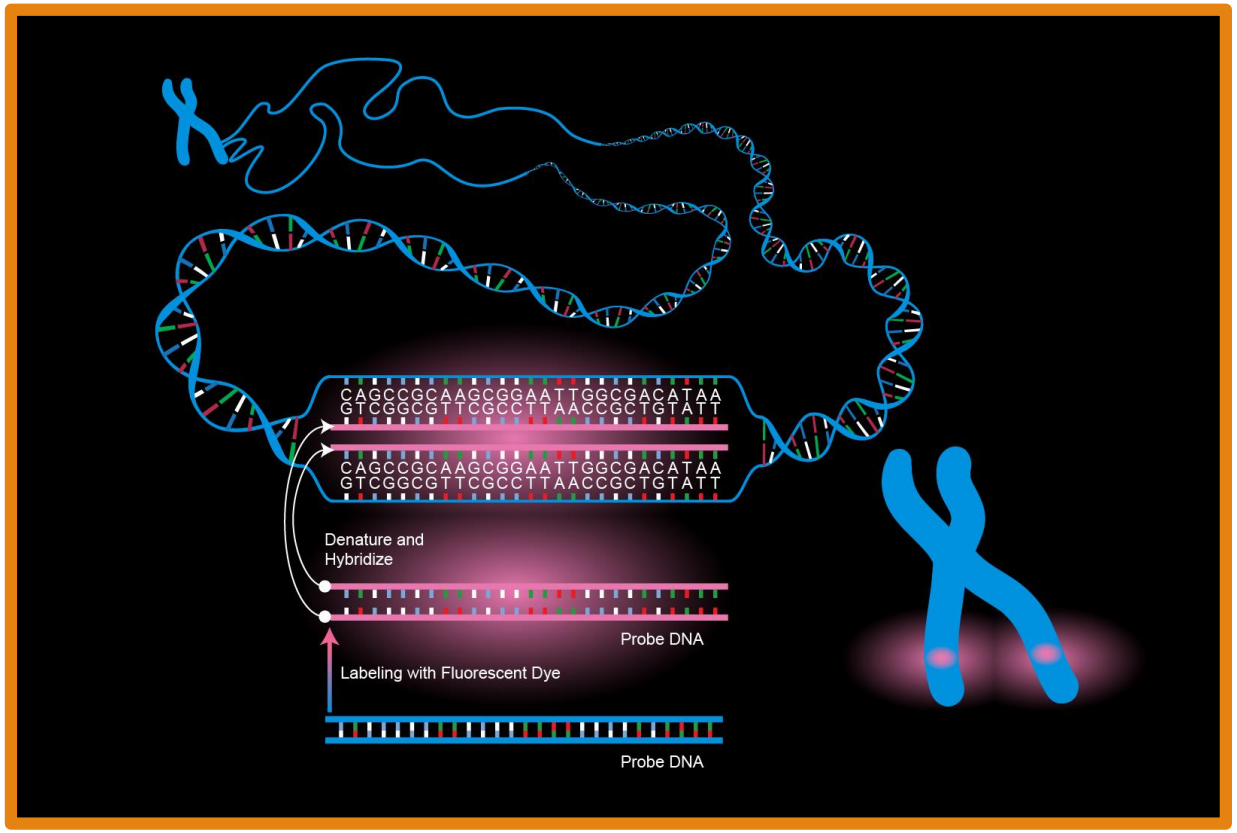




https://www.nature.com/scitable/topicpage/copy-number-variation-and-human-disease-741737/#

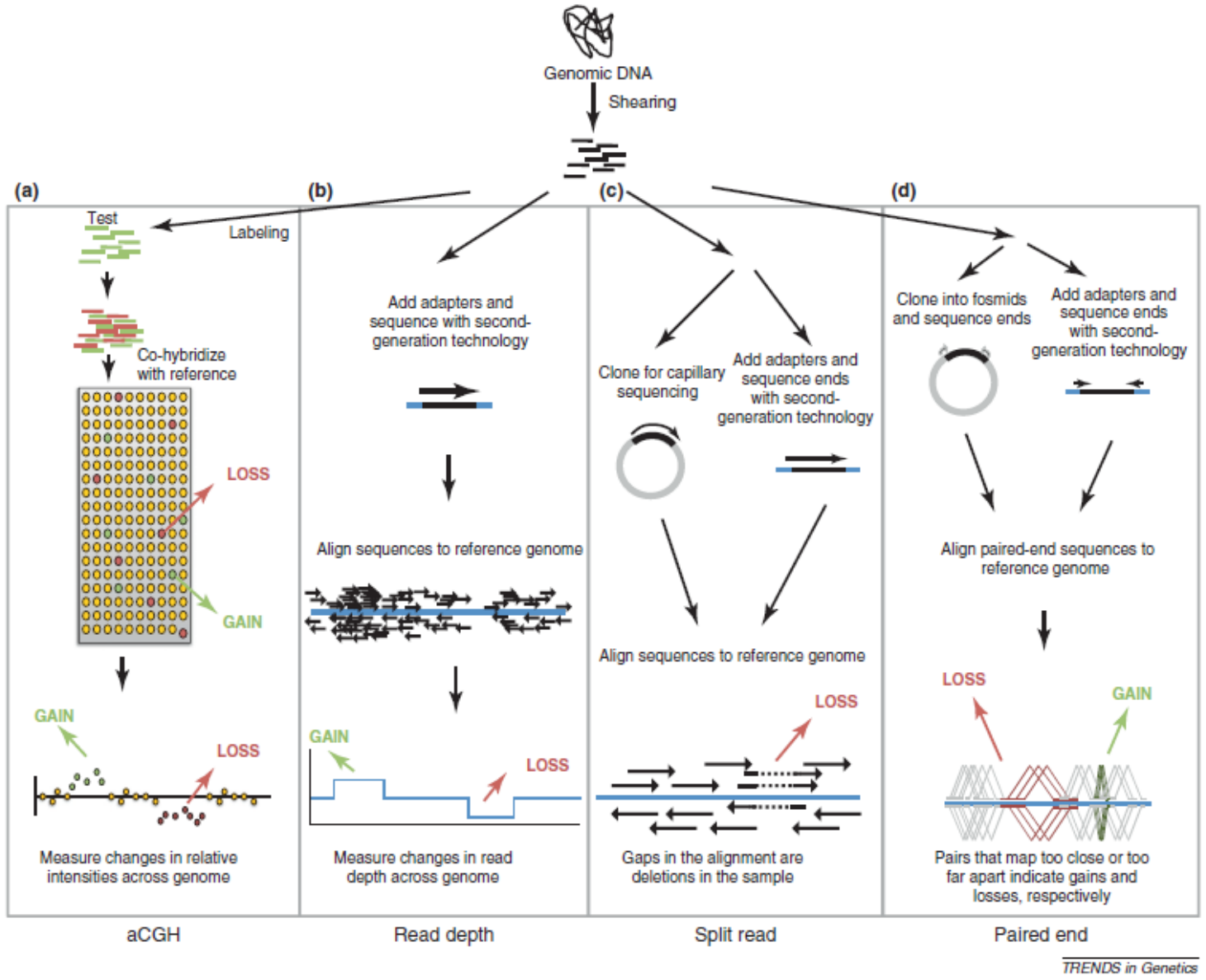
Variación en el número de copias de un gen (CNV)

- ¿Cómo las podemos identificar?
- Citogenética clásica.
- Hibridación fluorescente *in situ* (FISH).



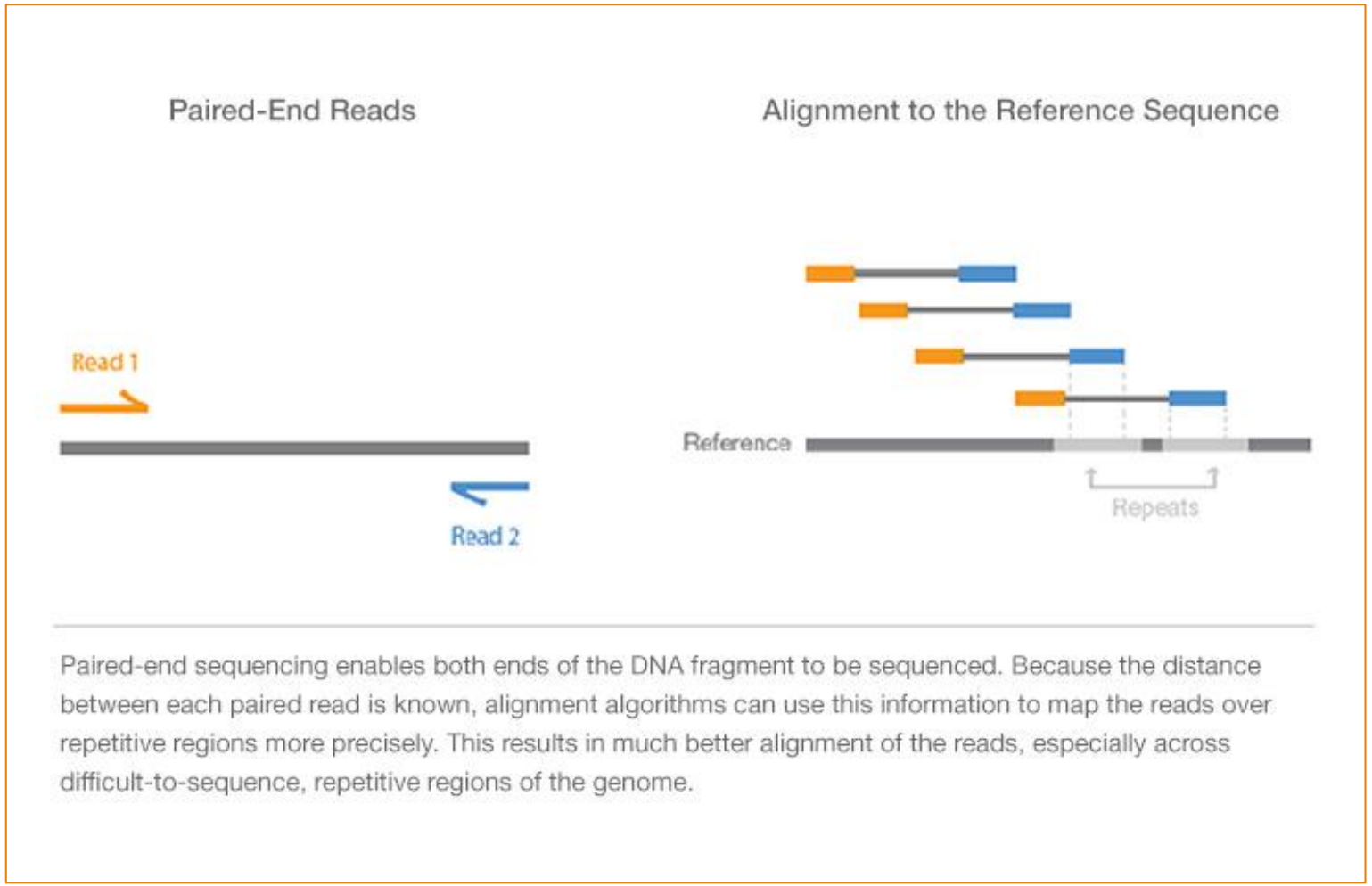
https://www.genome.gov/genetics-glossary/Fluorescence-In-Situ-Hybridization

¿Cómo podemos identificar las CNVs?



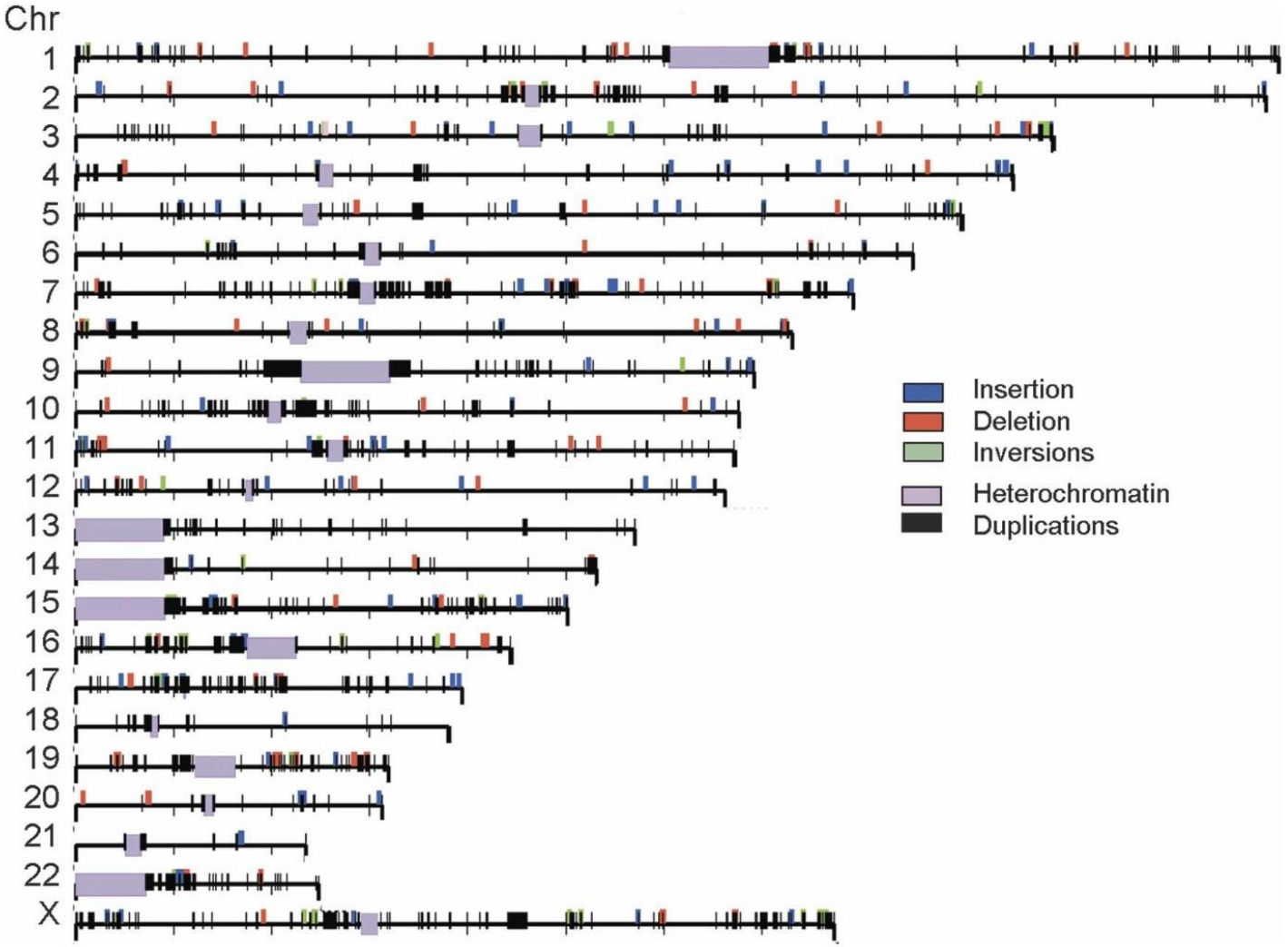
Iskow et al. 2012, doi:10.1016/j.tig.2012.03.002.

◦ ¿Cómo podemos identificar las CNVs?



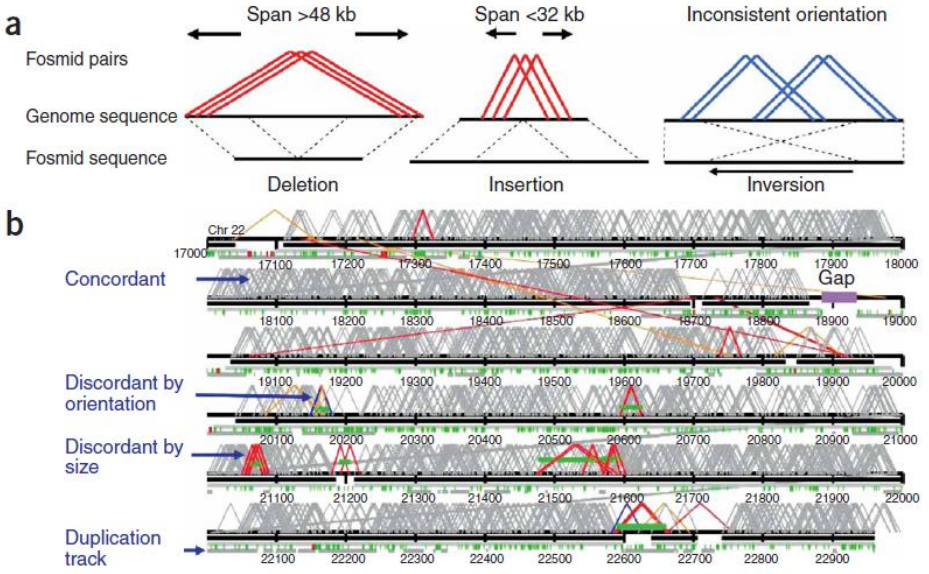
https://www.illumina.com/science/technology/next-generation-sequencing/plan-experiments/paired-end-vs-single-read.html

¿Cómo podemos identificar las CNVs?



Fine-scale structural variation of the human genome

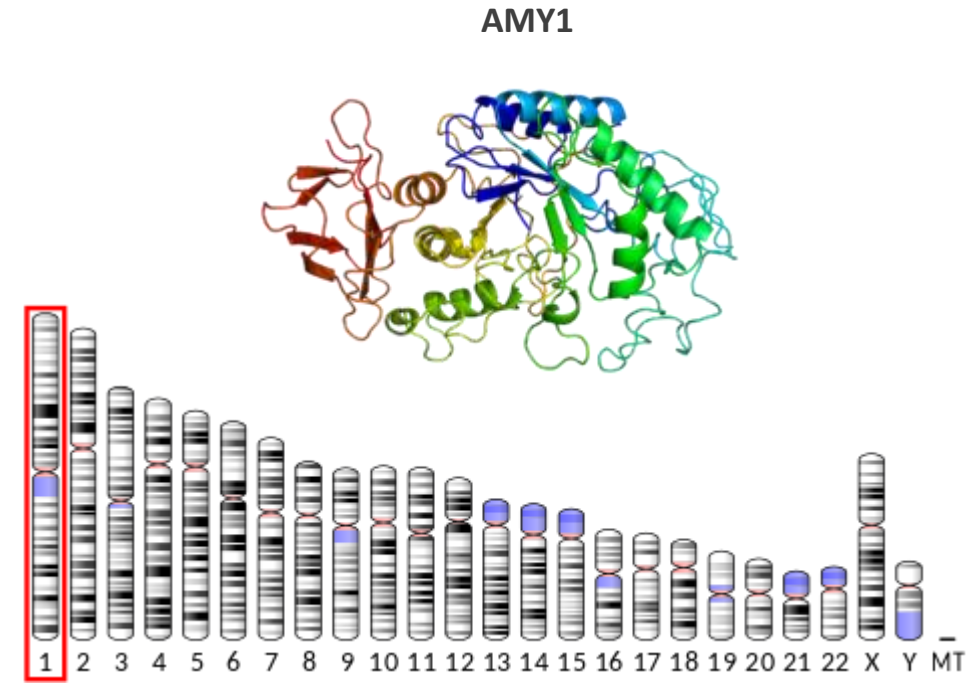
Eray Tuzun[1,5], Andrew J Sharp[1,5], Jeffrey A Bailey[2,5], Rajinder Kaul[3], V Anne Morrison[1], Lisa M Pertz[2], Eric Haugen[3], Hillary Hayden[3], Donna Albertson[4], Daniel Pinkel[4], Maynard V Olson[3] & Evan E Eichler[1]



Tuzan et al. 2012, doi:10.1038/ng1562.

CNVs en el genoma humano: amilasas

- **AMY1** (salival) y **AMY2** (pncreática) forman un cluster en el cromosoma 1.
- **AMY1** con 2-18 y **AMY2** de 2-12 copias por persona.
- Correlación positiva entre CNVs de AMY1 y niveles de proteína en saliva (Perry *et al*. 2007).

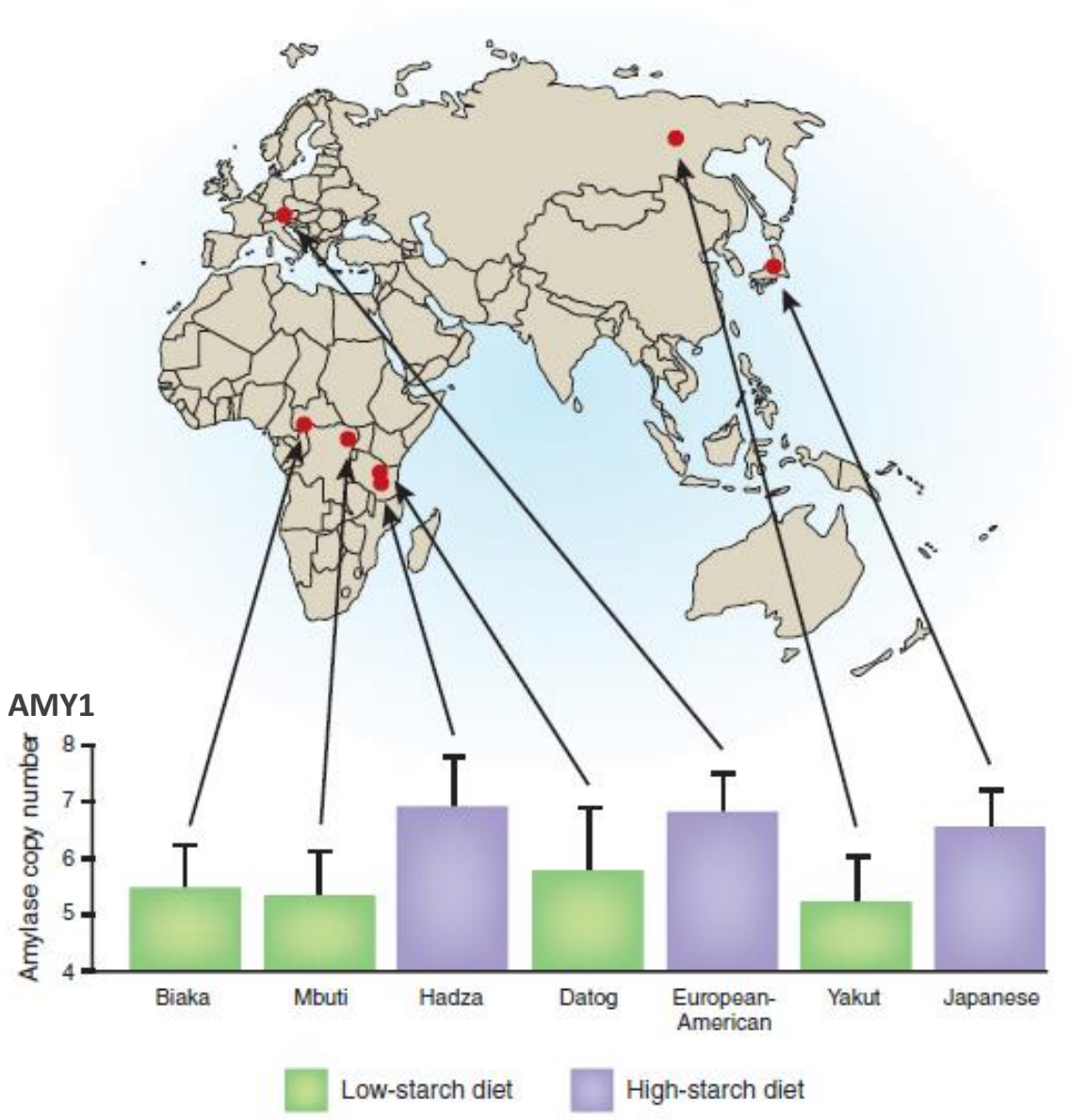


- Pero la función de la amilasa puede estar también afectada en mayor medida por modificaciones de la proteína o la formación de complejos (Carpenter *et al*. 2017).

CNVs en el genoma humano: AMY1

Hadza

Datoga



Japonés

Yakut

Adaptive drool in the gene pool

John Novembre, Jonathan K Pritchard & Graham Coop

Novembre *et al*. 2007, Nature Genetics 39:1188-1190.

Pruebas para estudiar apartamientos de la neutralidad

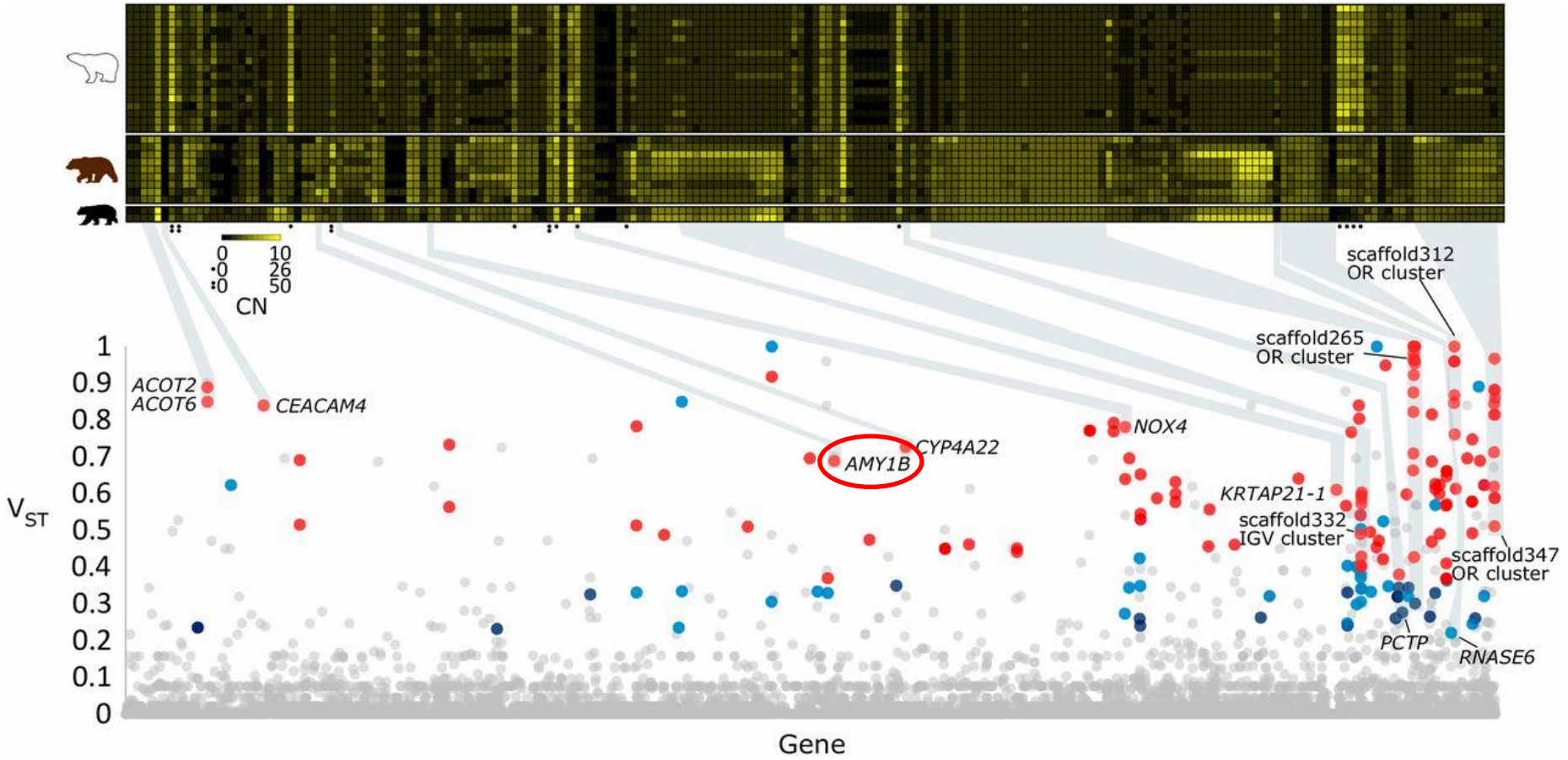
Table I. Select examples of tests of neutrality broadly split into three categories: frequency based, linkage based and substitution based

Test	Brief description	Refs
Frequency based		
Tajima's *D*	Measures the excess of high and low frequency alleles in a population. An excess of both high and low frequency alleles is indicative of recent positive selection.	[100]
Fay and Wu's *H*	Measures the excess of high frequency variants compared to intermediate frequency variants. An excess of high frequency alleles is indicative of recent positive selection.	[101]
F_{ST}	Determines whether a variant has differentiated allelic frequencies between populations more so than within populations. High population differentiation is indicative of positive selection acting in one or more populations.	[102]
V_{ST}	Determines whether a variant has differentiated array comparative genomic hybridization intensity data between populations, more so than within populations. High population differentiation is indicative of positive selection acting in one or more populations.	[103]
Linkage based		
LD	Determines whether multiple alleles occur together more often than expected by chance. Regions under positive selection tend to have high LD.	[104]
Extended haplotype homozygosity (EHH)	Measures the length of haplotypes for which variants exist in a homozygous state. Long stretches of homozygosity are indicative of recent selective sweeps.	[105]
Integrated haplotype score (iHS)	An extension of EHH that adjusts for whether the SNP in question is ancestral or derived for more sensitivity in detecting recent sweeps. Regions of positive selection tend to have long stretches of homozygosity.	[106]
Substitution based		
K_a/K_s	Determines the ratio of nonsynonymous to synonymous substitutions as those genes with high ratios are more likely to be under positive selection.	[98]
McDonald-Kreitman	Uses the ratio of fixed and polymorphic synonymous and nonsynonymous sites to determine the likelihood of neutrality. Genes with a high proportion of nonsynonymous fixed differences are indicative of positive selection.	[99]

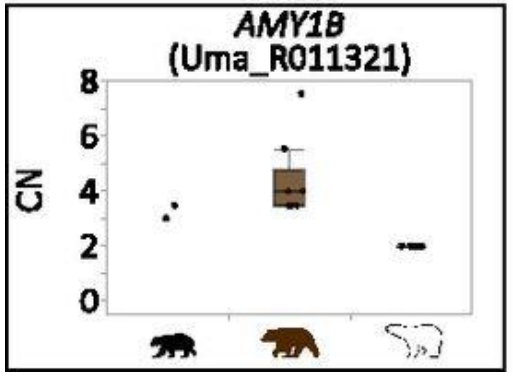
(Iskow et al. 2012, doi:10.1016/j.tig.2012.03.002.

Polar bear evolution is marked by rapid changes in gene copy number in response to dietary shift

David C. Rinker[a,1], Natalya K. Specian[b,1], Shu Zhao[c,d], and John G. Gibbons[c,d,e,2]



A



CN = *Gene copy number* = $\frac{\bar{x}\ gene\ depth}{\bar{x}\ depth\ of\ all\ genes} \times 2.$

V = varianza de **CN**

$$V_{ST} = \frac{(V_{total} - (V_{polar\ bear} \times N_{polar\ bear} + V_{brown\ bear} \times N_{brown\ bear}))/N_{total}}{V_{total}},$$

Rinker *et al*. 2019, www.pnas.org/cgi/doi/10.1073/pnas.1901093116.

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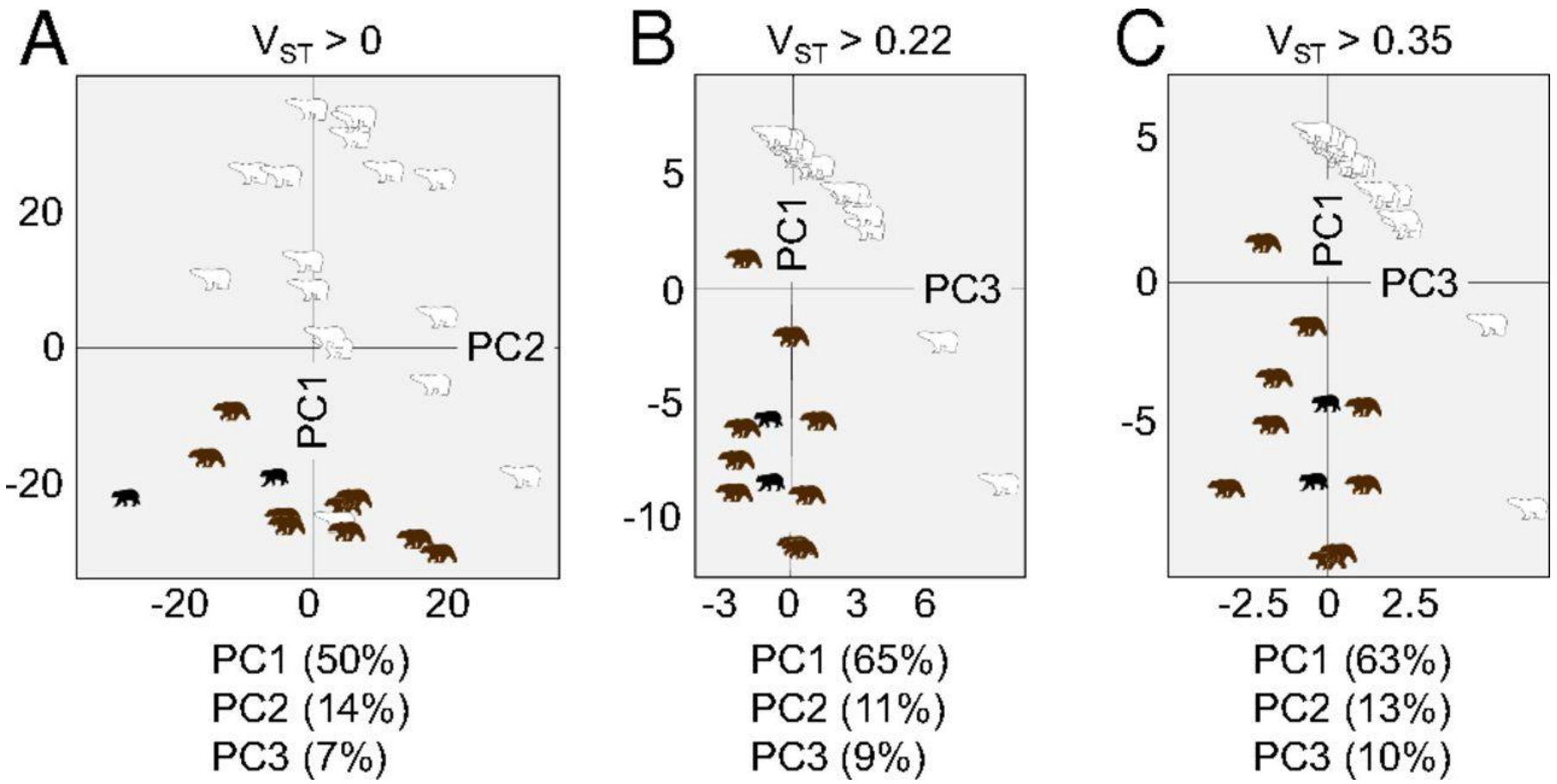
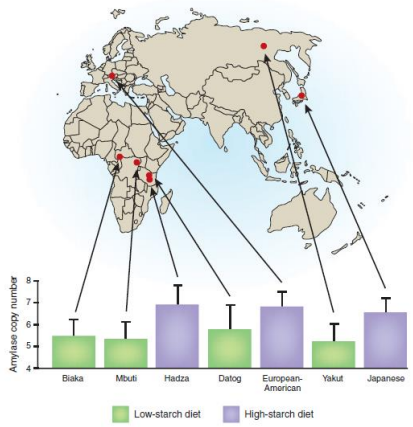
Los osos polares exhiben perfiles de CN divergentes al ser comparados con los osos pardos y negros



Rinker *et al*. 2019, www.pnas.org/cgi/doi/10.1073/pnas.1901093116.

Evolución por variación en CNVs



- Polimorfismos o fijación de CNVs – deriva génica y selección natural.
- Efecto del tamaño poblacional y de la eficacia darwiniana.
- CNVs y surgimiento de familias multigénicas.