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Sex-specific phenotypic effects and evolutionary history of an ancient deletion polymorphism of the human growth hormone receptor

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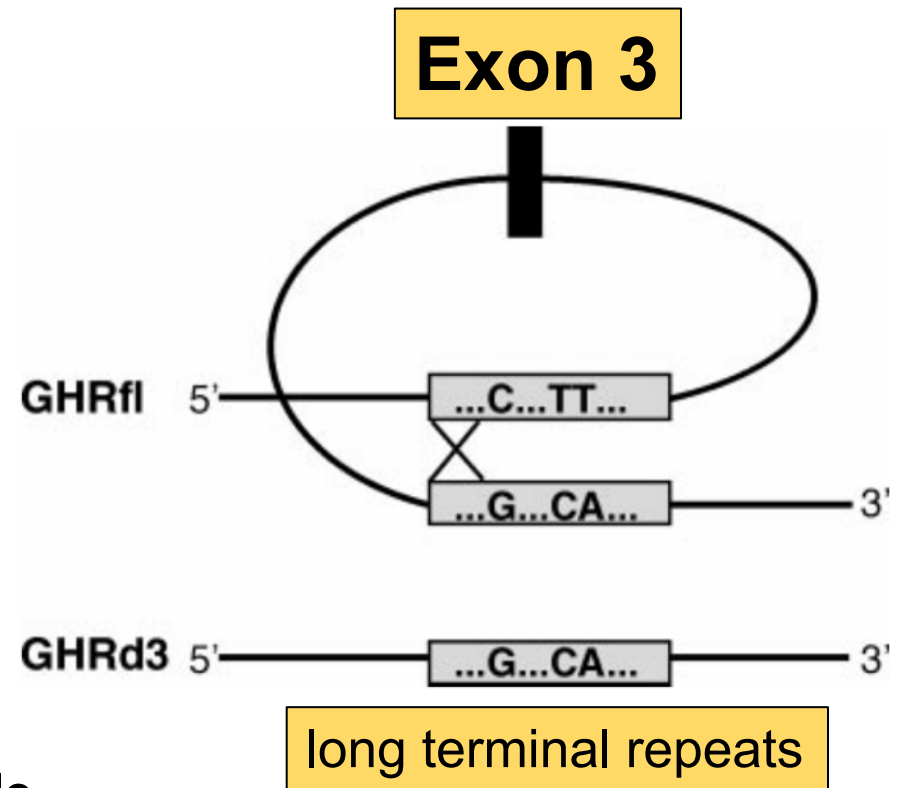
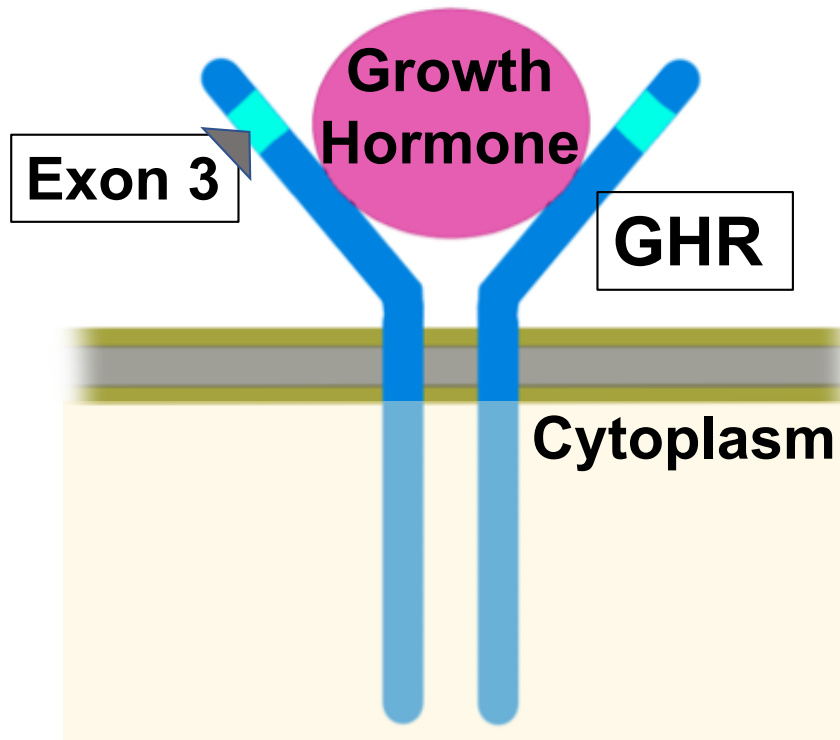
Summary

The exon3 of the growth hormone receptor gene (GHRd3) is commonly deleted in modern and archaic humans

- **Our haplotype-based analysis showed that**
 - (1) GHRd3 allele is associated with height
 - (2) Natural selection favored non-deleted allele in the East Asian populations
 - **Using a CRISPR-Cas9 based mouse model, we showed that GHRd3 affects**
 - (1) the growth rate
 - (2) metabolic and nutrient-dependent signaling gene expression
 - (3) lipid composition in blood
- > Evolution of human life history traits, food resource availability



The deletion in growth hormone receptor exon 3 (***GHRd3***) mediated by long terminal repeats



- Development – bone and muscle
- Metabolism

The effect of *GHRd3* in humans

Biochemical effect

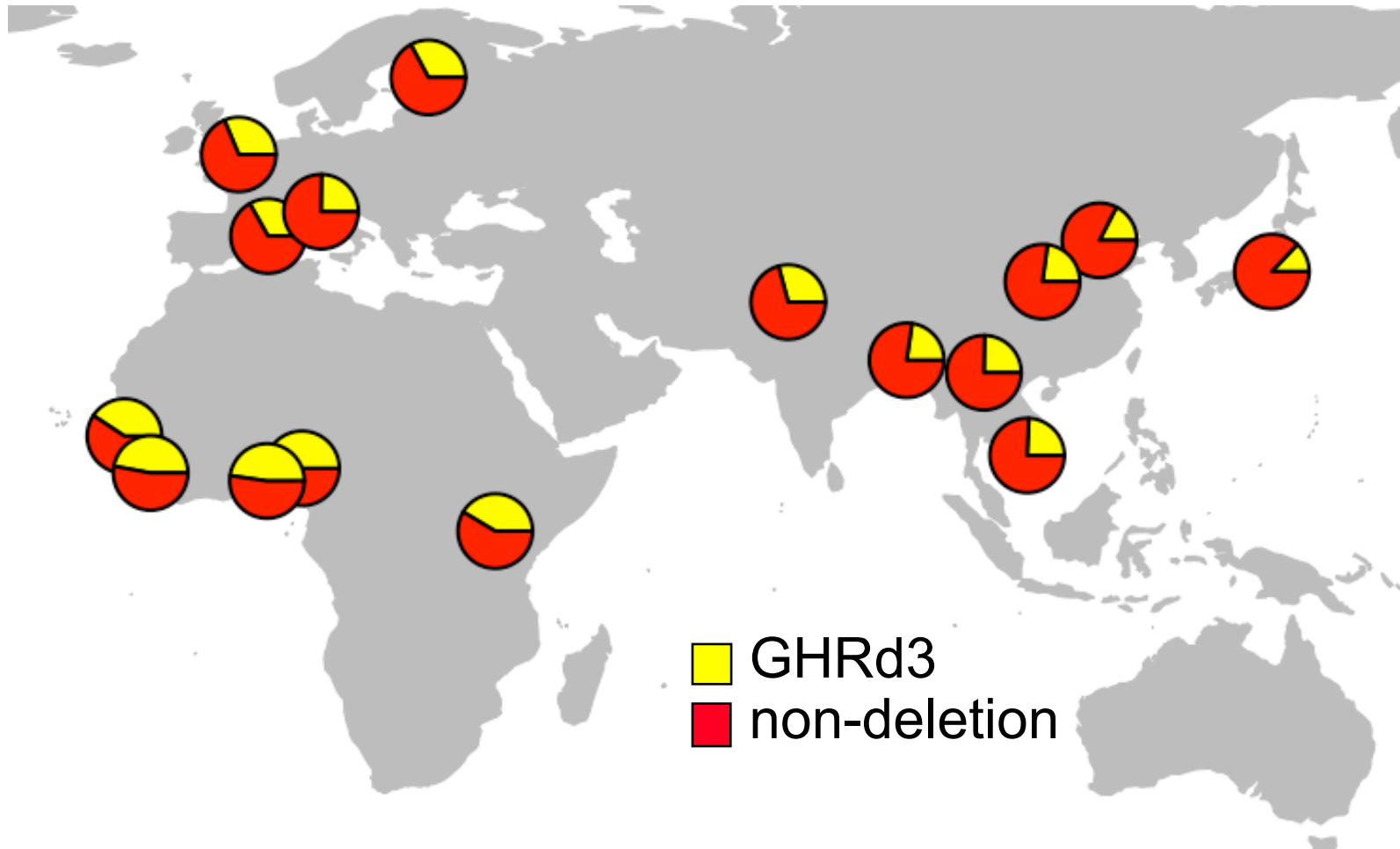
- More GHR activity (Dos Santos, et al., 2004)
- Insulin secretion (Sorensen et al., 2009)

Life history traits

- Development (Jorge et al., 2006)
- Timing of sexual maturity (Sørensen et al., 2010)
- Height and longevity (Ben-Avraham et al., 2017)
- Placental weight (Padidele et al., 2012)



The distribution *GHRd3* allele

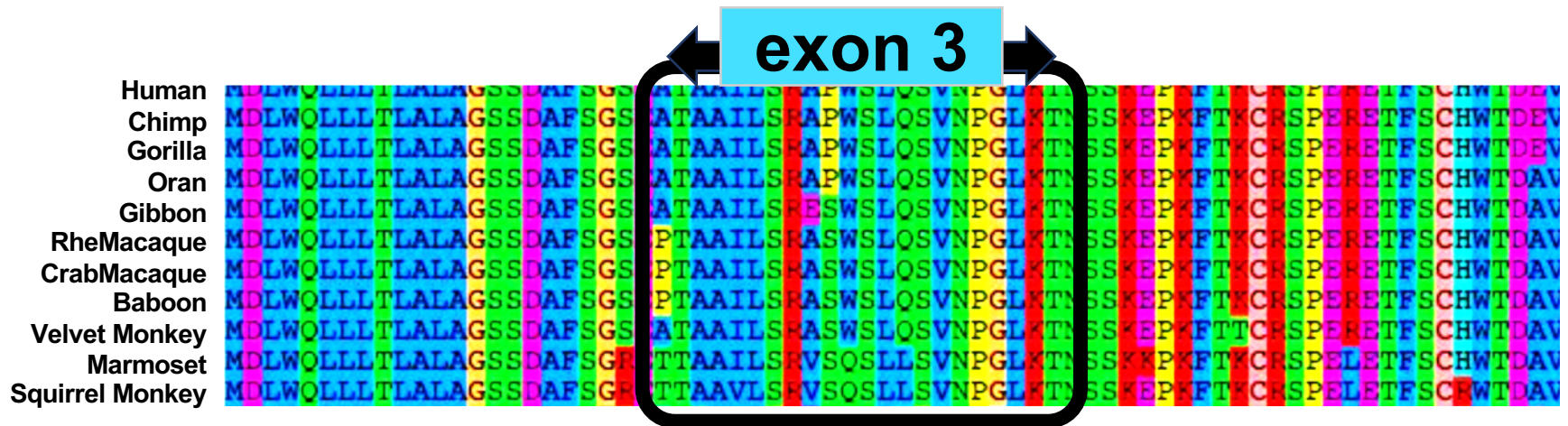


Why has **the *GHRd3*** been commonly maintained in human populations?

- > Evolutionary genomics analysis
- > CRISPR-Cas9 mouse model

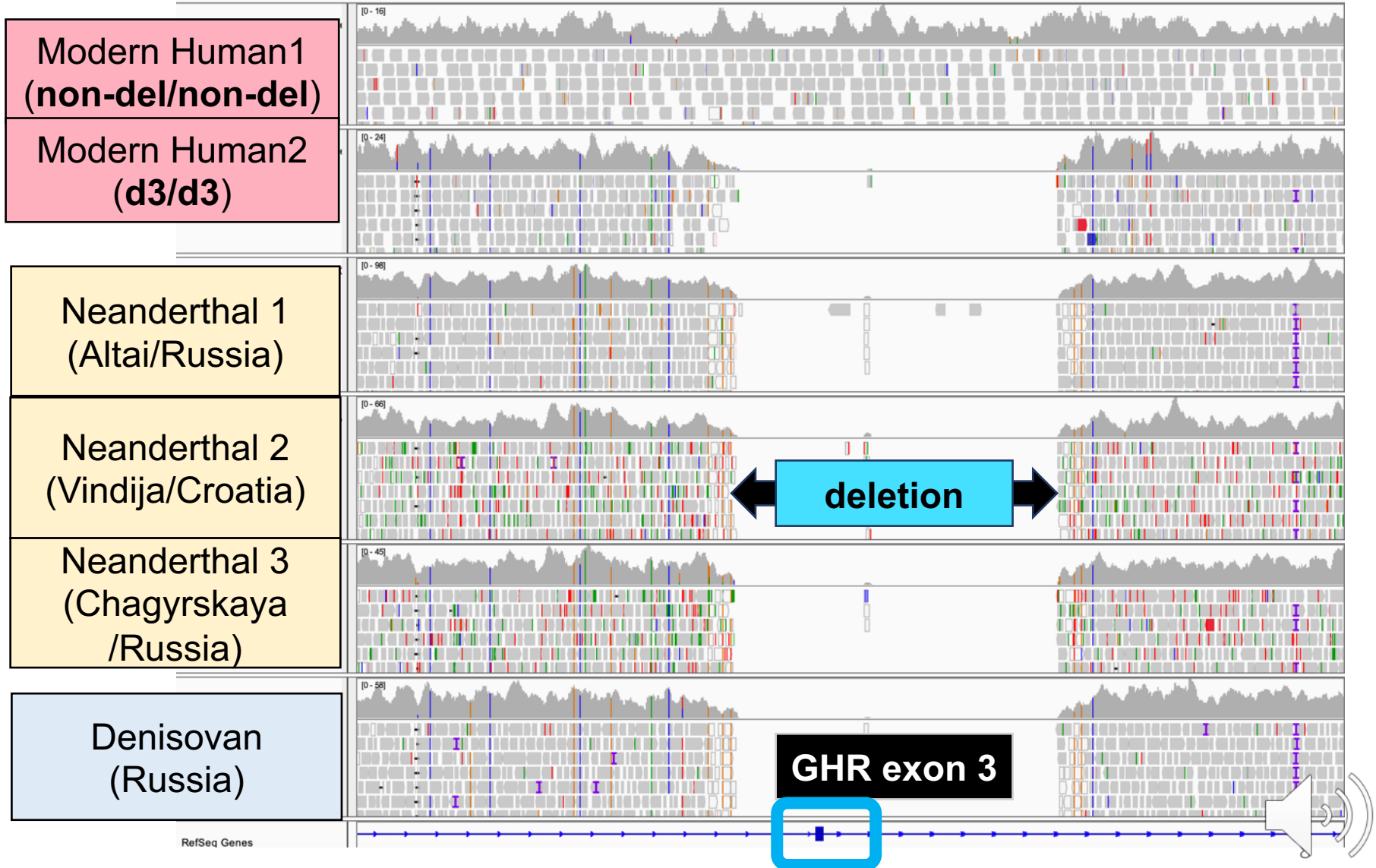


GHR exon3 is conserved among primates



GHRd3 in archaic hominin genomes

Human chr5:42,625,642-42,633,228



Are there non-neutral forces
to maintain the *GHR* polymorphism?

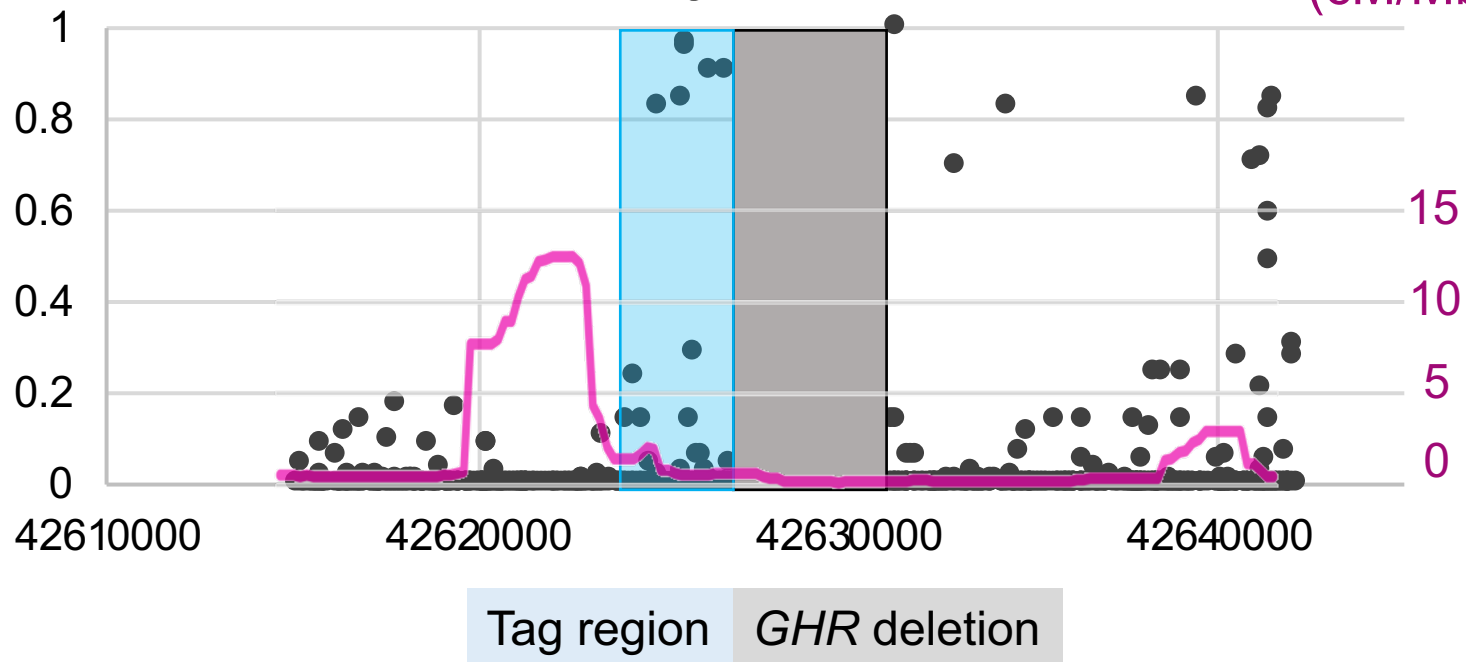
-> Haplotype-based
population genetics analyses



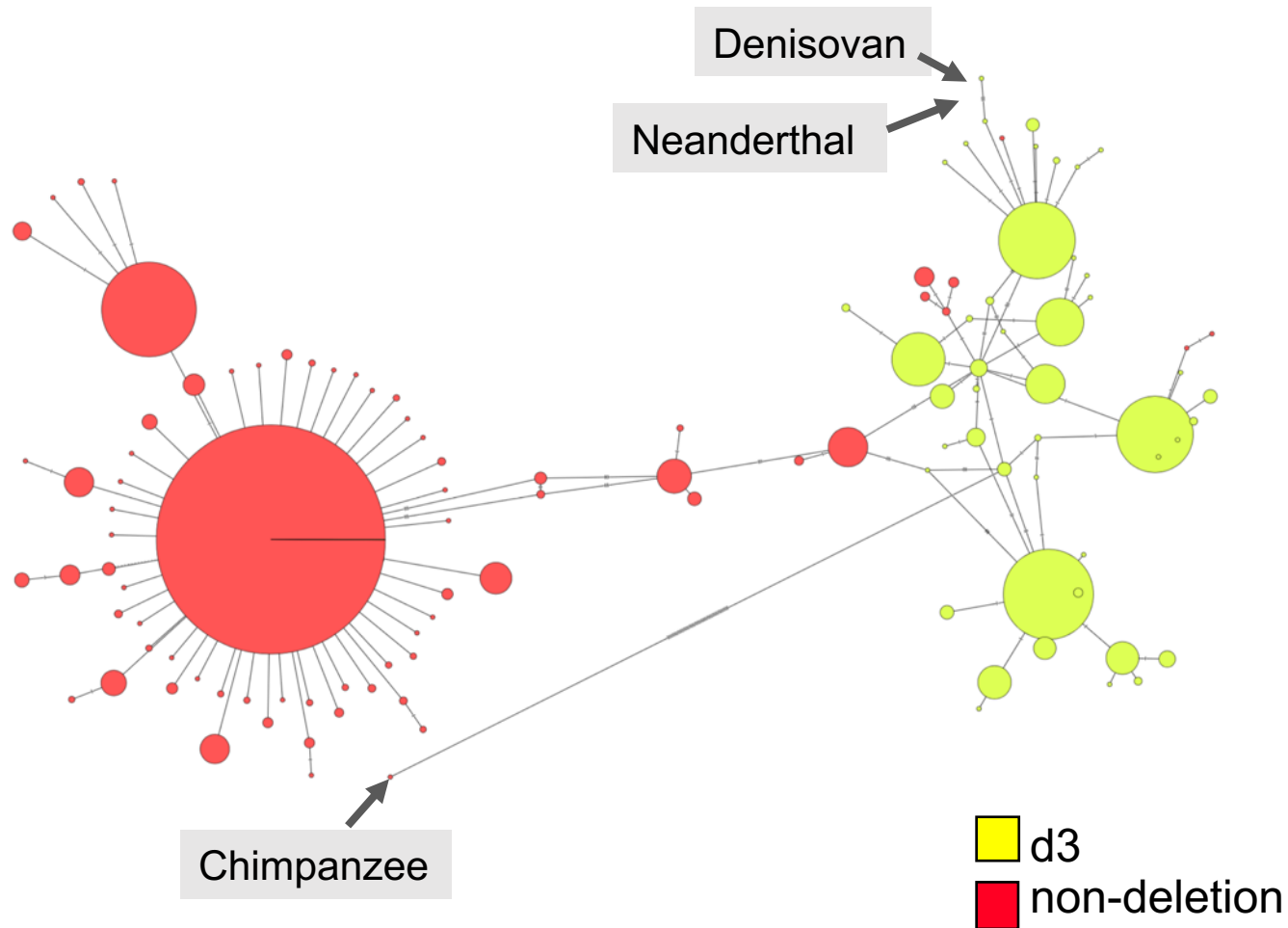
Haplotype-based evolutionary analyses on *GHRd3*

R^2 values

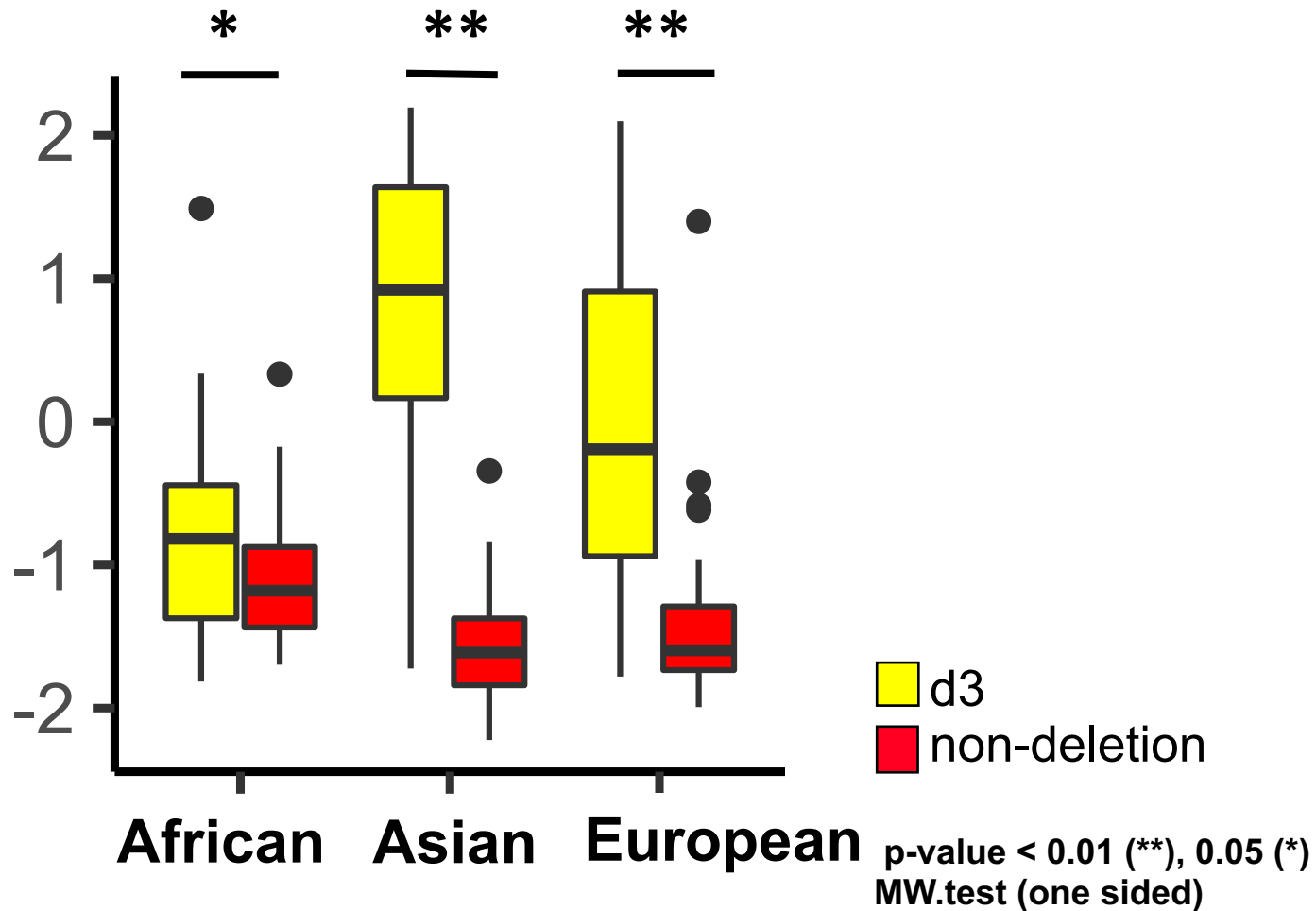
between the deletion and flanking SNPs



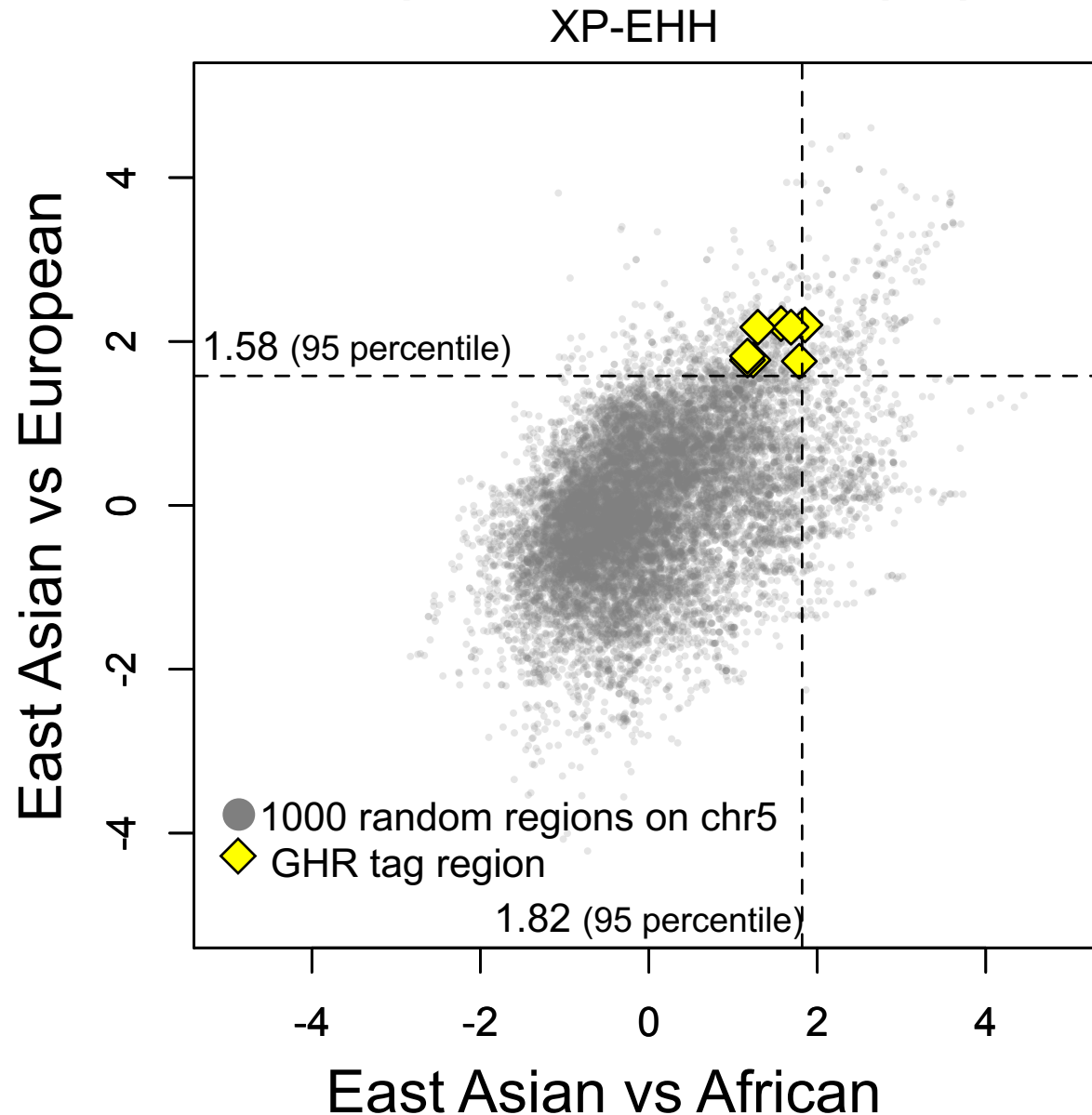
Reduction of diversity of *GHR* non-del haplotypes



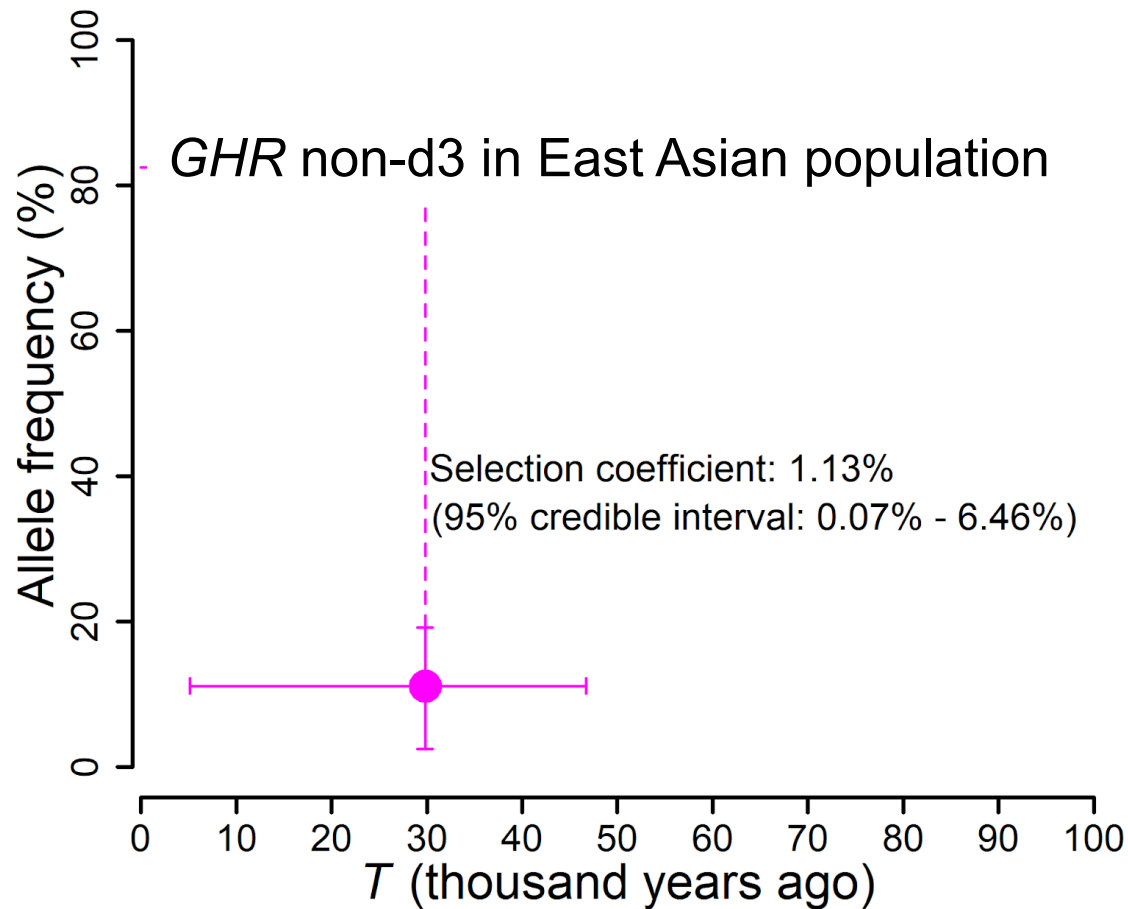
Tajima's D on the *GHRd3* tag region: Different evolutionary history of d3/non-del



XP-EHH on the *GHRd3* tag region: Selective sweep in East Asian populations



Simulation of the natural selection on *GHR* non-d3 in East Asian population

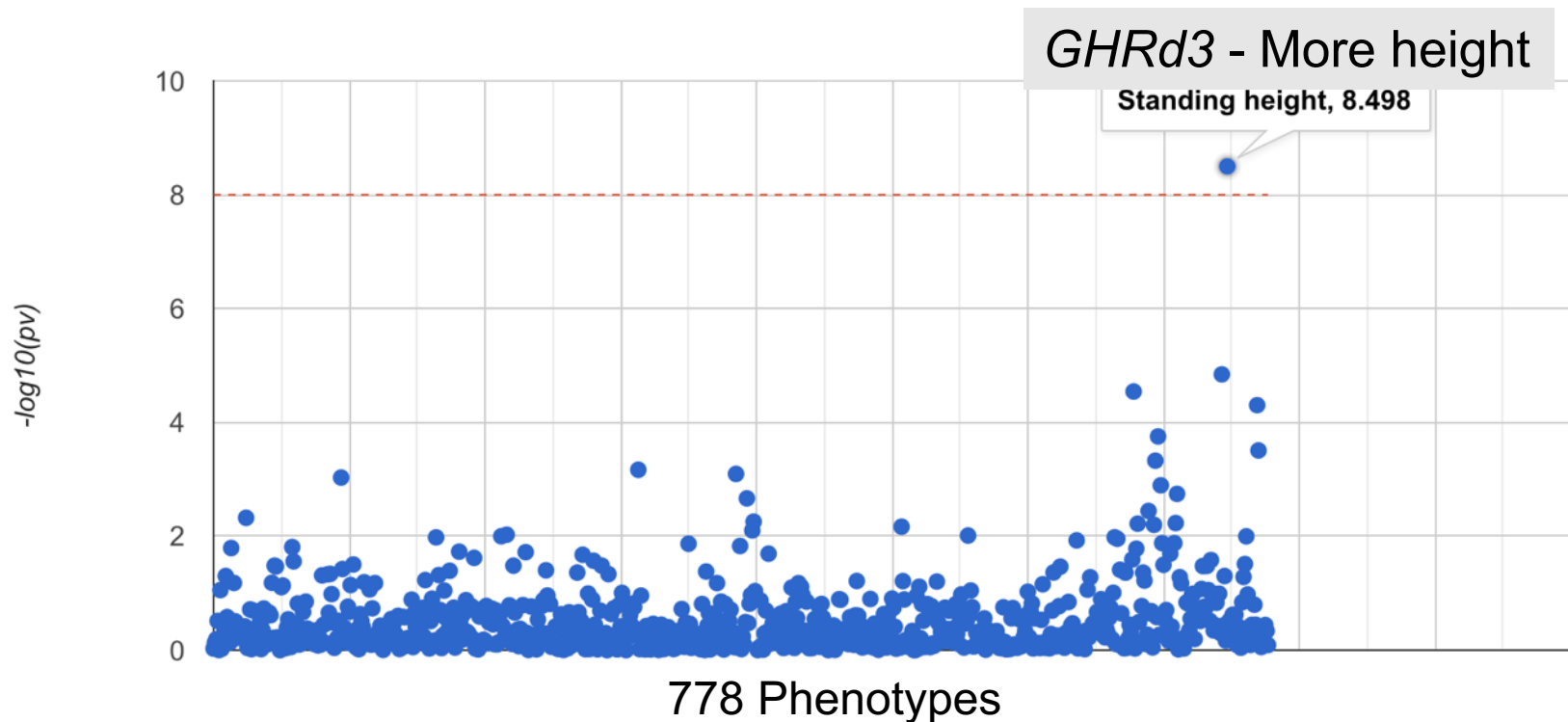


Evolutionary model

The diagram illustrates an evolutionary model for the GHRd3 gene. A central black line represents the hominid lineage, which splits into two main branches: one leading to 'Other Great Apes' and another leading to modern humans. The human lineage is highlighted in red. Key events on the human lineage are marked with red arrows and text: 'GHRd3 evolves' (near the top), 'Near fixation of GHRd3' (further down), and 'Fixation of GHRd3' (at the base of the modern human clade). The modern human clade is further divided into several lineages: 'Denisova', 'Altai N', 'Chagyrskaya', 'Vindija', 'Africa', and 'Eurasia'. A red arrow points to the 'Eurasia' branch with the text '~30K YBP non-deletion was favored in Asia'. The 'Africa' branch is also highlighted in red.

GHRd3 showed association with standing height in the UK population

452,264 Individuals, 30 Million Variants



- *GHRd3* was dominant among ancient hominins
- Non-neutral evolution of *GHRd3*

What is the impact of *GHRd3*
on gene pathways and development?

CRISPR-Cas9 mouse model



WT/WT

WT/d3

d3/d3


- RNA-seq analysis
- Growth pattern analysis
- Lipidomics

Expression change of metabolic genes in *GHRd3* mice



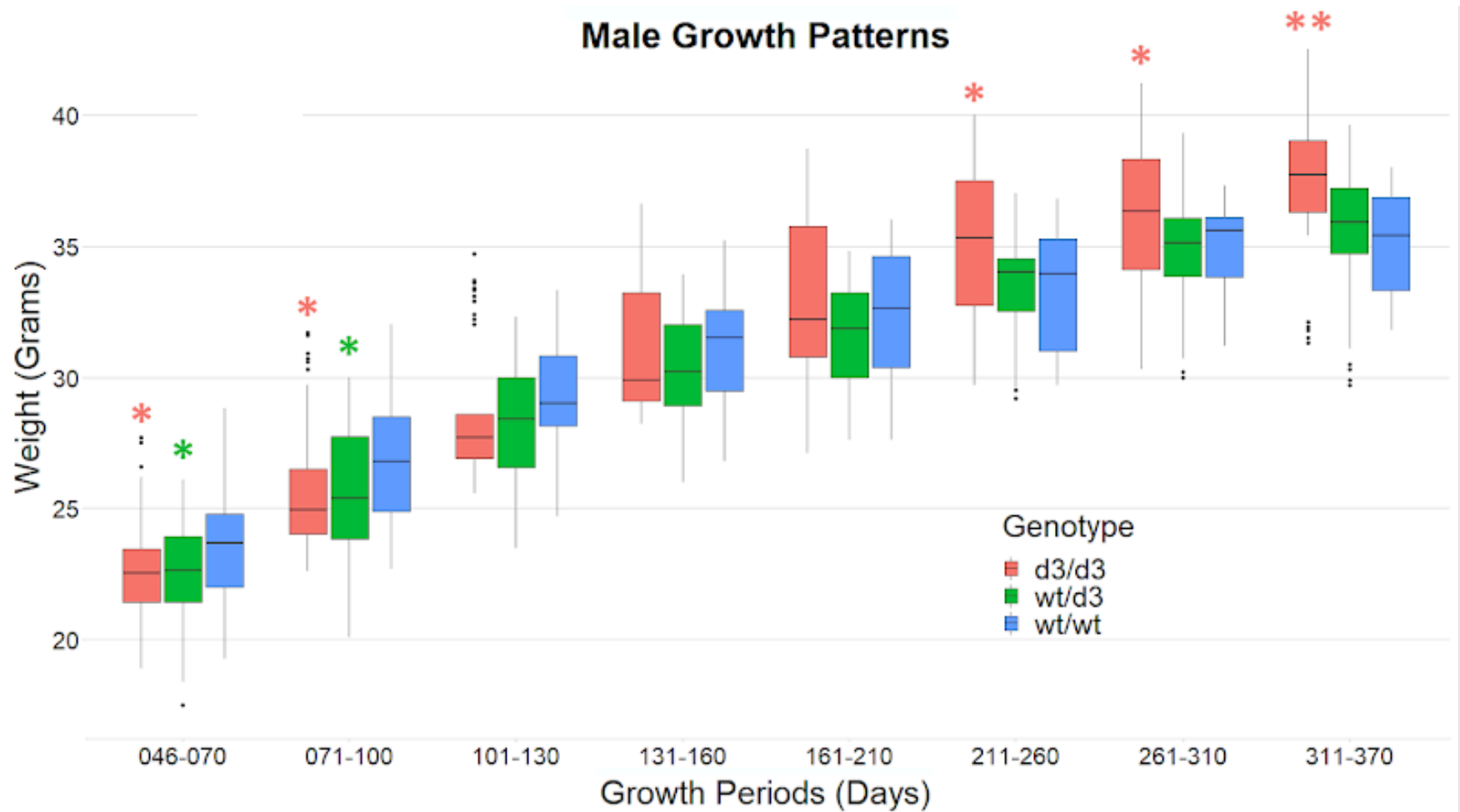
 Less expressed in d3/d3 mouse

- Lipid metabolism genes

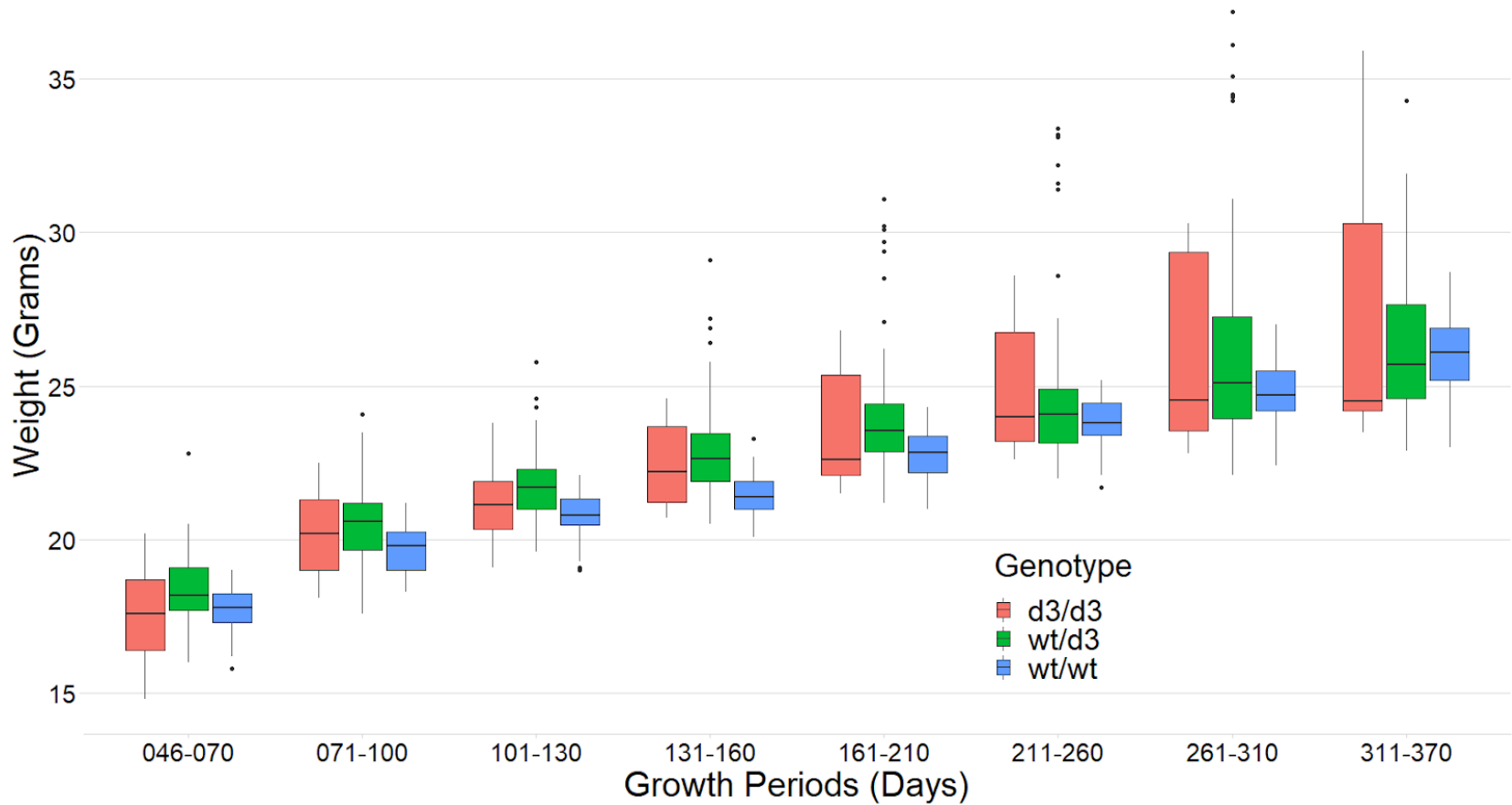
 More expressed in d3/d3 mouse

- mTORC1 (**nutrient-dependent**) signaling pathway
- Biogenesis genes

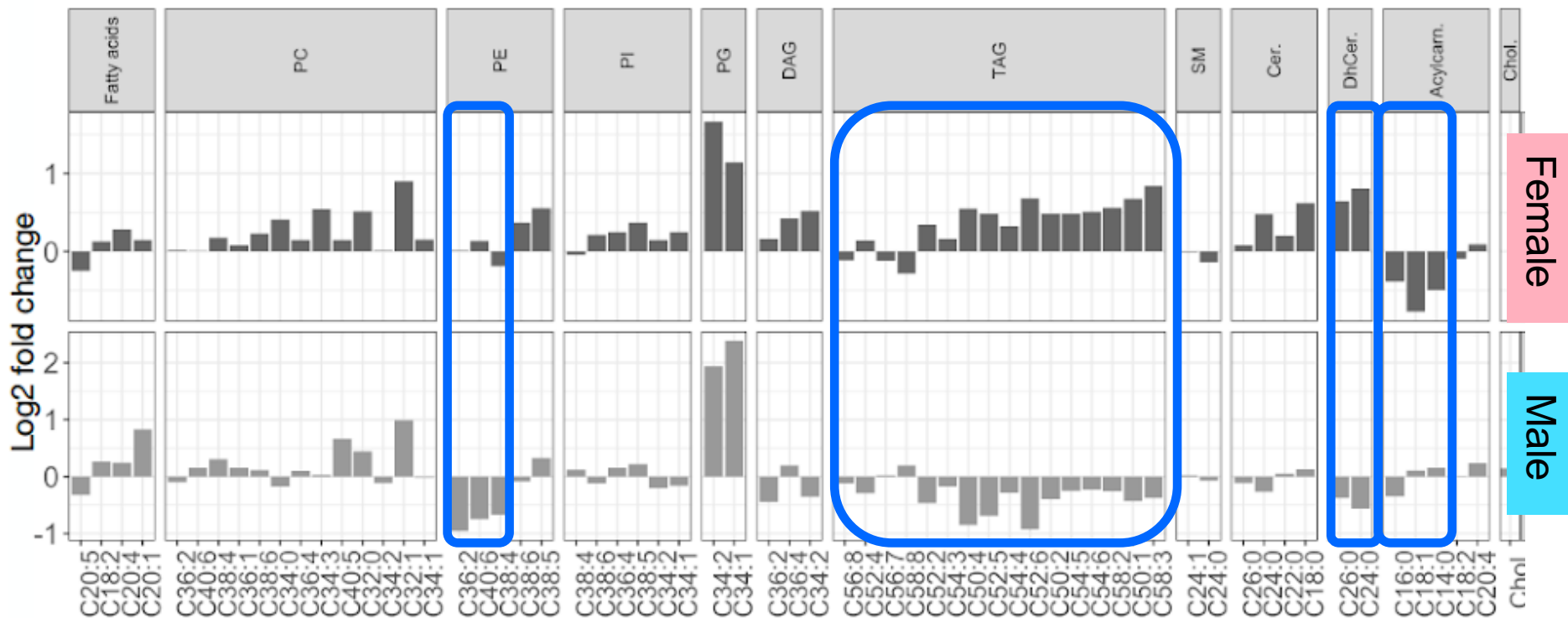
Male Growth Patterns



Female Growth Patterns



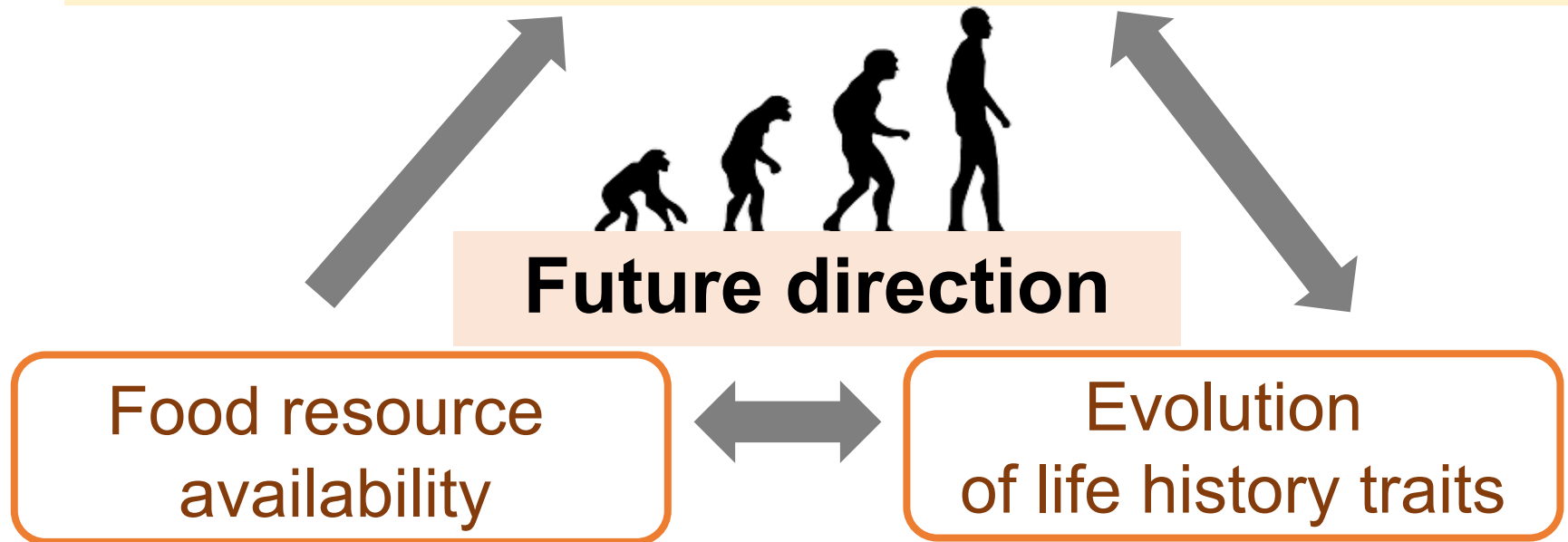
Sex-specific lipid composition change in blood



PC=phosphatidylcholine, PE=phosphatidylethanolamine, PI=phosphatidylinositol, PG=phosphatidylglycerol, DAG=diacylglycerol, TAG=triacylglycerol, SM=sphingomyelin, Cer.=ceramide, DhCer.=dihydroceramide, Acylcarn.=acylcarnitine, Chol.=cholesterol.

Summary

- *GHRd3* was dominant among ancient hominins
- Non-neutral evolution of *GHRd3*
- *GHRd3* affects growth pattern
- *GHRd3* affects metabolic gene expressions



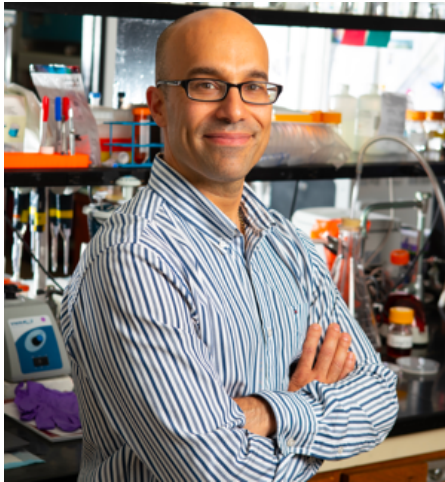
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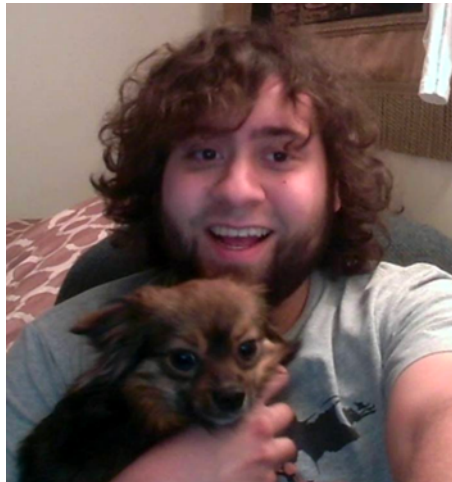
Acknowledgement

Gokcumen lab

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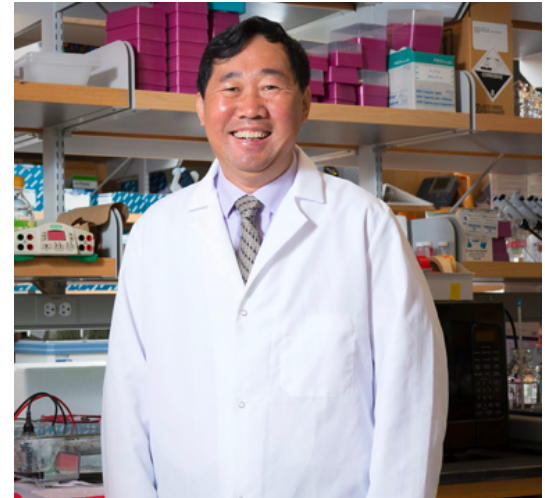
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