Genomic perspectives on malaria in the Guiana Shield

AgiT Conference, Cayenne, French Guiana

Daniel Neafsey

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HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

BROAD INSTITUTE

Every mosquito, or drop of blood from a malaria-infected person, contains genetic information useful for effectively treating and eliminating malaria.

This encoded information is increasingly straightforward to read.

Malaria molecular surveillance

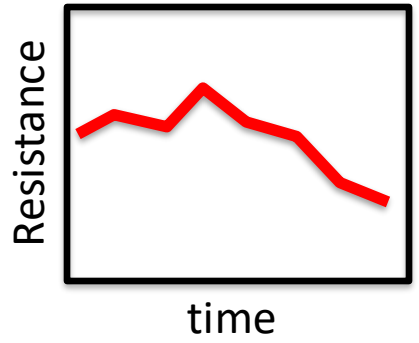
Sample collection

DNA Testing

Data Analysis:

Local or

In the cloud



Transmission levels

Dr. Caroline Buckee
Professor, Dept. of Epidemiology, HSPH

BILL & MELINDA GATES foundation

Role of malaria drug resistance surveillance in Guyana

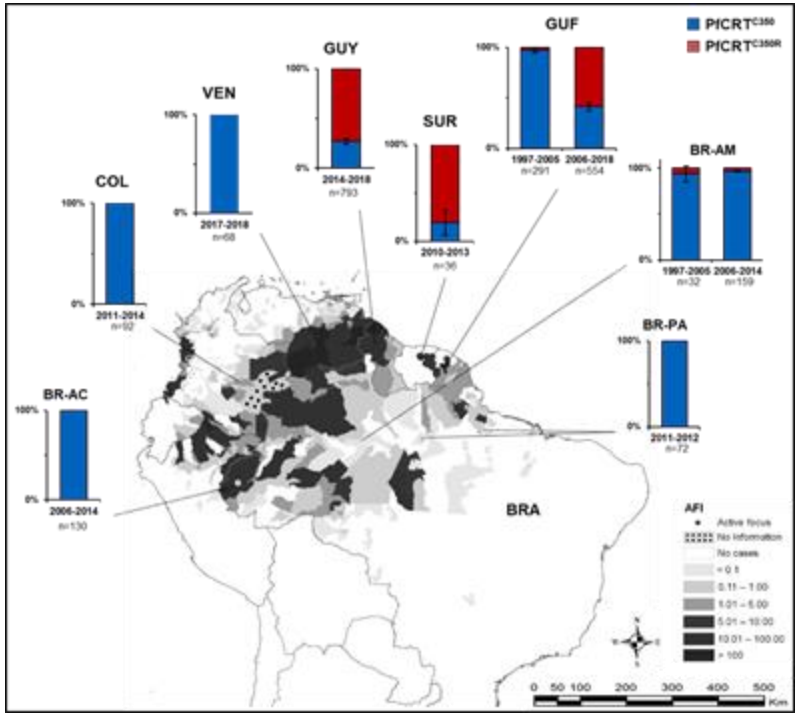
- Difficult to implement therapeutic efficacy studies
- Difficult to track actual drug treatment in mobile miner population
- Continued volatility in resistance mutation frequencies (PPQ resistance mutations are now decreasing)

Dr. Horace Cox
Head of Vector-borne Diseases
CARPHA

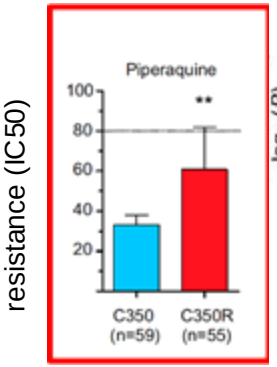
Dr. Reza Niles-Robin
Director of Vector Control Services,
Guyana MoH

Dr. Lise Musset
Group Leader
IP Guyane

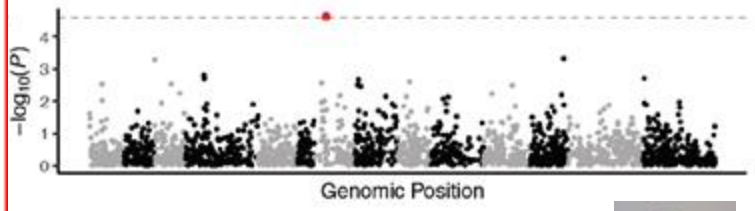
Example: piperaquine resistance mutations



Florimond et al., 2023



pfCRT C350R GWAS hit for PPQ resistance



Angela Early (Broad)

Lise Musset
(Institut Pasteur
de la Guyane)

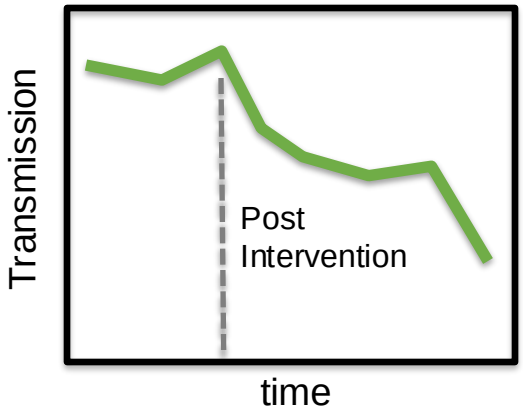
Celia Florimond

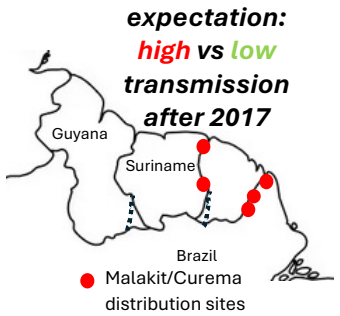
Piperaquine is the partner drug to the most common self-medication used by miners (DHA+PPQ+TMP)

Weakened piperaquine partner drug efficacy could have allowed for emergence of the Kelch13 C580Y resistance mutation

Measuring changes in transmission with genomic indicators

- Complementary to traditional epidemiological measures (case incidence, prevalence), especially when those are hard to measure
- Highly mobile populations are well suited (eg gold miners)

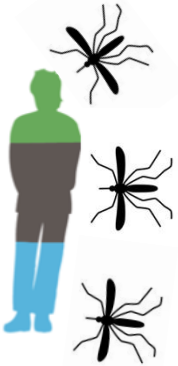




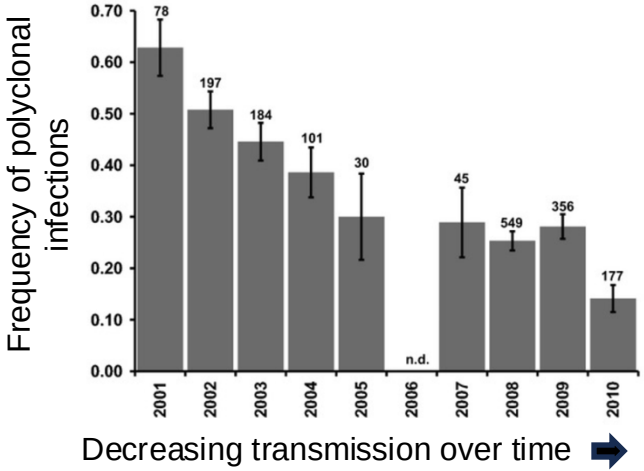
Dr. Maylis Douine, CHC

Polyclonality reflects transmission intensity

Clonal infection
(1 strain)



Polyclonal infection
(3 strains)

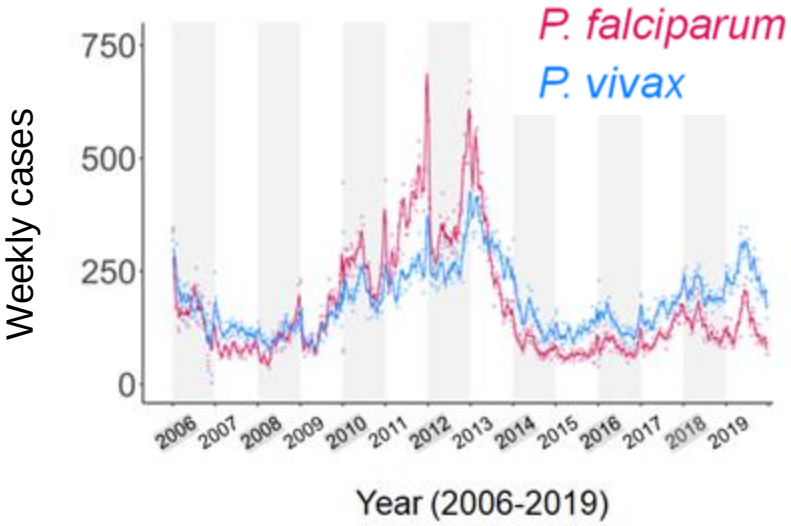


Nkhoma et al. 2012

High Transmission
High polyclonality

Low Transmission
Low Polyclonality

Comparing *P. falciparum vs. P. vivax* in Guyana

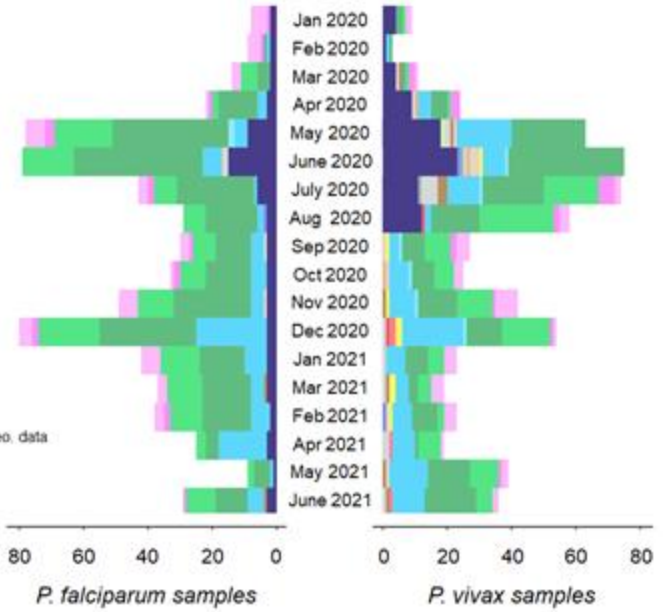


Philipp Schwabl (HSPH)

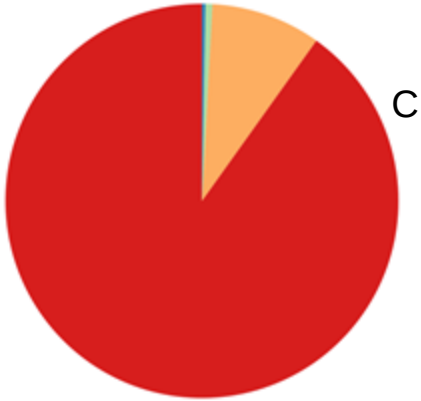
Flavia Camponovo (HSPH)

Reza Niles-Robin (Guyana MoH)

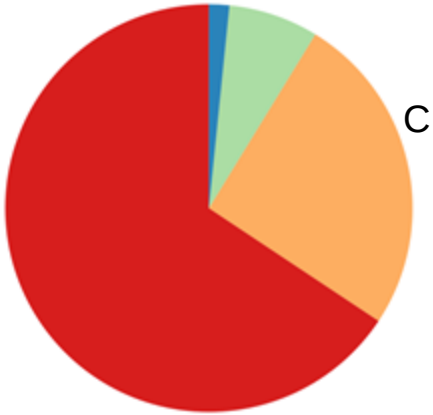
700 genomes from each species, matched over time and geography



Lower polyclonality within infections in Guyana for *P. falciparum vs. P. vivax*

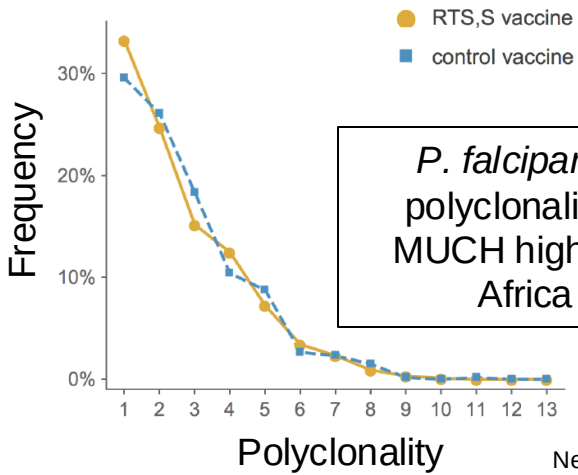


P. falciparum



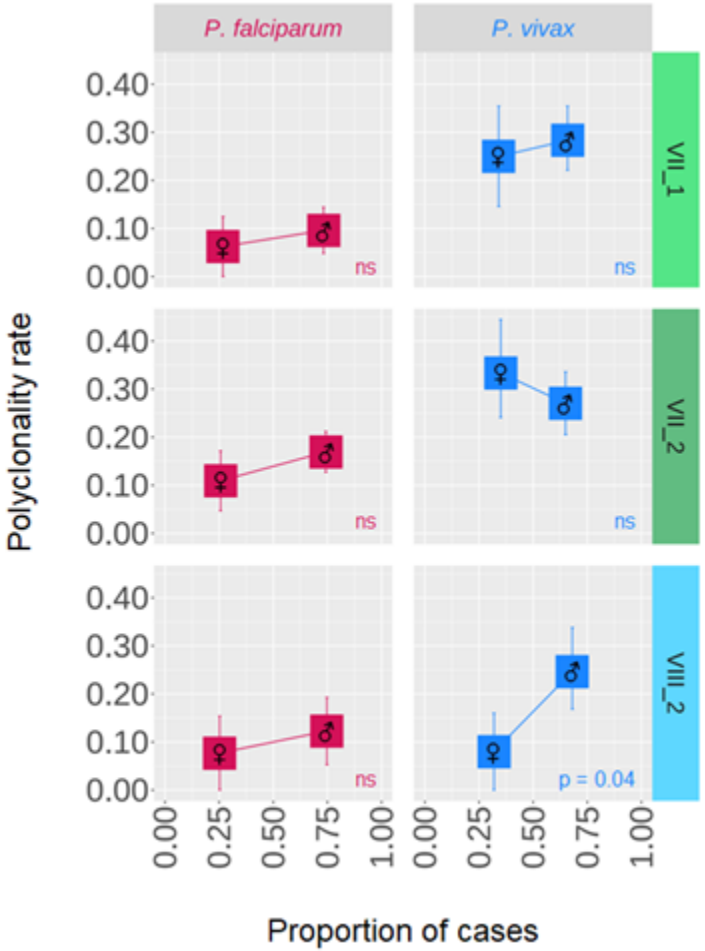
P. vivax

Hypothesis: Lower *P. falciparum* transmission, as well as relapse of *P. vivax* infections, cause higher polyclonality in *P. vivax* infections



P. falciparum polyclonality is MUCH higher in Africa

Neafsey et al. 2015



Polyclonal infections are typically more common in males than females for both parasite species

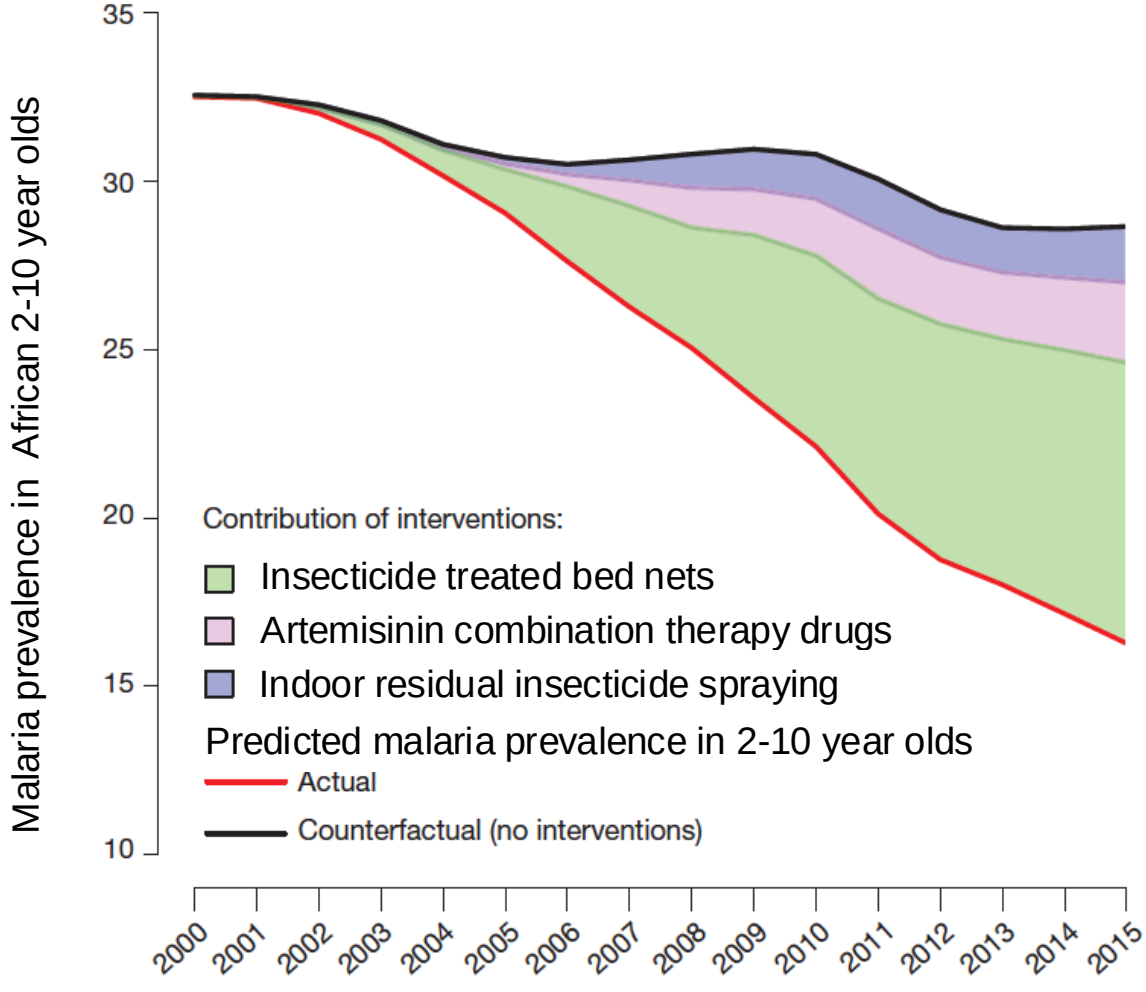
Polyclonality varies by geographic region in *P. vivax*

Why do mosquito genomes matter for malaria?

Vectors are evolutionarily dynamic.

Understanding vectors is important for targeting effective control.

Malaria elimination progress depends on effective drugs and insecticides



Bhatt et al. 2015

Disease transmission competence is a complex trait

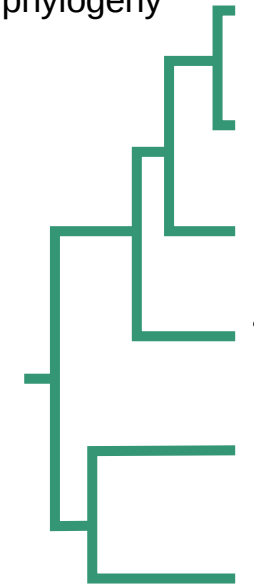
- Biting behavior (time/location)
- Immunity

- Insecticide resistance
- Anthropophily (biting preference)
- Ecology

Vectorial Competence

Changes in vectorial capacity happen quickly

Whole-genome consensus phylogeny



An. gambiae

An. coluzzii

An. arabiensis

An. quadriannulatus

An. melas

An. merus

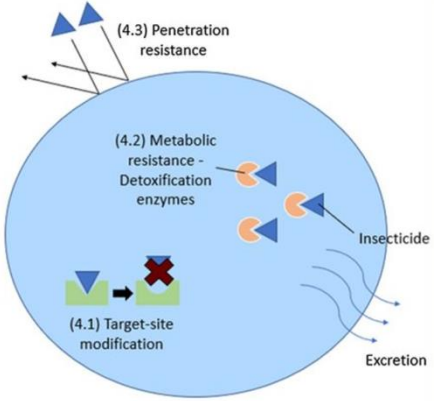
C. Costantini

All thought to be one species until the 1960s

Does *Anopheles darlingi* evolve like *Anopheles gambiae?*

An. gambiae complex
An. funestus comples

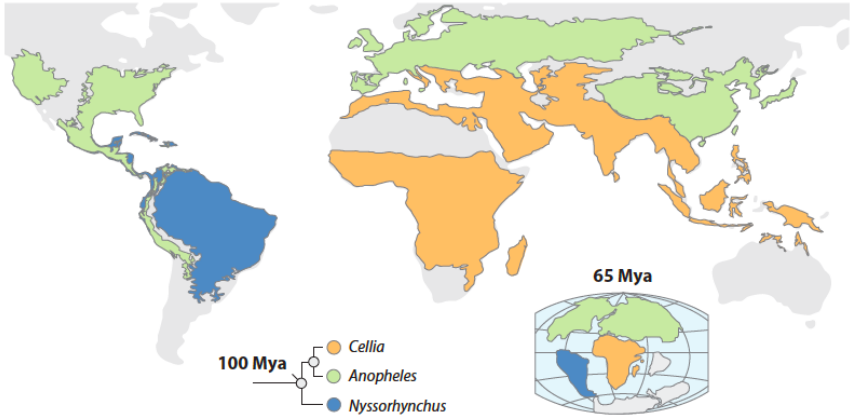
- Semi-isolated cryptic taxa
- High diversity partitioned into large inversions
- Target-site & metabolic insecticide resistance



Gan et al. 2021

An. darlingi

?



Molina-Cruz et al. 2016

Anopheles darlingi sampling

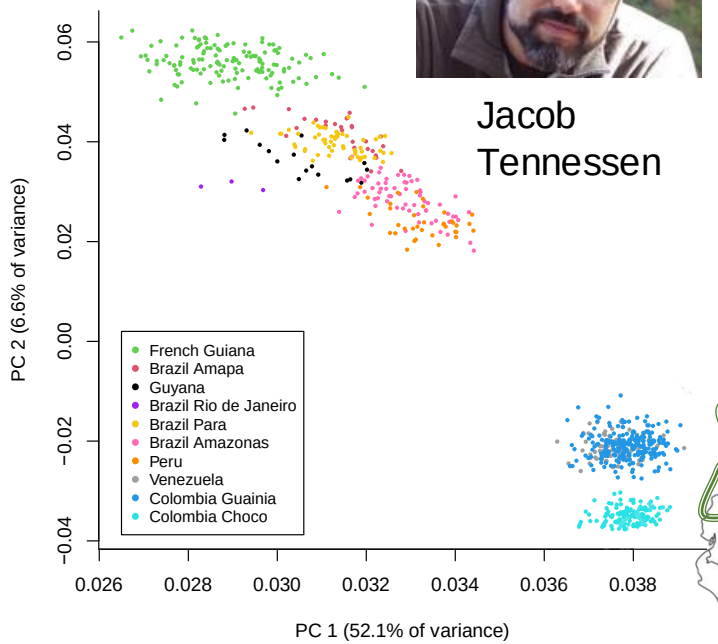
Collection:
Mathilde Gendrin, Martha Quiñones, Jan Conn, Maria Eugenia Grillet, Maria Anice Mureb Sallum

Country	Location	N	N ≥8×	Median Coverage
French Guiana	Blondin	73	73	42×
French Guiana	Cacao	39	39	44×
French Guiana	La Césarée	27	27	46×
Guyana	Georgetown	18	17	20×
Brazil	Calçoene	45	29	10×
Brazil	Peixe-Boi	63	59	17×
Brazil	Manacaparu	54	11	4×
Brazil	Barcelos	46	25	8×
Brazil	Coari	59	28	7×
Brazil	Juturnaiba	6	3	7×
Peru	Loreto	89	37	4×
Venezuela	Sifontes	77	35	7×
Venezuela	Morichalito	49	45	20×
Colombia	Guainía	265	244	33×
Colombia	Chocó	184	143	18×

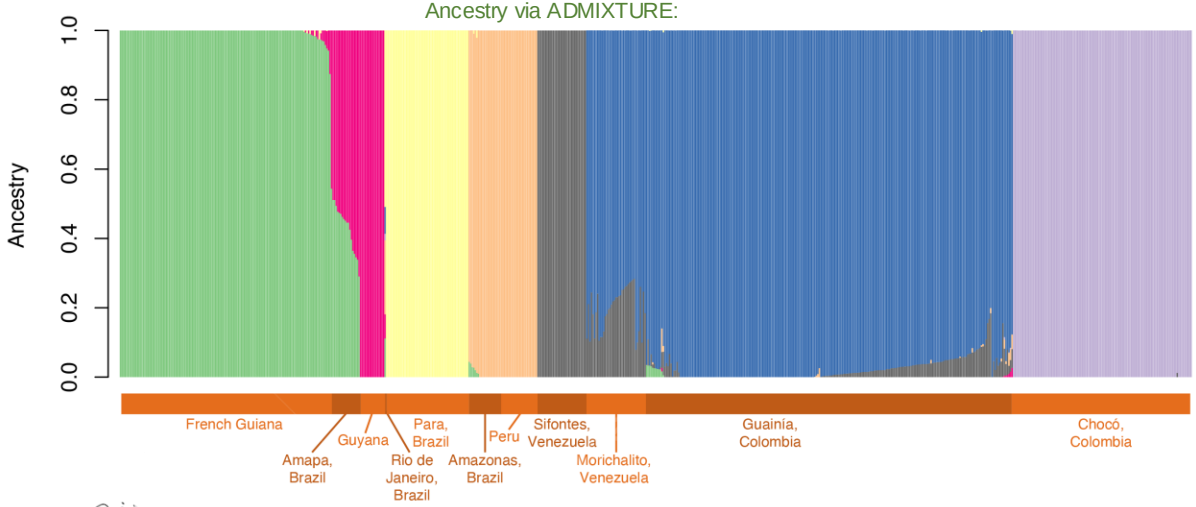
1094 total
815 ≥8× depth

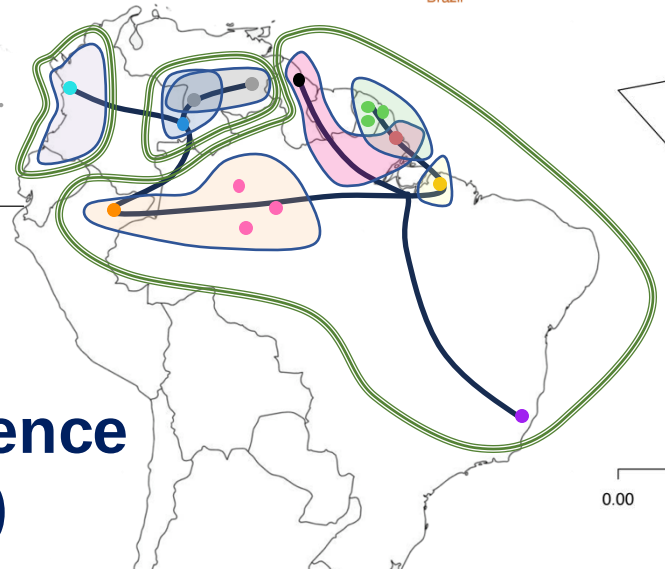
Jacob Tennessen

PCA:

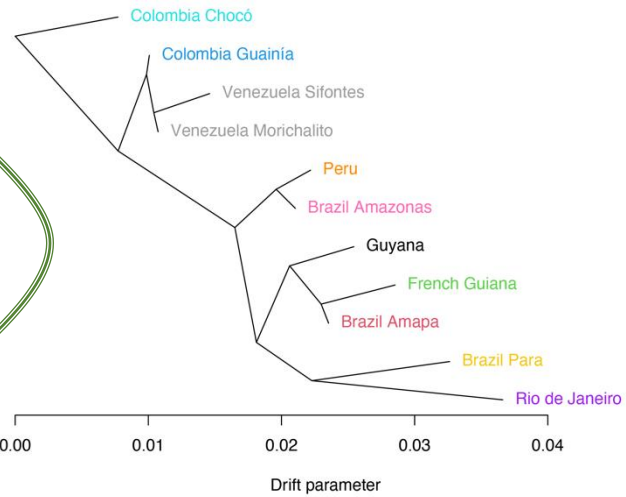


Ancestry via ADMIXTURE:



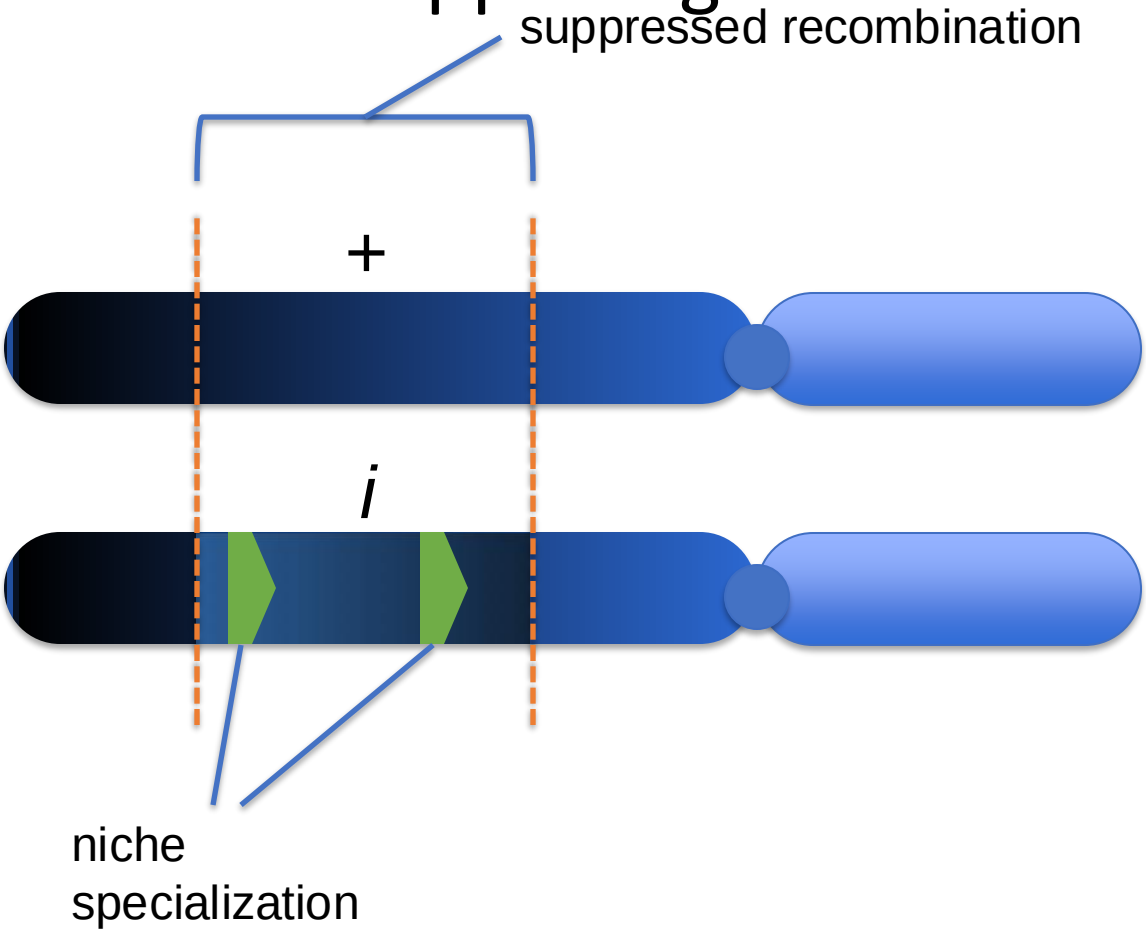


TreeMix:

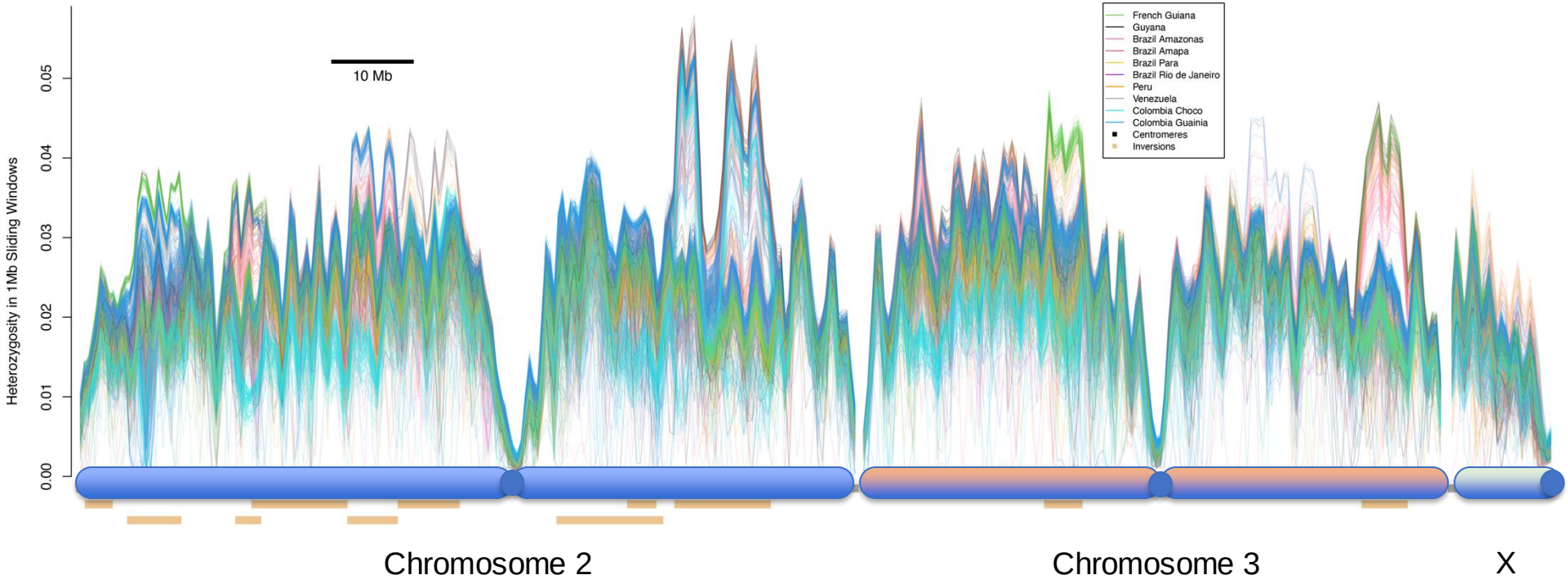


Strong population structure (but no evidence of cryptic species)

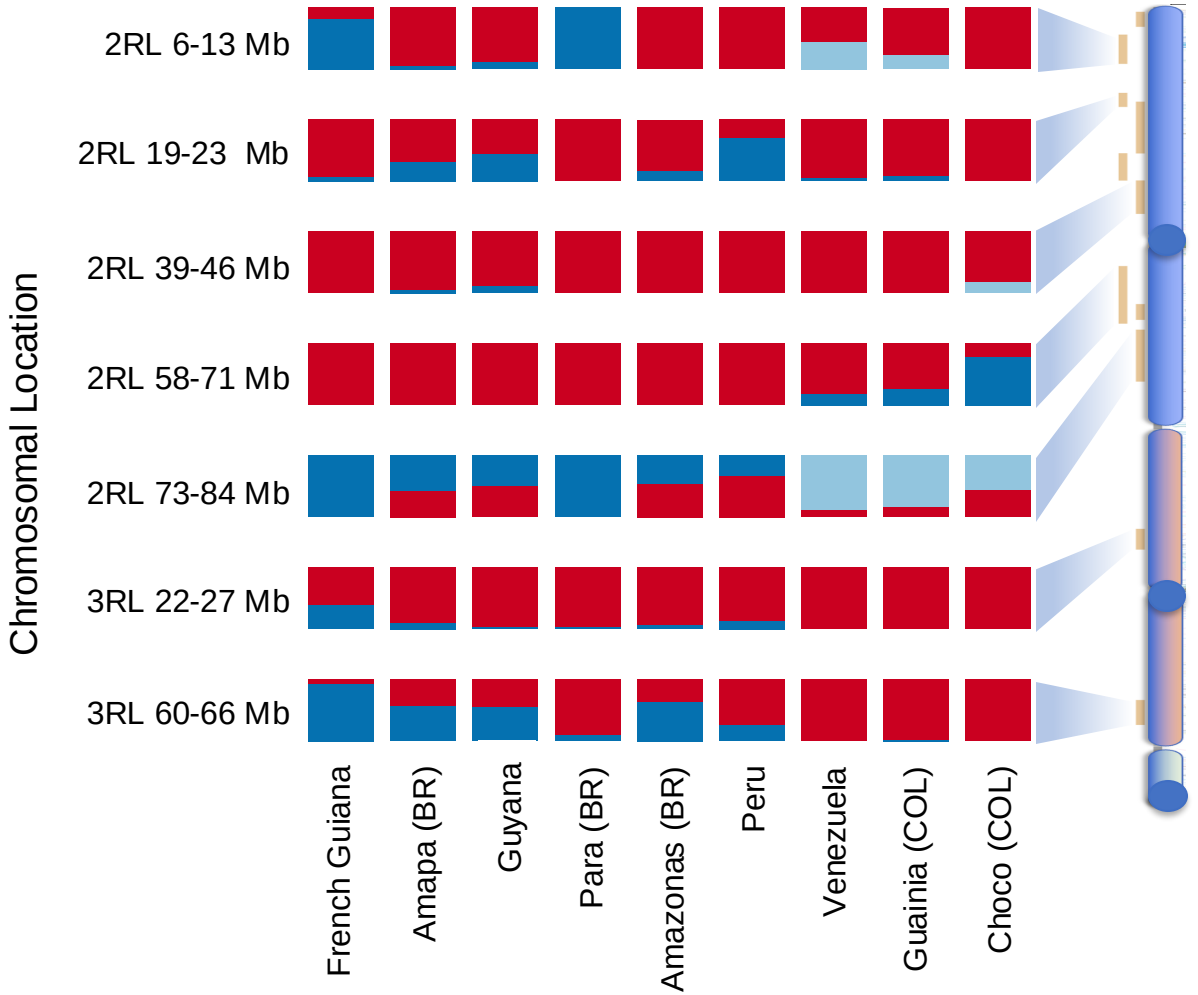
Inversions suppress gene flow locally



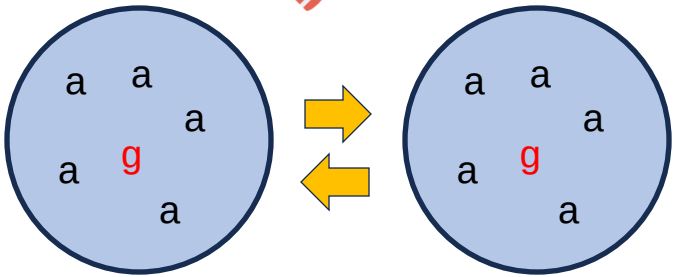
High genetic diversity across the genome, especially in inversions

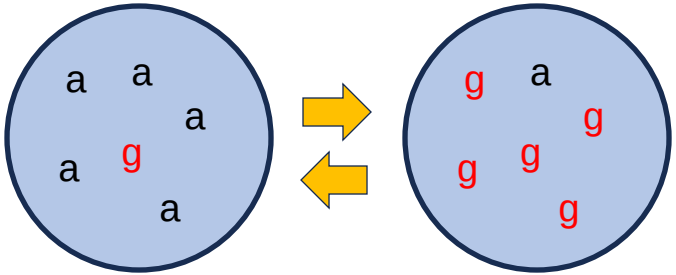


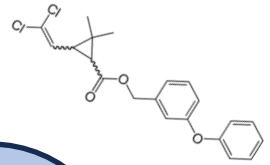
Inversions vary markedly in frequency across geographic locations; natural selection?



Detecting natural selection from genomic divergence

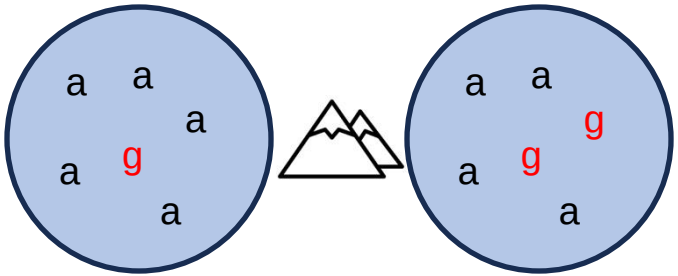






FAST Divergence

Often caused by natural selection

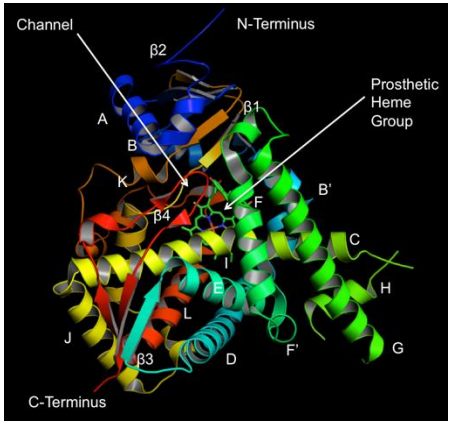


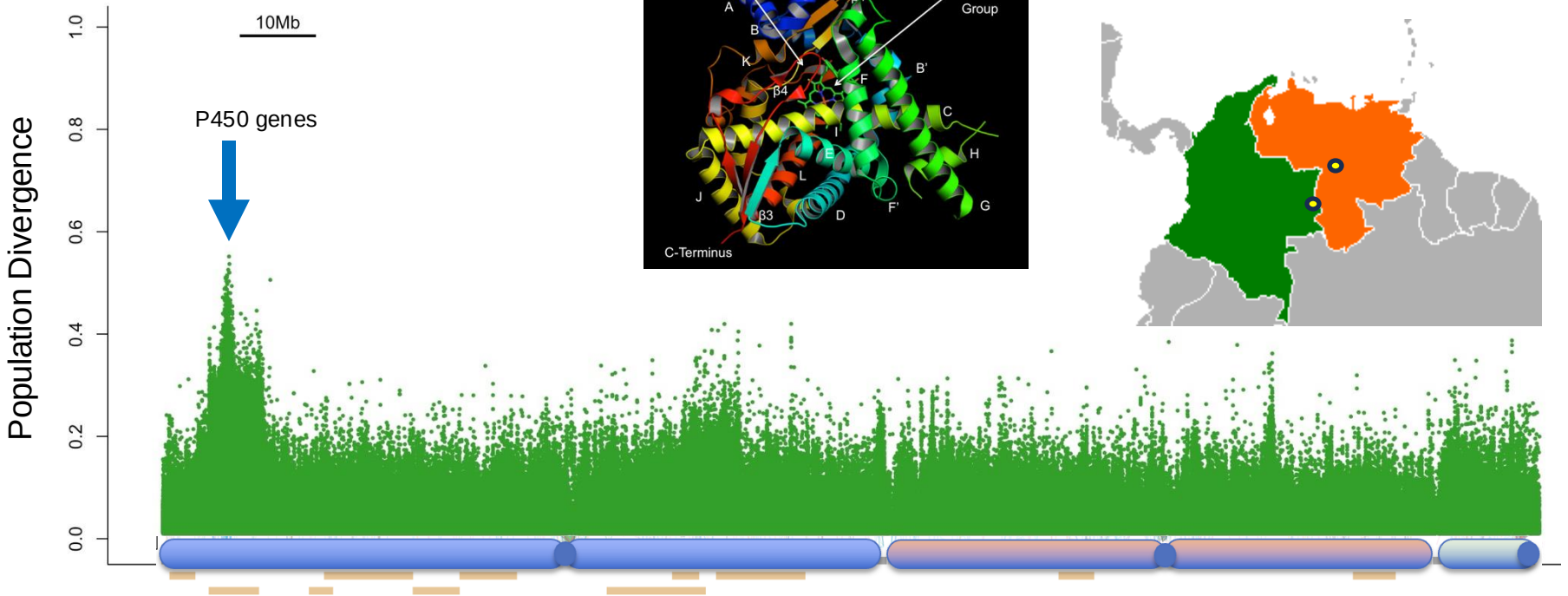
"genetic drift"

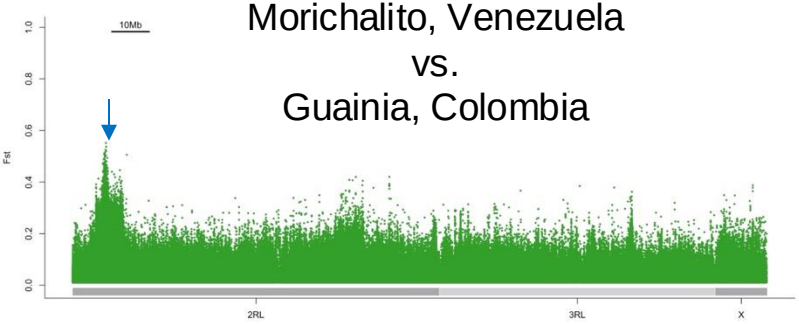
(slow divergence)

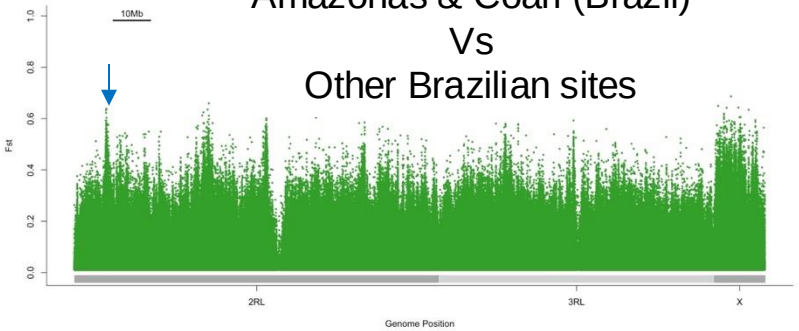
Genomic divergence near a P450 gene cluster within inversion

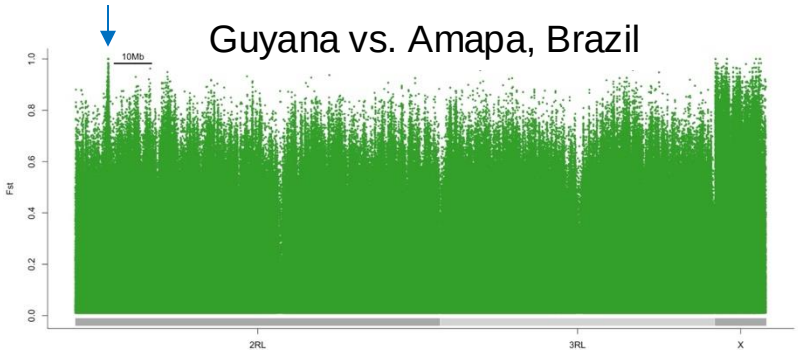
Morichalito, Venezuela
vs.
Guainia, Colombia

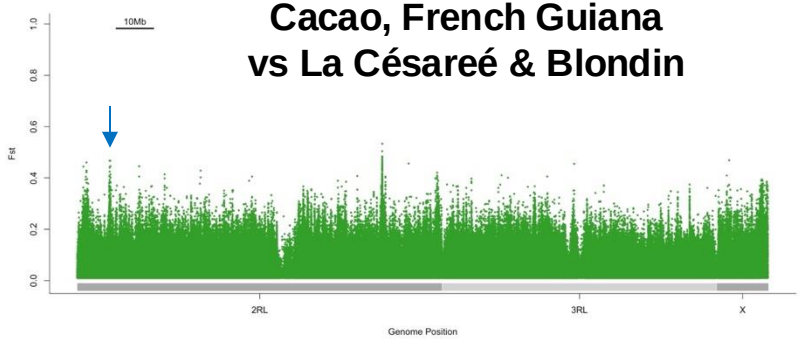












Similar p450 selection signals in other populations

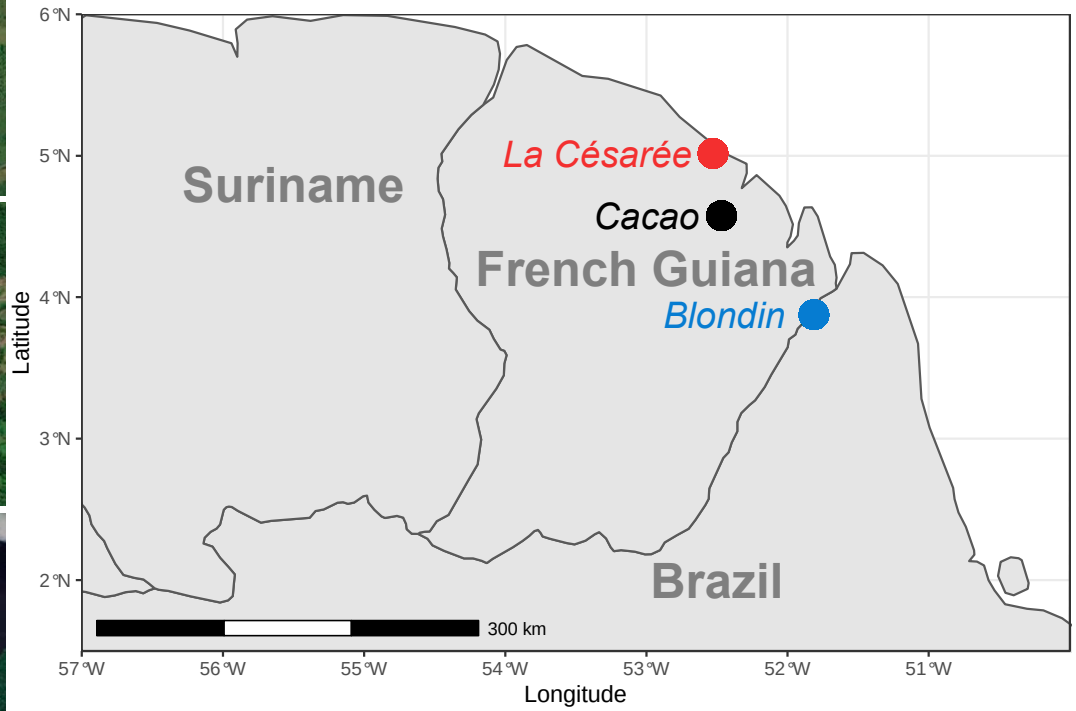
<u>But, NO</u> polymorphisms at insecticide target sites:

vgsc L995 (*kdr*)

rdl A296

ace1 G280

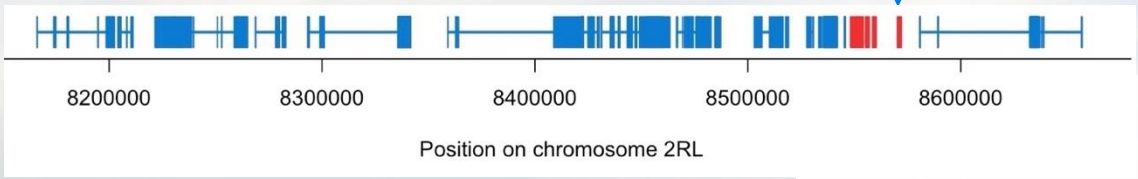
French Guiana: a clue to selection?



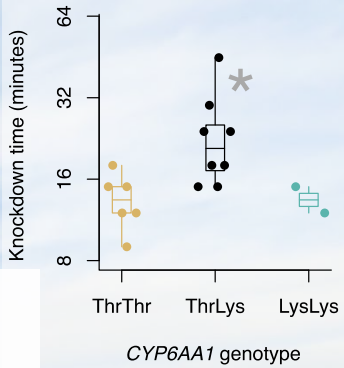
P450 gene

Other gene

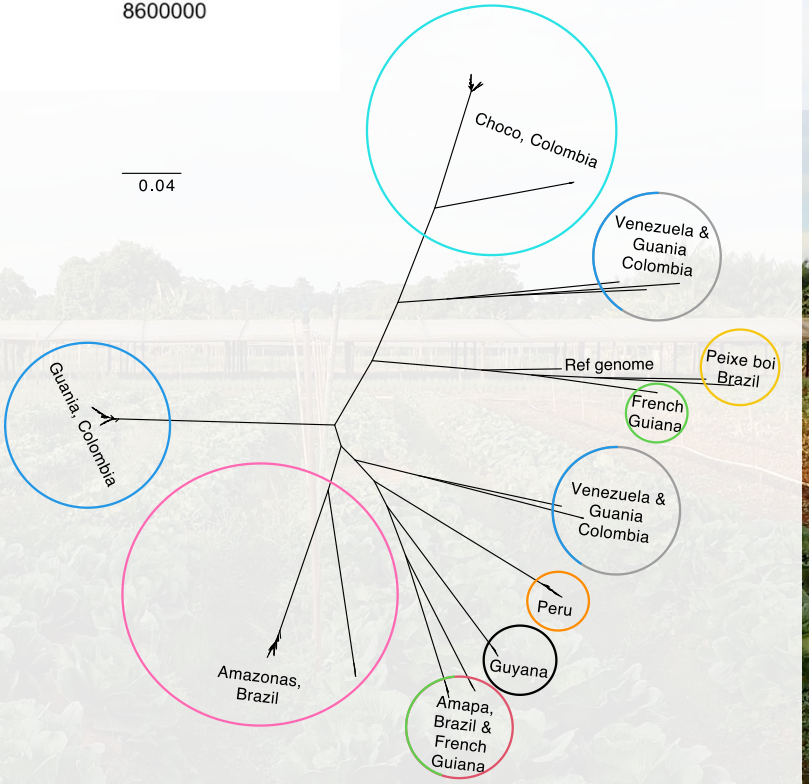
Thr-Lys in *CYP6AA1*
33% frequency in Cacao
0% frequency elsewhere



Jean-Bernard Duchemin



Insecticide resistance is evolving independently in localities across South America.



Summary

	An. gambiae complex *An. funestus* complex	*An. darlingi*
Widespread across continent	✓	✓
Exceptionally high diversity	✓	✓
Large inversions	✓	✓
Sympatric cryptic taxa	✓	✗
Pop gen patterns driven by anthropophily	✓	✗
Target-site insecticide resistance	✓	✗
Metabolic insecticide resistance	✓	✓

Thank you!

Neafsey Lab, especially:
Jacob Tennessen
Raphael Brosula
Angela Early
Annie Laws
Katrina Kelley

Mosquito Sample Contributors:
Estelle Chabanol
Maria Eugenia Grillet
Dionicia Gamboa
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Martha Quiñones
Maria Anice Mureb Sallum
Jorge Moreno
Mathilde Gendrin
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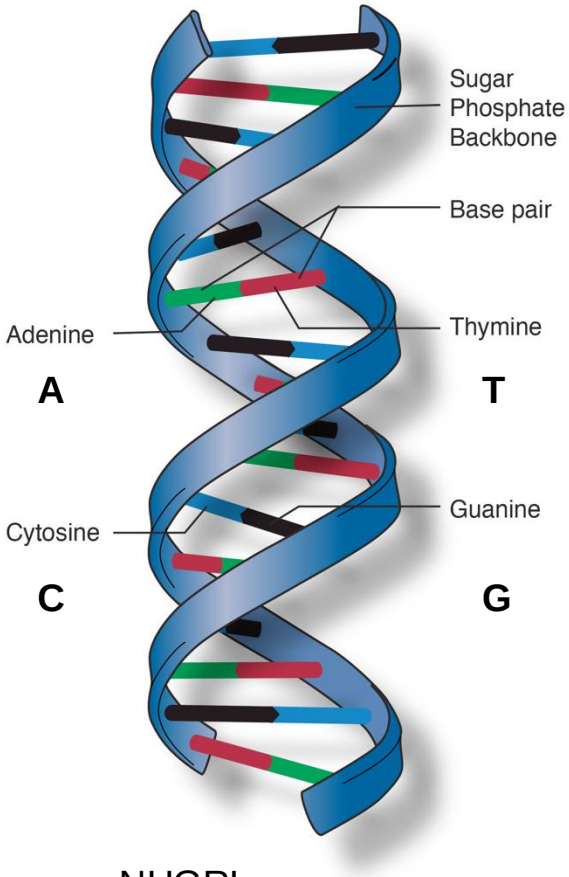
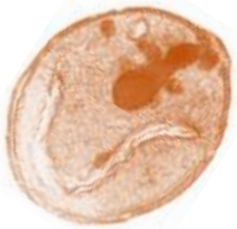
UNIVERSIDAD CENTRAL CARACAS - VENEZUELA
Institut Pasteur de la Guyane
CONSORCIO PARA L INVESTIGACION CIENTIFICA
MINISTRY OF HEALTH GUYANA
anr agence nationale de la recherche AU SERVICE DE LA SCIENCE
UNIVERSIDAD NACIONAL DE COLOMBIA
Center for Communicable Disease Dynamics
BILL & MELINDA GATES foundation
NIH National Institute of Allergy and Infectious Diseases

Every malaria parasite and mosquito cell contains DNA



NHGRI



- *Plasmodium falciparum/vivax*
- ~23 million base pairs (A/T/G/C)
- Haploid (one genome copy per cell)
- 14 chromosomes
- ~5,000 genes

- *Anopheles spp.*
- ~225 million base pairs (A/T/G/C)
- Diploid (two genome copies per cell)
- 3 chromosomes
- 12-15,000 genes