

Population genomics of anthelmintic response in *Onchocerca volvulus*

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Postdoctoral Fellow

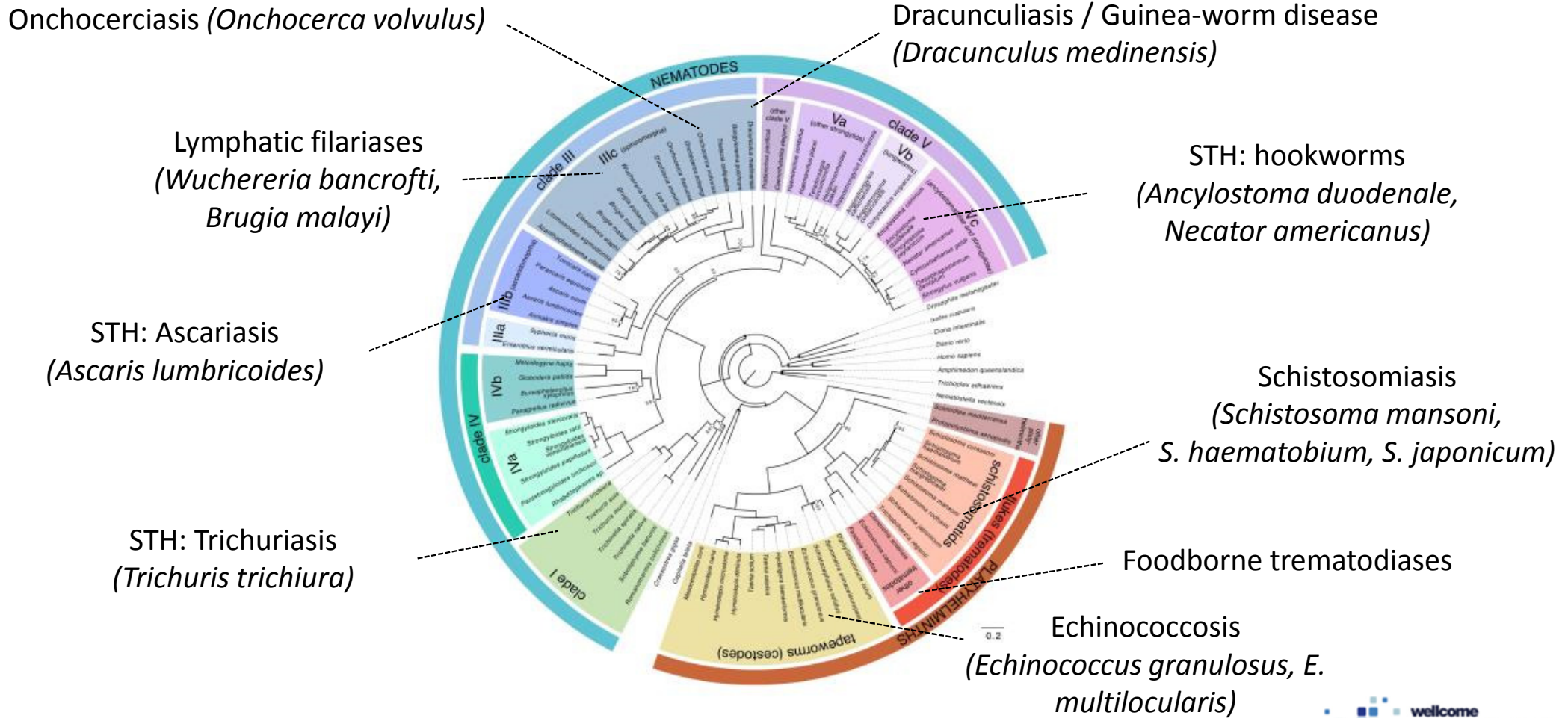
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Genetic diversity of NTD pathogens, LCNTDR

23 May 2018, Natural History Museum, London

Genomic resources are increasingly important for NTD research



Genomic resources are increasingly important of NTD research

WormBase ParaSite


Version: WBPS10 (WS263)

Search WormBase ParaSite...


e.g. *O. volvulus*, PRJNA60051, WBGene00262434, Bma-eat-4, eat-4 or metallopeptidase

Genome List BLAST BioMart REST API VEP Downloads WormBase Login Register Help and Documentation


Genomes




BLAST




BioMart




API



Downloads



WormBase



Find a genome

[\[+\] Nematoda \(Roundworms\)](#)

[\[+\] Platyhelminthes \(Flatworms\)](#)

Statistics

- Version: WBPS10 (March 2018)
- WormBase Version: WS263
- 138 genomes, representing 118 species

Announcements

[Announcing WormBase ParaSite 10](#)

posted 1 month ago by [Wojtek Bazant](#)

We are pleased to announce the tenth release of WormBase ParaSite. We have included genomes of four new species, bringing the total number of genomes to 138, representing 118 distinct species, and updated the assemblies or annotations of an additional four. This includes results of recent efforts to sequence Ascaridae genomes (Wang et al, 2017): [\[read more\]](#)

Blog

[What would you like to learn about in our BSP workshop?](#)

posted 2 months ago by [fayerodgerssanger](#)

We're looking forward to presenting a workshop at the upcoming BSP Spring meeting in Aberystwyth. To help us prepare, we'd love to know what our users would find most useful for us to cover. Please fill in our quick survey (one question only!): <https://www.surveymonkey.co.uk/r/8LYF2YW>

[Announcing WormBase ParaSite Release 9](#)

posted 1 year ago by [Bruce Boll](#)

We are pleased to announce the ninth release of WormBase ParaSite. In this release, we have included genomes for two new species and an additional alternative genome for one species. Additionally, we have introduced a new genome browser: JBrowse.


[Parasitic Nematodes: Bridging the Divide workshop abstract solicitation](#)

posted 1 year ago by [michaelpaulin](#)

As part of the 21st International C.elegans conference, we would like to solicit contributions to the workshop on parasitic nematodes. We are pleased to invite student and postdoc abstract submissions for 5 minute lightning talks to be presented at the NSF-sponsored, 3rd Parasitic Nematodes: Bridging the Divide workshop. We encourage submissions that address the broad [\[read more\]](#)

Twitter

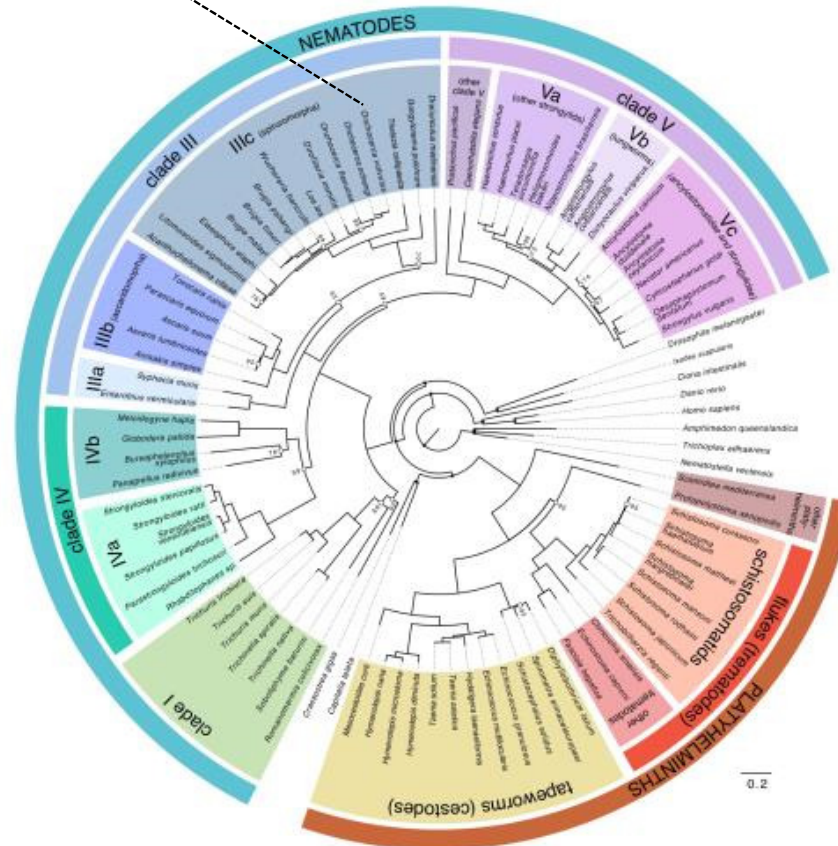
[Tweets by @WBParasite](#)



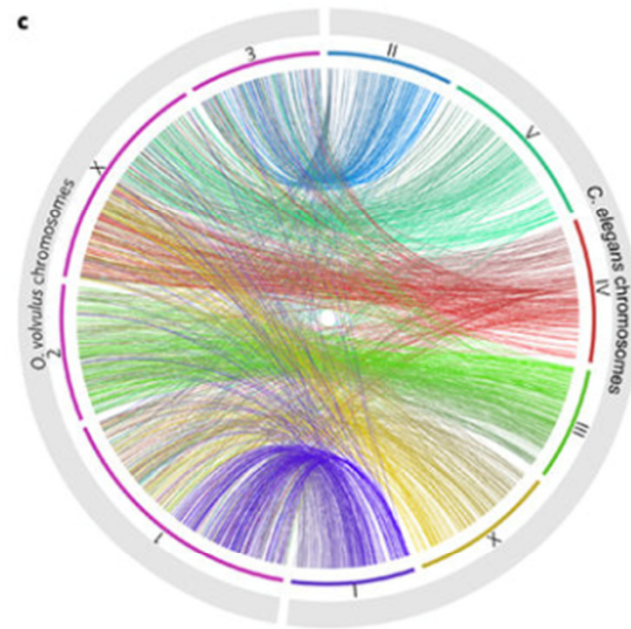
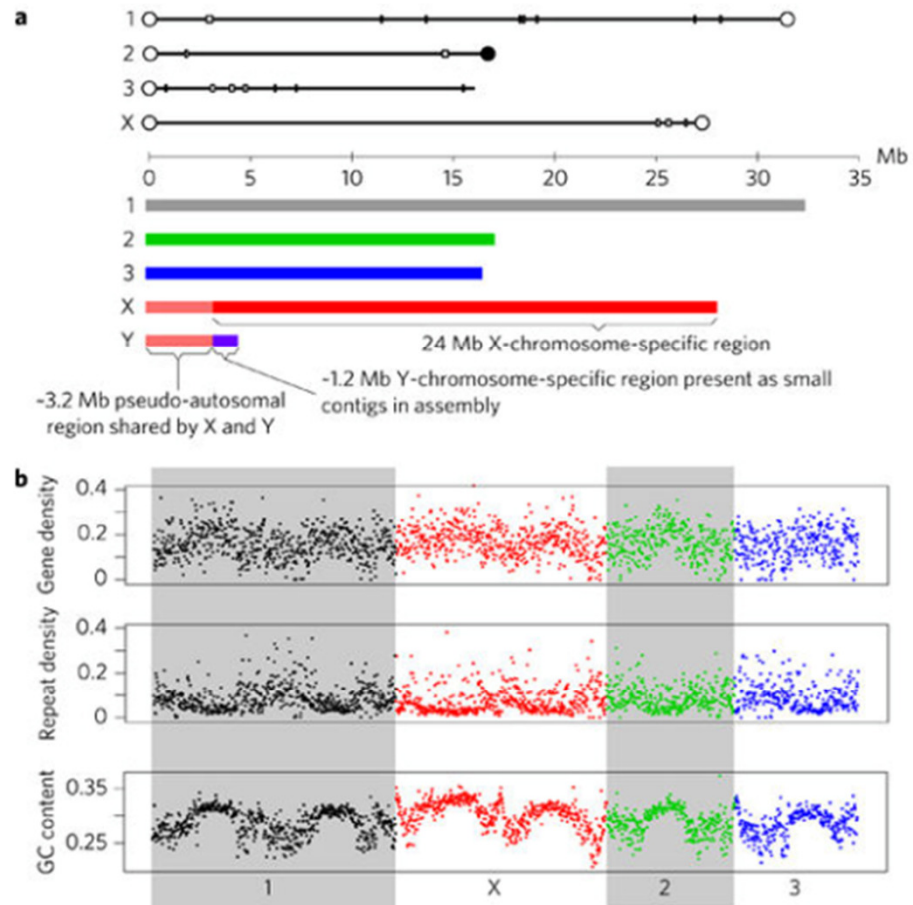
wellcome
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Onchocerca volvulus, agent of river blindness

Onchocerciasis (Onchocerca volvulus)



Complete genome of *Onchocerca volvulus*



Onchocerca volvulus, agent of river blindness

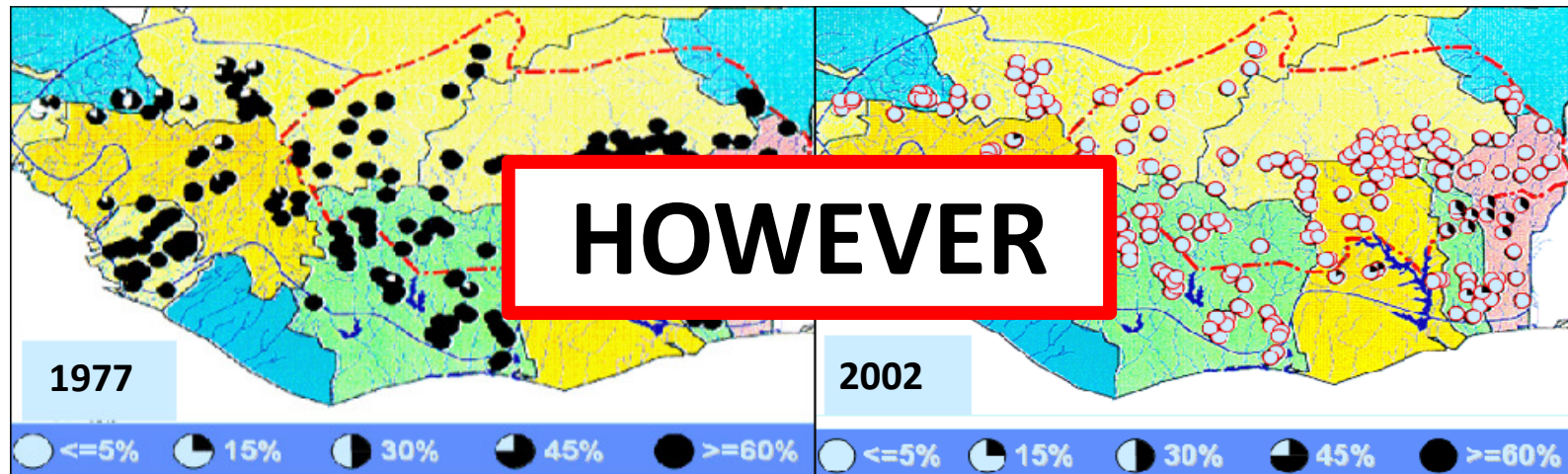


- Adults are long living: < 15 yrs
- Intermediate host: Blackfly
- Prepatent period: 12-18 mths
- Causes severe **morbidity**



Anthelmintic control using the macrocyclic lactone, ivermectin

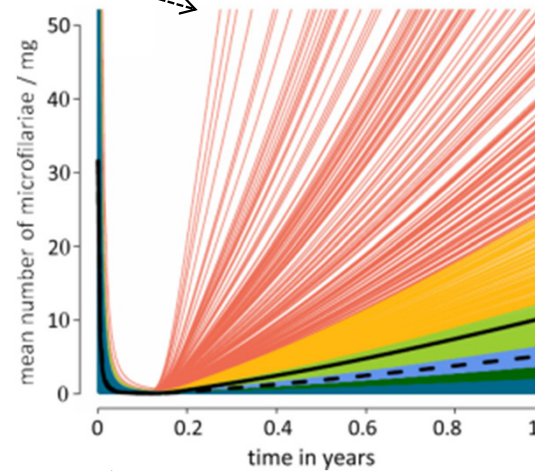
- Target: Glutamate-gated chloride channels
- Effect: Does **not** kill adult worms....
 - >99% of microfilaria disappear
 - Inhibits reproduction
 - Interrupts transmission



Phenotypic variation in ivermectin response by *O. volvulus*

Sub-optimal or atypical response

- HOST: High skin microfilaria density
- HOST: Faster repopulation rates
- PARASITE: embryograms show live / developing microfilaria



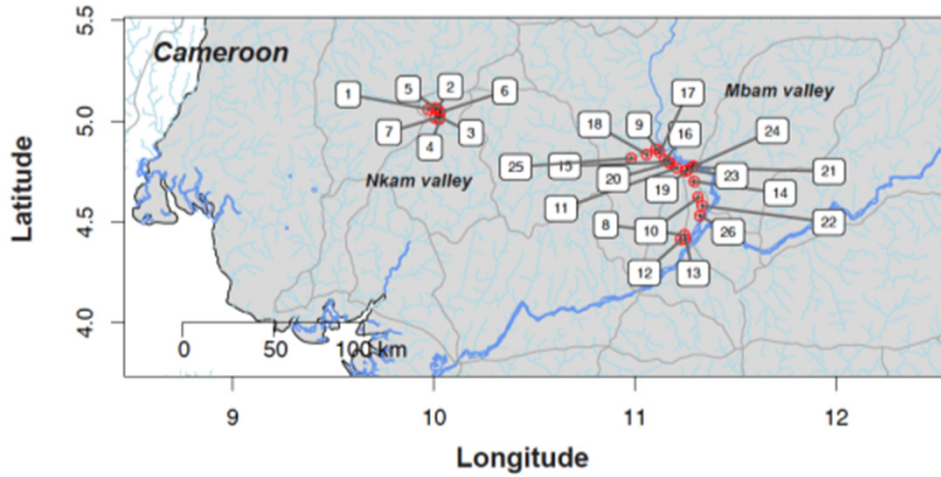
Ivermectin

Susceptible response

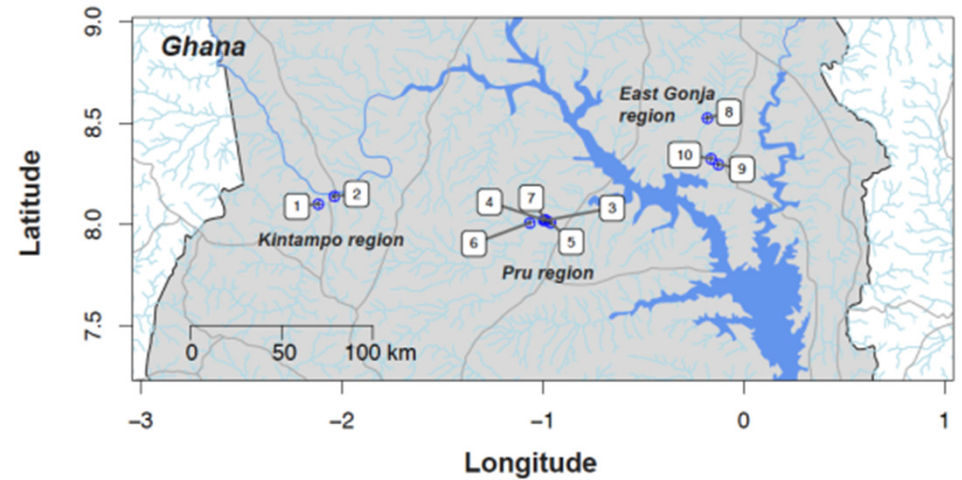
- HOST: Low skin microfilaria density
- HOST: Slower repopulation rates
- PARASITE: Embryograms are clear or show only degenerate microfilaria

Sampling and experimental design

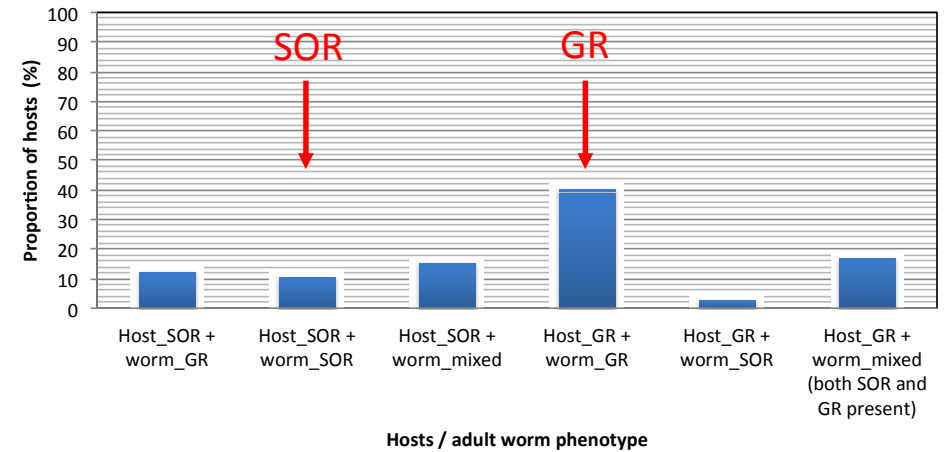
(Gardon et al., 2002; Nana-Djeunga et al., 2014; Pion et al., 2013)



(Osei-Atweneboana et al., 2011; Osei-Atweneboana et al., 2007)

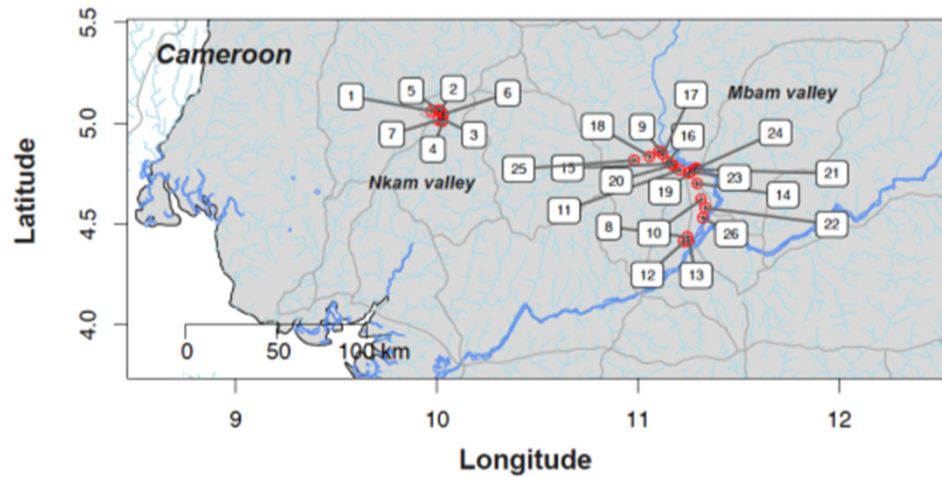


Phenotype	Defined at the host level (microfilarial (mf) density in skin determined by skin snip)	Defined at parasite level (intra-uterine microfilariae determined by embryogram of adult female parasites)
Good response (GR)	Day 0 ^a : < 25 mf/mg skin Day 80/90 ^b : 0 mf/mg skin Day 180: < 6% of pre-Tx value	Day 80/90 ^b : Viable stretched microfilariae absent <i>in utero</i>
Sub-optimal response (SOR)	Day 80/90 ^b : > 7% of pre-Tx value	Day 80/90 ^b : Viable, stretched microfilariae present <i>in utero</i>

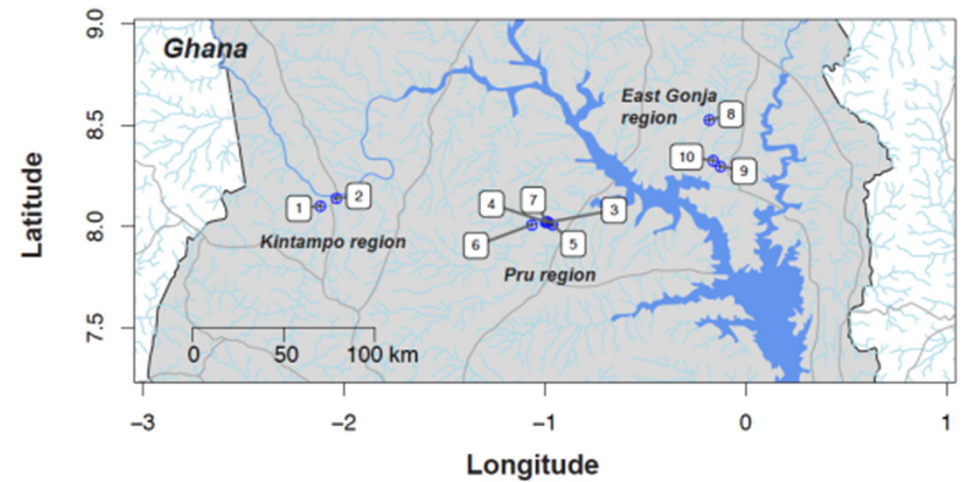


Sampling and experimental design

(Gardon et al., 2002; Nana-Djeunga et al., 2014; Pion et al., 2013)



(Osei-Atweneboana et al., 2011; Osei-Atweneboana et al., 2007)



GR



SOR



Naive



GR



SOR



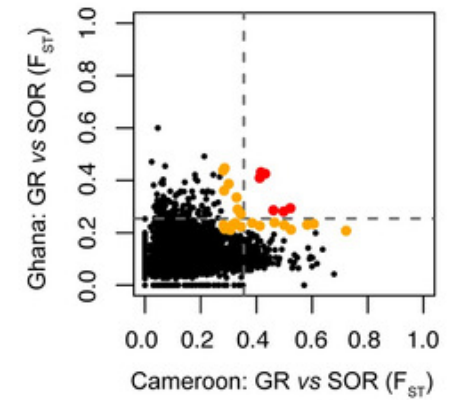
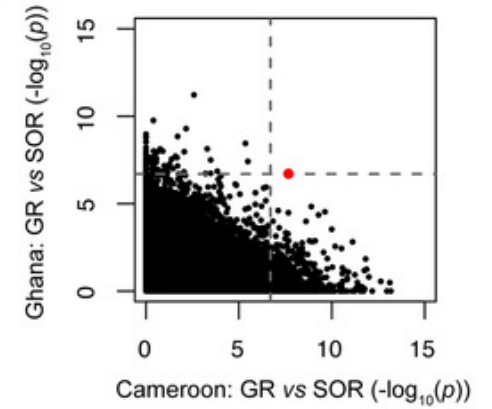
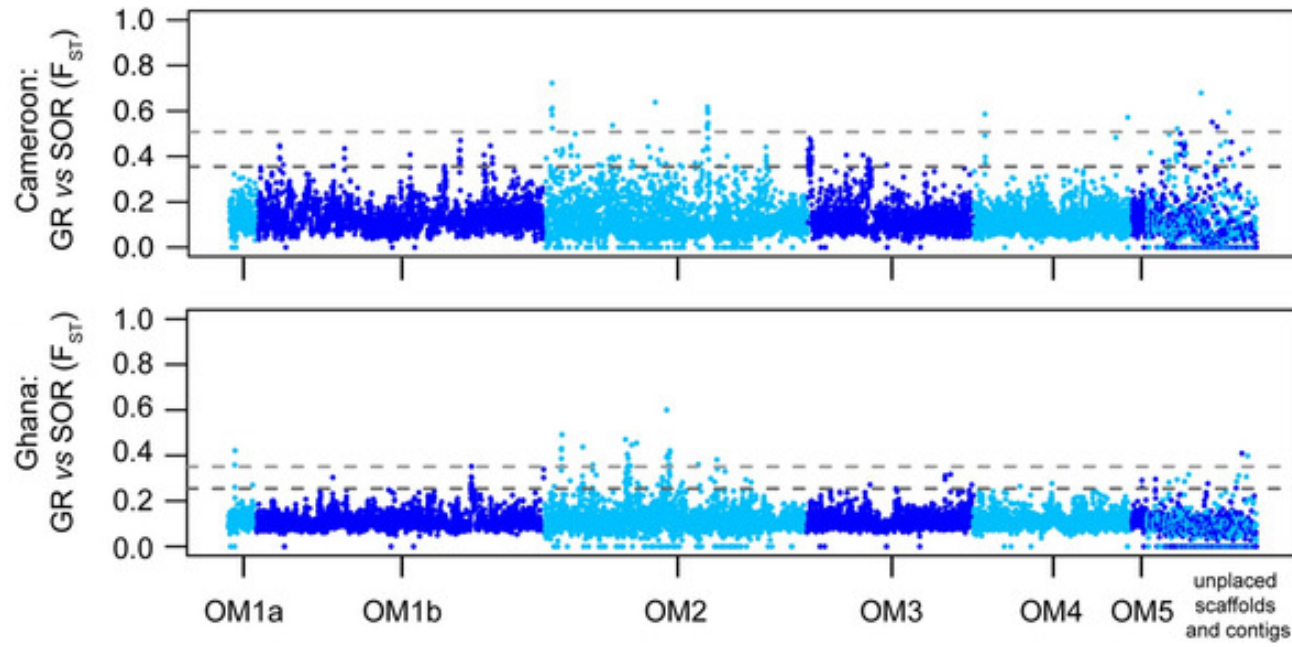
Naive



Sequencing: 15-20 worms per pool, 20-30X coverage for each group (8 lanes GAI, $\sim 280 \times 10^6$ reads)

Analysis: variant read frequency \approx allele frequency, scan genome for regions where GR and SOR differ

Genome-wide variation differentiates phenotypic response

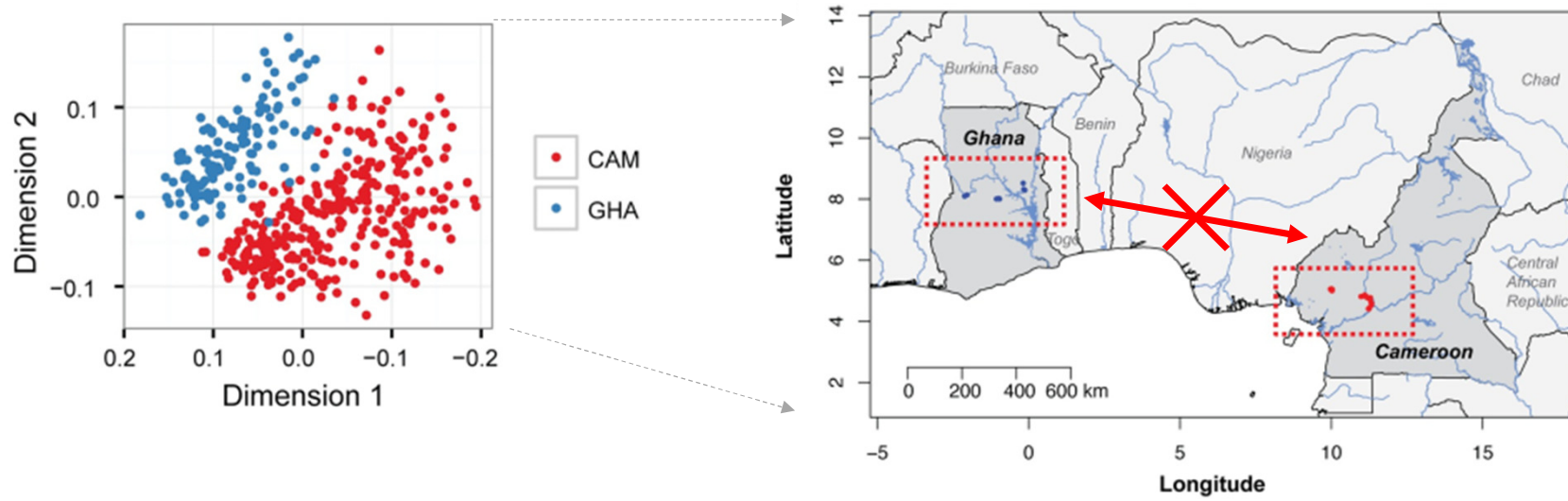


Enrichment of genes in a limited number of functional pathways

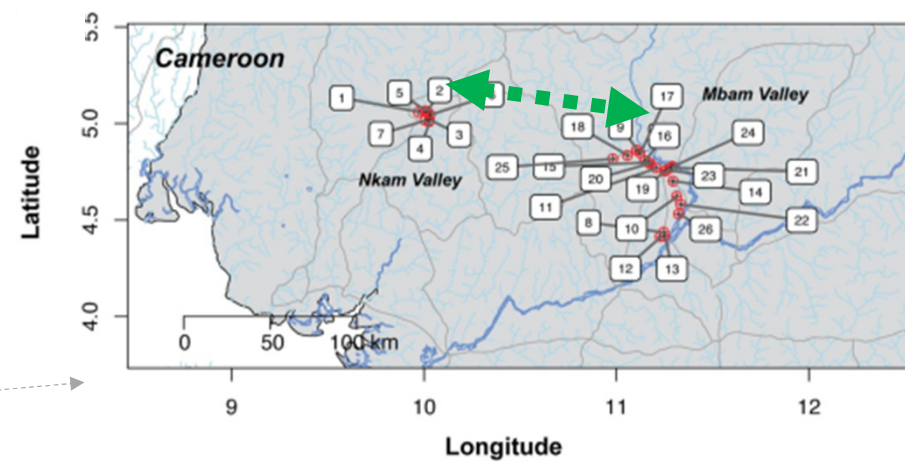
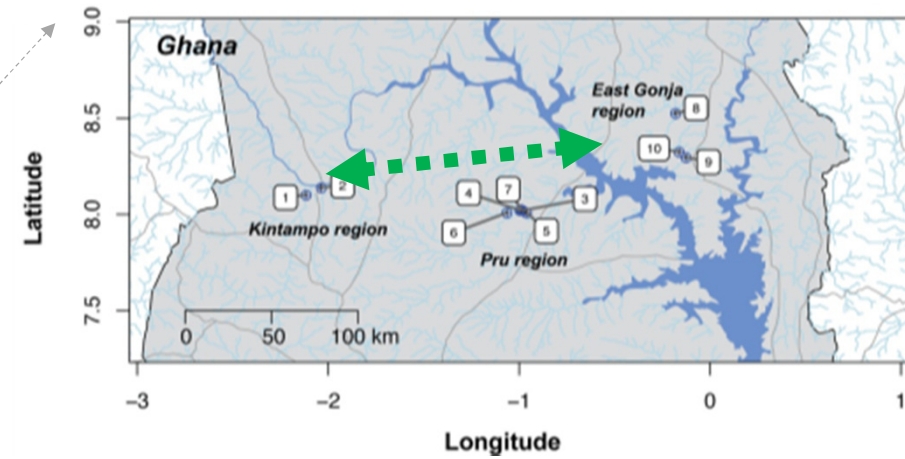
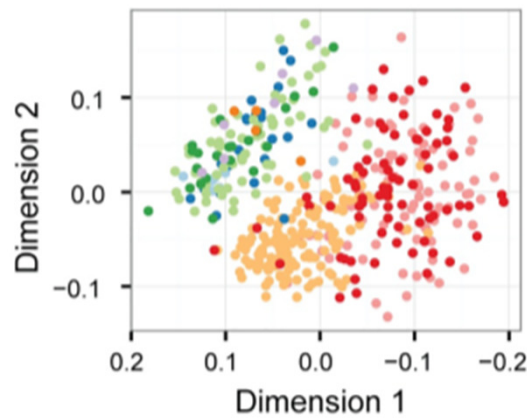
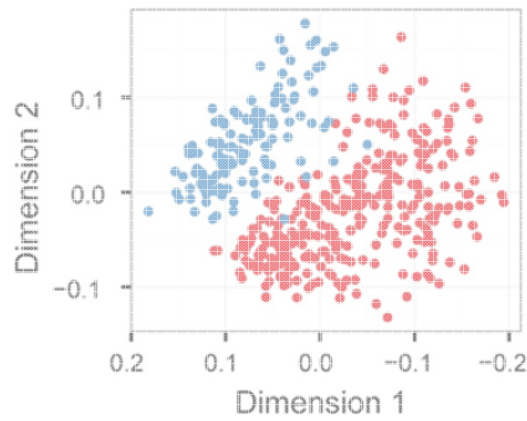
- Known IVM sensitivity alleles
 - *unc-44, klp-11, inx-5*
- Neurotransmission, particularly ACh
 - ion channels (*acc-1, lgc-46, lgc-47*)
 - acetylcholine synthesis (*cha-1*),
 - transport (*unc-17, aex-3*),
 - regulation (*stg-1, nrfl-1, emc-6, snb-1, nud-1, kin-2, unc-26*)
 - structural (*inx-5*)
- Lipid synthesis (*acs-16, fat-4*) and regulation and storage (*acs-16, math-46, obr-2, cuc-1, sms-1, tat-2*)
- Suppression (*sel-7, bre-5*) or cleavage (*pen-2, crb-1*) of the LIN-12 receptor

Cameroon
Ghana

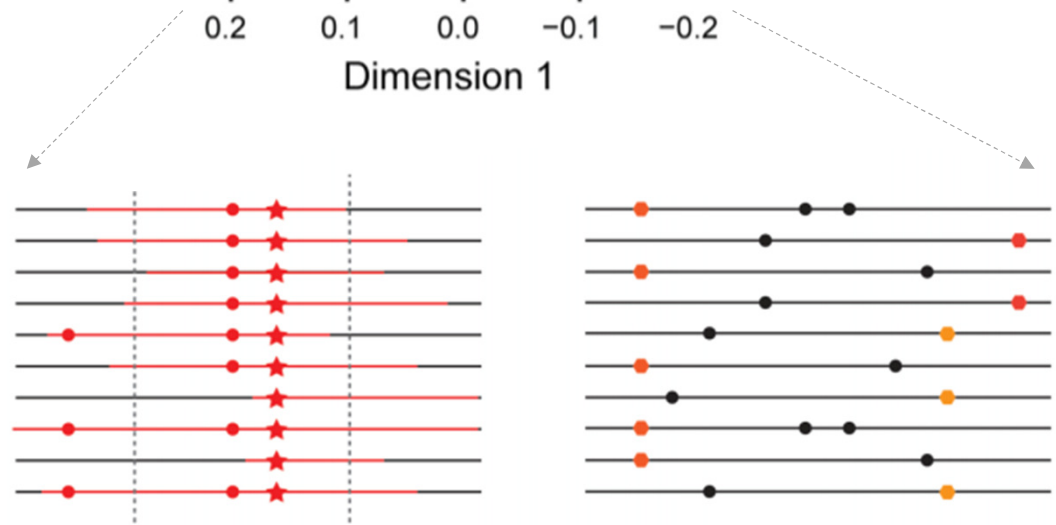
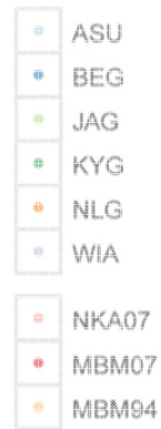
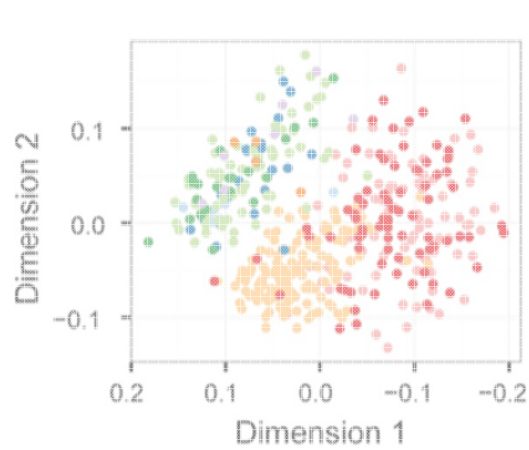
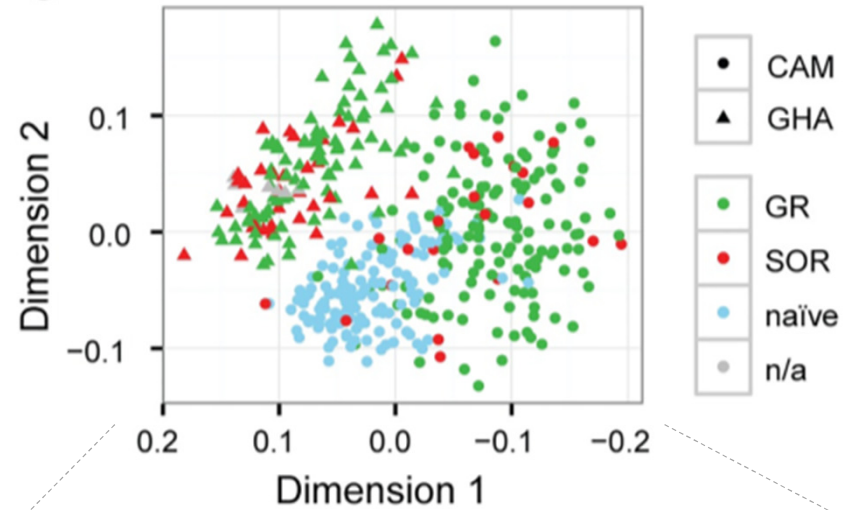
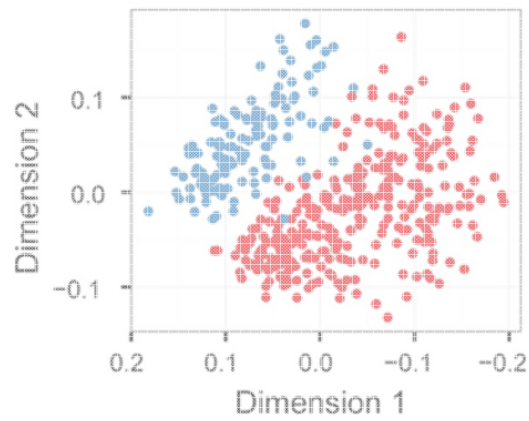
Geography rather than drug response defines population genetic structure



Geography rather than drug response defines population genetic structure



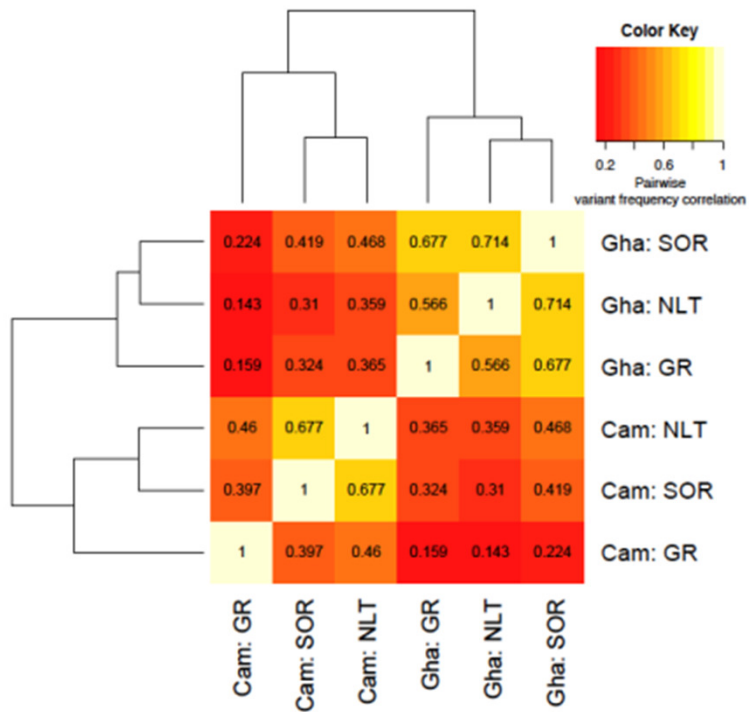
Geography rather than drug response defines population genetic structure



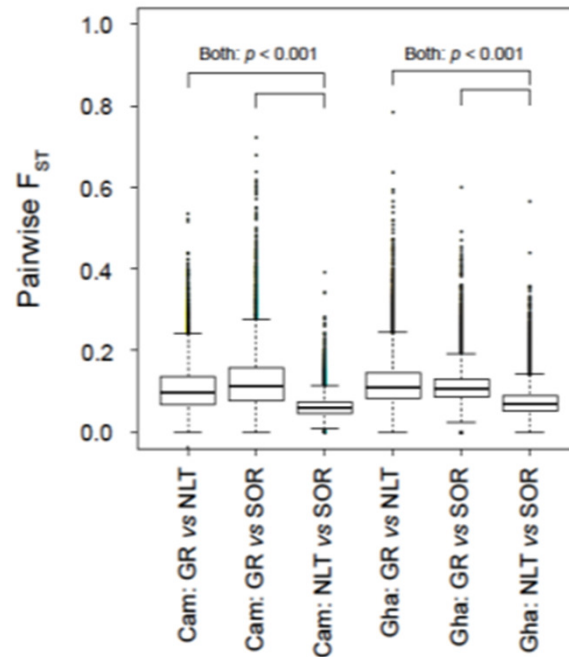
"hard" selection

"soft" selection

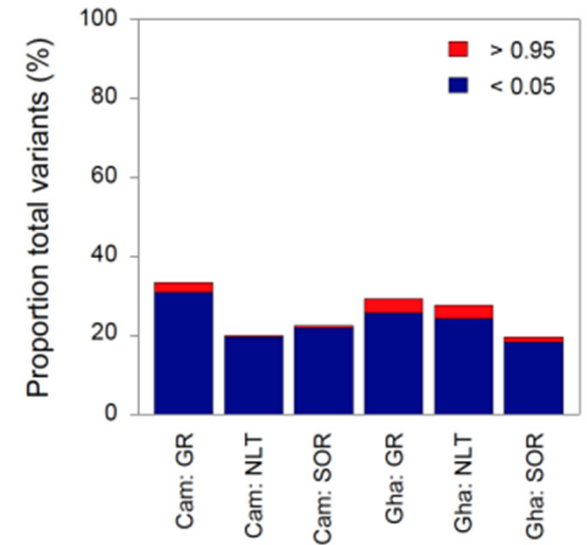
Genetic determinants of SOR are likely derived from pre-treatment standing genetic variation



1. Allele frequency correlation



2. Genetic similarity between groups



3. Proportion of invariant sites

Summary

- Multiple regions of the genome differentiate GR and SOR parasites, and these regions differ between Ghana and Cameroon
 - Consistent with soft- rather than hard-selective sweeps on multiple loci
- Different genes differentiate GR from SOR in each country, but pathways involving neurotransmission & stress response are shared
- Understanding underlying genetic variation and its distribution is critically important in drug response analyses

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Jean Bopda



Mike Osei-Atweneboana
Daniel Boakye

REFOTDE (Cameroon)

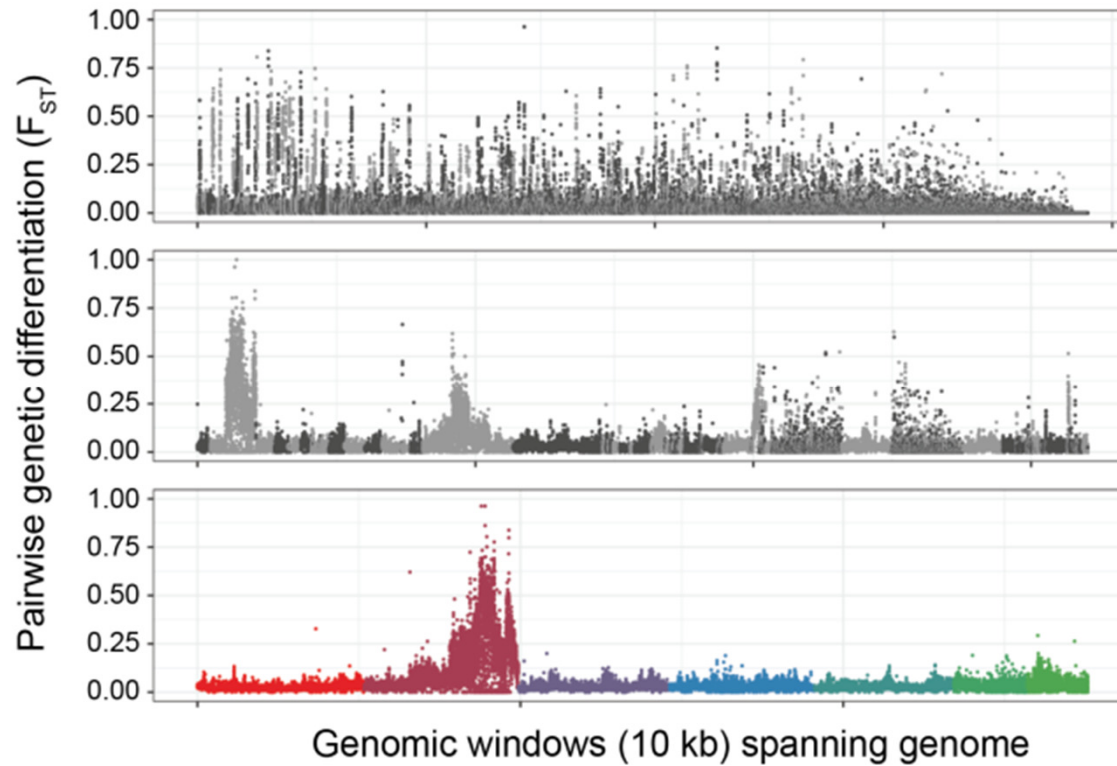
Samuel Wanji
Jonas Kengne-Ouafo



Maria-Gloria Basáñez
Martin Walker



Interpretation of genetic diversity critically relies on a contiguous genome sequence



Published V1 (Laing 2013)

- N50 = 0.083 Mb
- N50(n) = 1,151
- n = 23,860

Intermediate assembly

- N50 = 5.2 Mb
- N50(n) = 16
- n = 6668

Complete chromosomes

- N50 = 47.4 Mb
- N50(n) = 3
- n = 8