BHIVA
British HIV Association

BASHH

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Wellcome Sanger Institute

Disclosures

None

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O25: BASHH, April 2018

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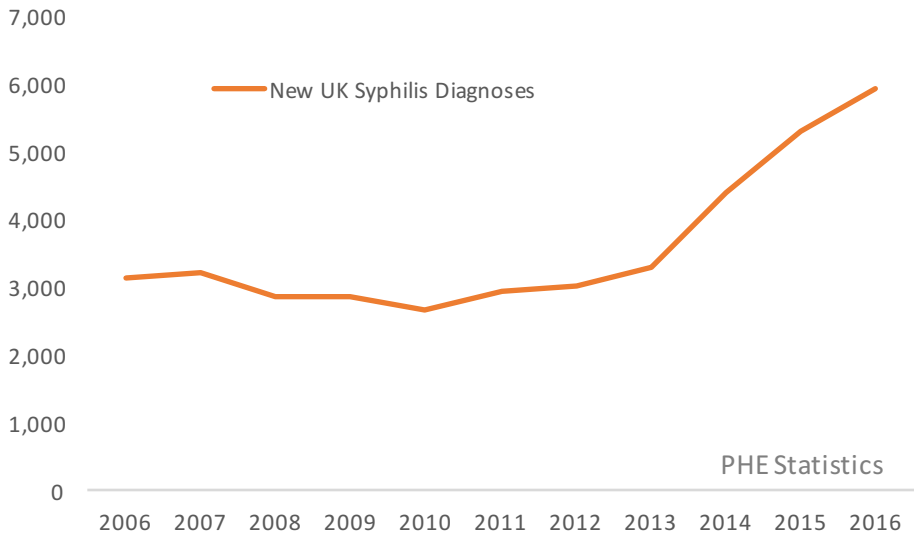
Building a genomic framework for ~~syphilis~~ Treponemas:

Novel approaches to whole genome sequencing



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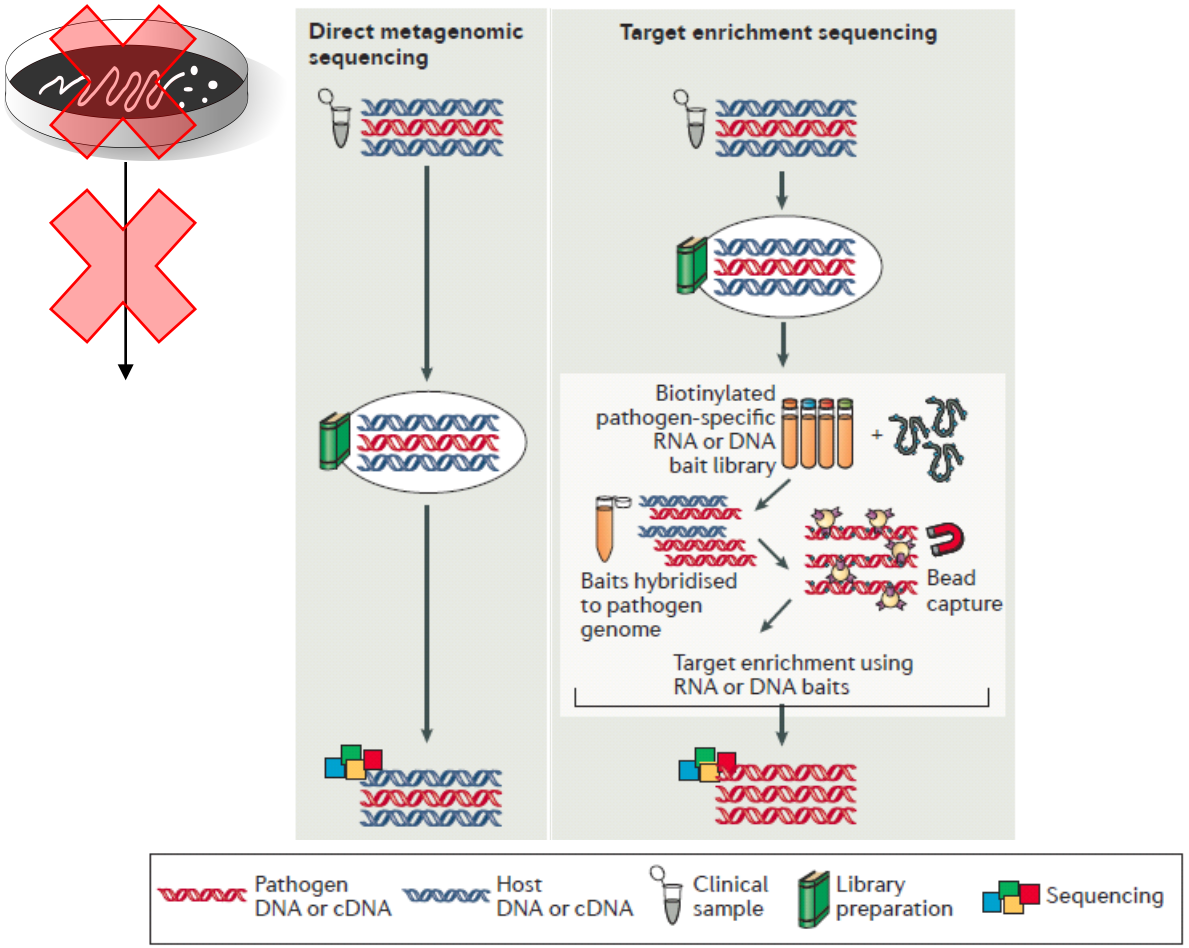
- Treponemas are difficult to sequence
  - Cannot currently be cultured
  - Sequencing must be performed directly on clinical specimens
  - Most of the extract (>95%) will contain host (human) DNA
- New method (target enrichment) now available
  - Enables robust high-throughput sequencing at scale
  - We can use residual samples from Syphilis PCR testing for WGS (some caveats)



Houldcroft, Beale et al. (2017) Nat Rev Micro, doi:10.1038/nrmicro.2016.182

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Spatiotemporal Global Genomic Diversity Study

- Detailed UK based study
- Ongoing project to sequence samples from around the world:
  - N. America
  - Europe
  - Africa
  - Asia
  - South/Central America

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Single Nucleotide Polymorphisms (SNPs)

```
Seq1  GTAAAATAGGCACCATCAAAACGCAGAGGGGAAGACGGGATG
Seq2  GCAAAATAGGCGCCACAGAAACGCAGAGGGGAAGACGGAATG
Seq3  GCAAAATAGGCGCCTCCGAAACGCAGAGGGGAAGACGGGATG
```

- Organisms accumulate genetic variation through natural processes, e.g. drift
- This can be seen when comparing a group of DNA sequences

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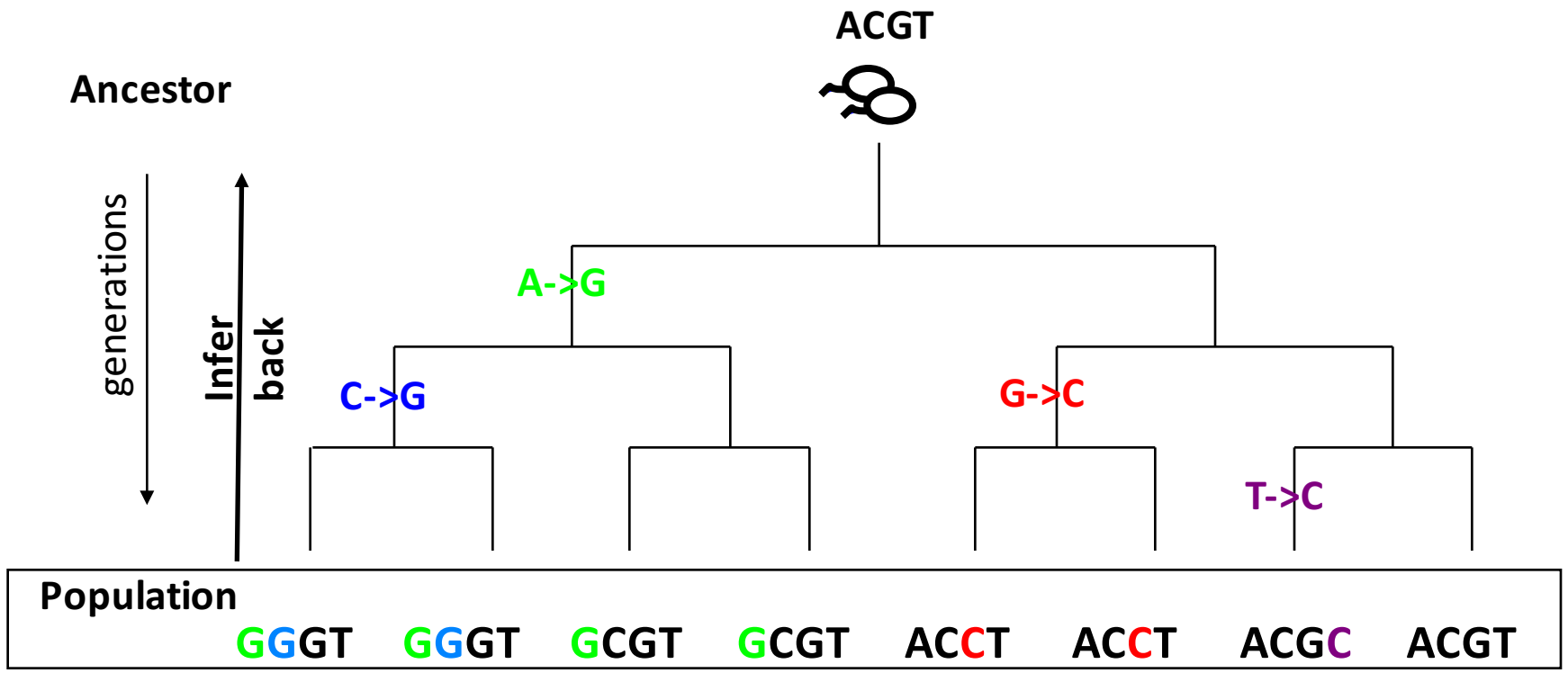
Mutations and population structure



- From a population of sequences we can use SNPs to infer relationships by phylogeny
- We can also infer the state at unsampled 'ancestral nodes'
- Since many SNPs are accumulated at a fixed rate of mutation, we can use this to infer timelines

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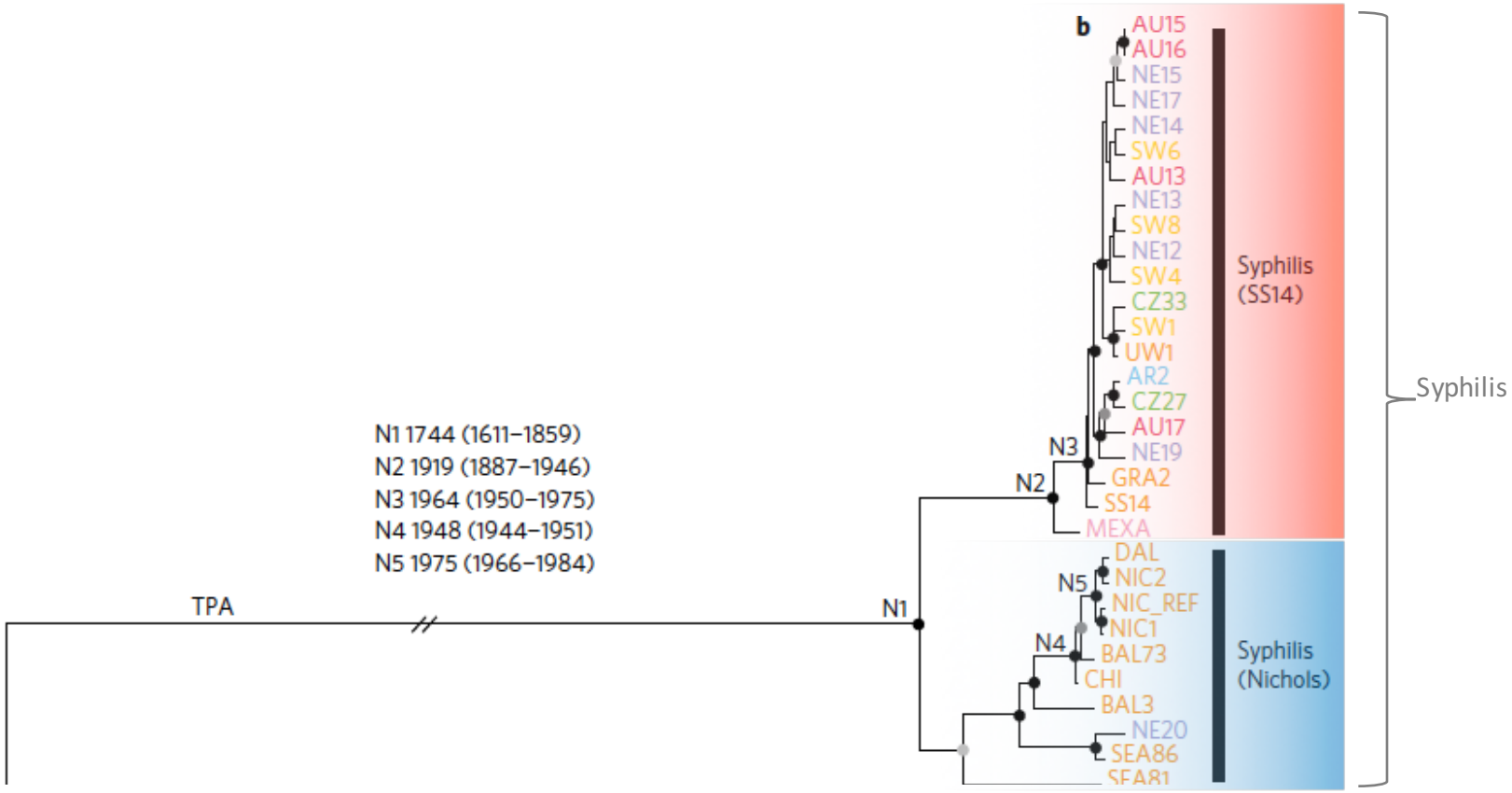
Limited genomics due to inability to culture



- Inability to culture syphilis has prevented large scale sequencing of syphilis genomes
- Available sequences of variable quality and subject to sampling biases
- Recent studies[1,2] suggest two syphilis (TPA) lineages diverging around the C18th
- SS14 lineage is often Macrolide resistant – this has been postulated as a cause for SS14 expansion.

[1]Arora et al 2016, Nat Micro 2:16245
[2]Pinto et al 2016, Nat Micro 2:16190

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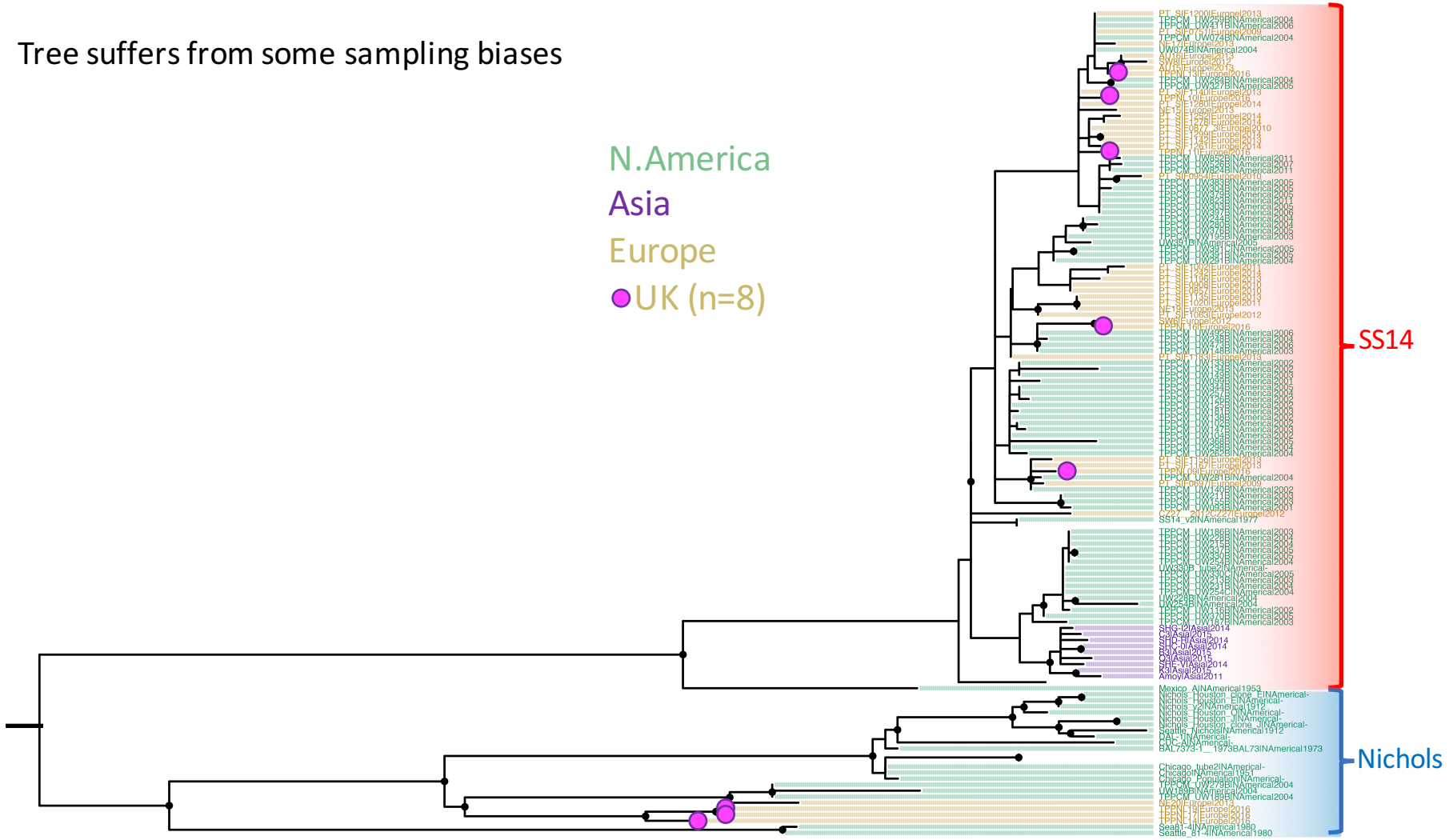
Global Genomic Diversity Study – Preliminary Analysis

Tree suffers from some sampling biases



- 137 global Tpa sequences
- 59 published
- 78 novel sequences at Sanger

- Substantial expansion of SS14 lineage (but sampling bias)

- Both SS14 and Nichols lineages represented in contemporary UK patients

Reference mapped (SS14 masked), post-Gubbins Maximum Likelihood phylogeny (nodes with black dots indicate UF bootstrap support >95%).

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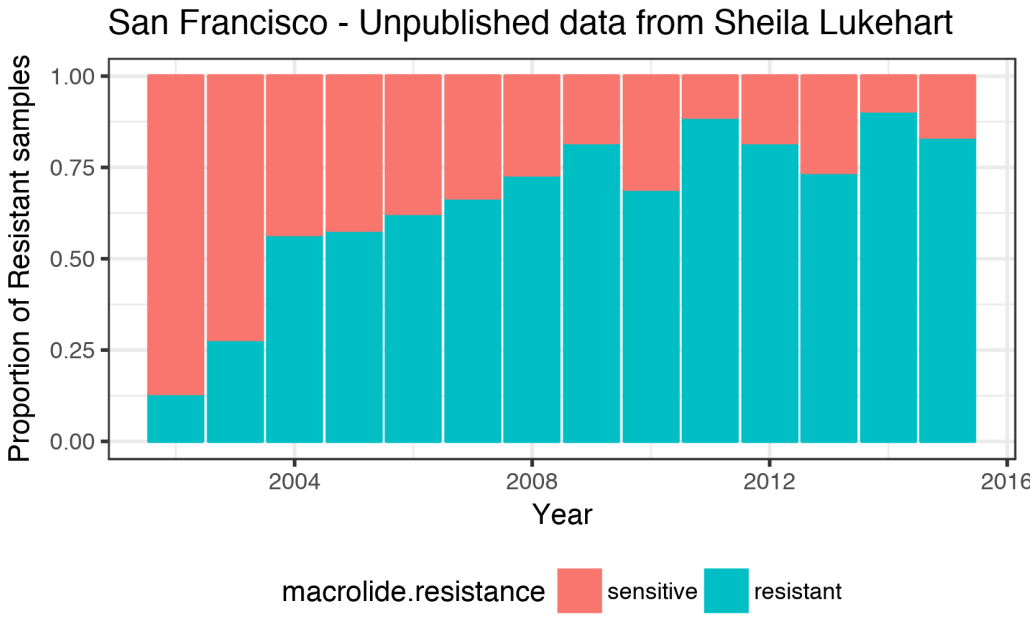
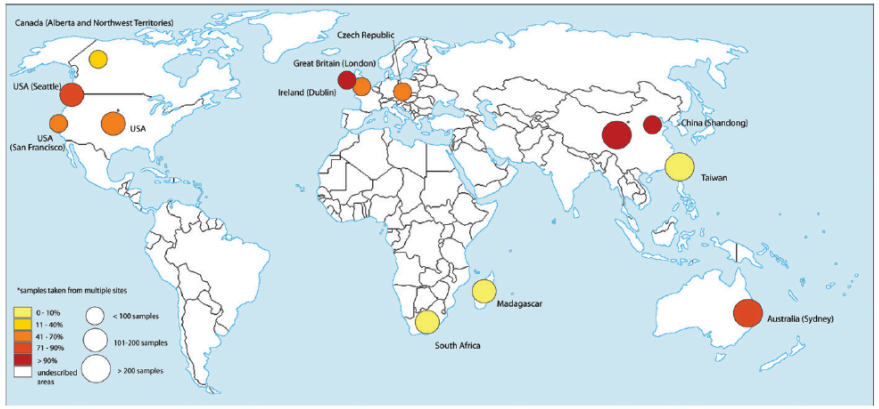
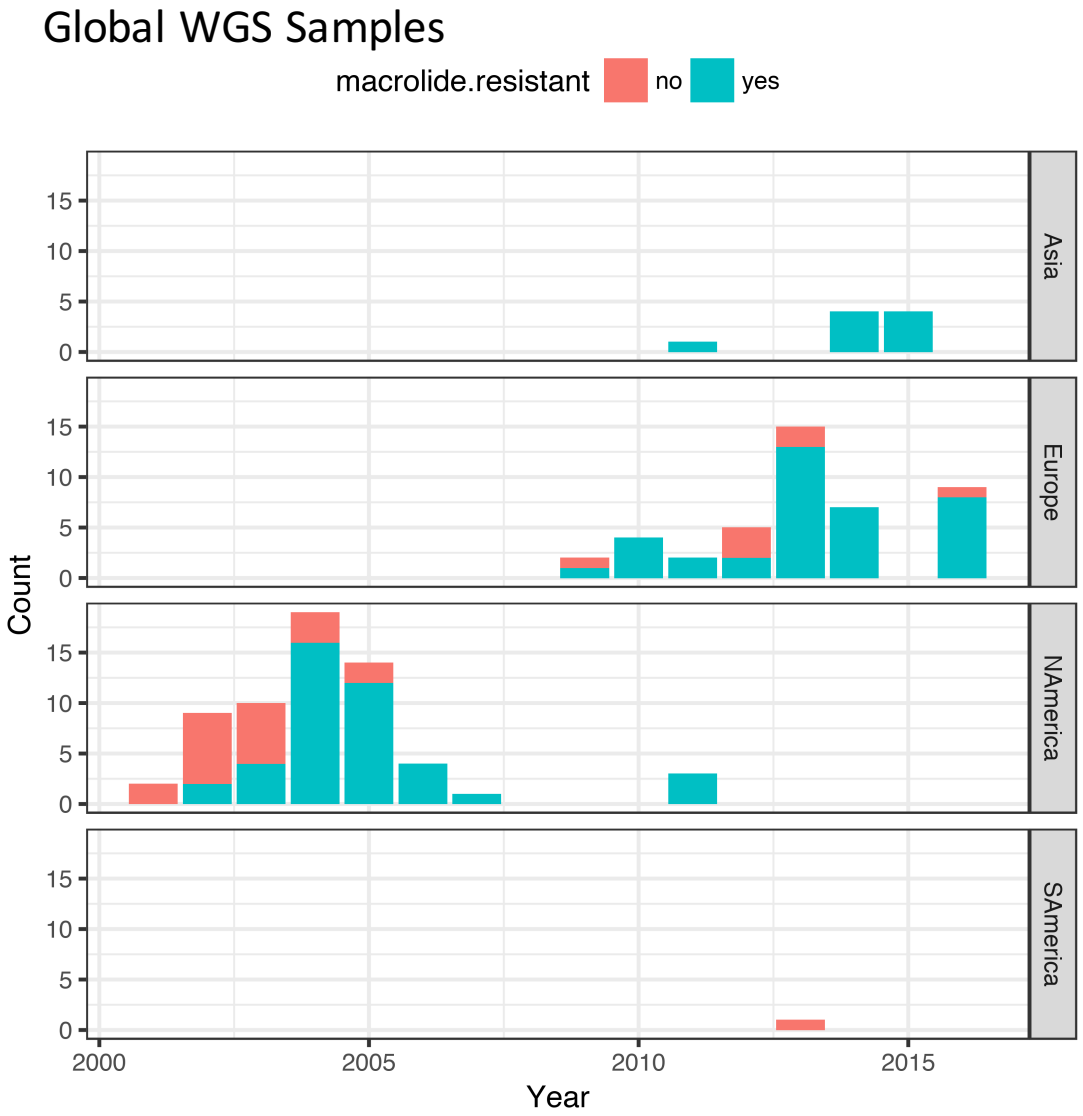
Rise of macrolide resistance



Geographical distribution of macrolide resistance in TPA



Smajs et al. 2015, Am J Trop Med Hyg 93(4):678-683



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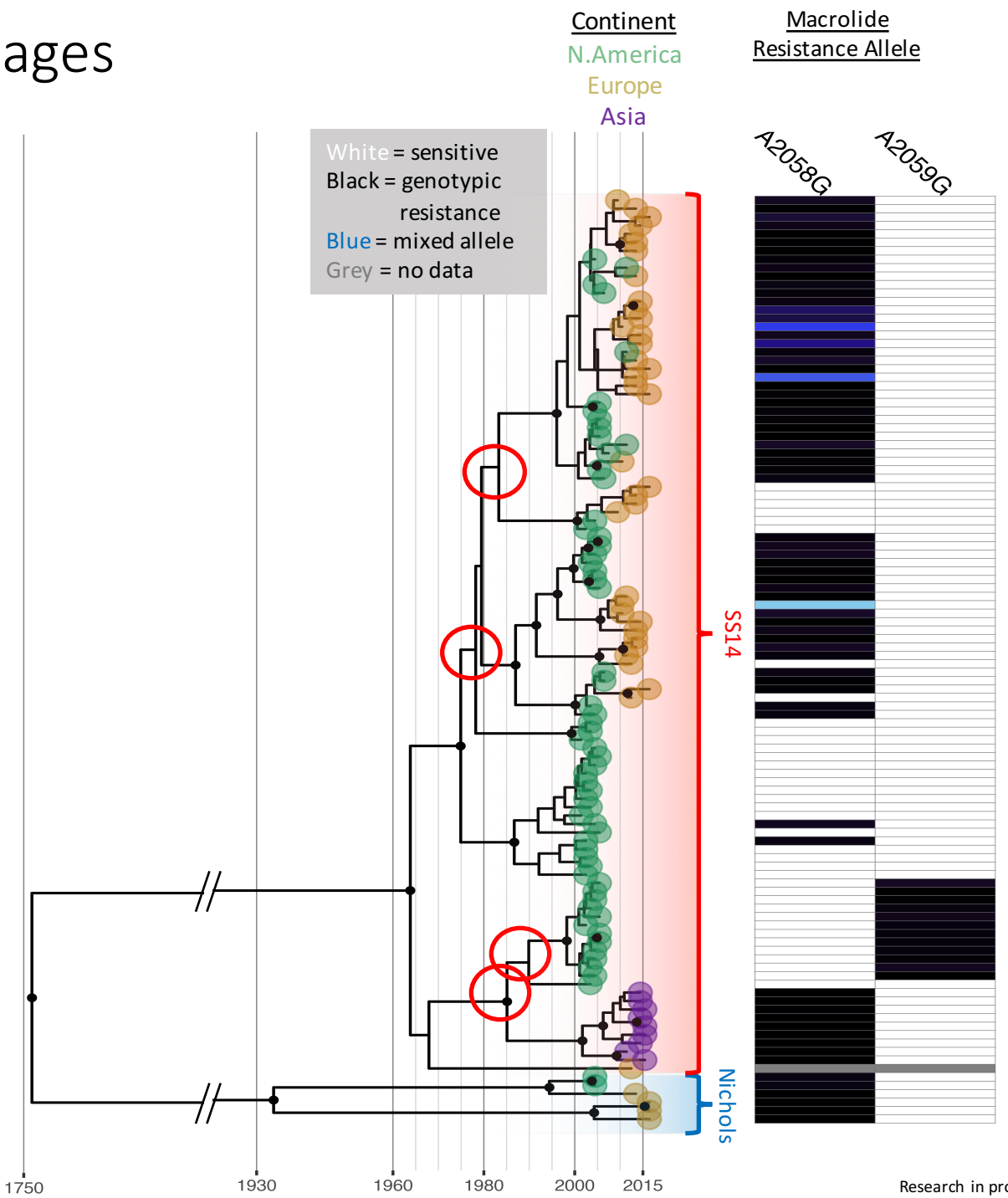
Emergence of macrolide resistant lineages

Single point mutation at 2058 or 2059 in 23s ribosomal sequence confers intrinsic macrolide resistance



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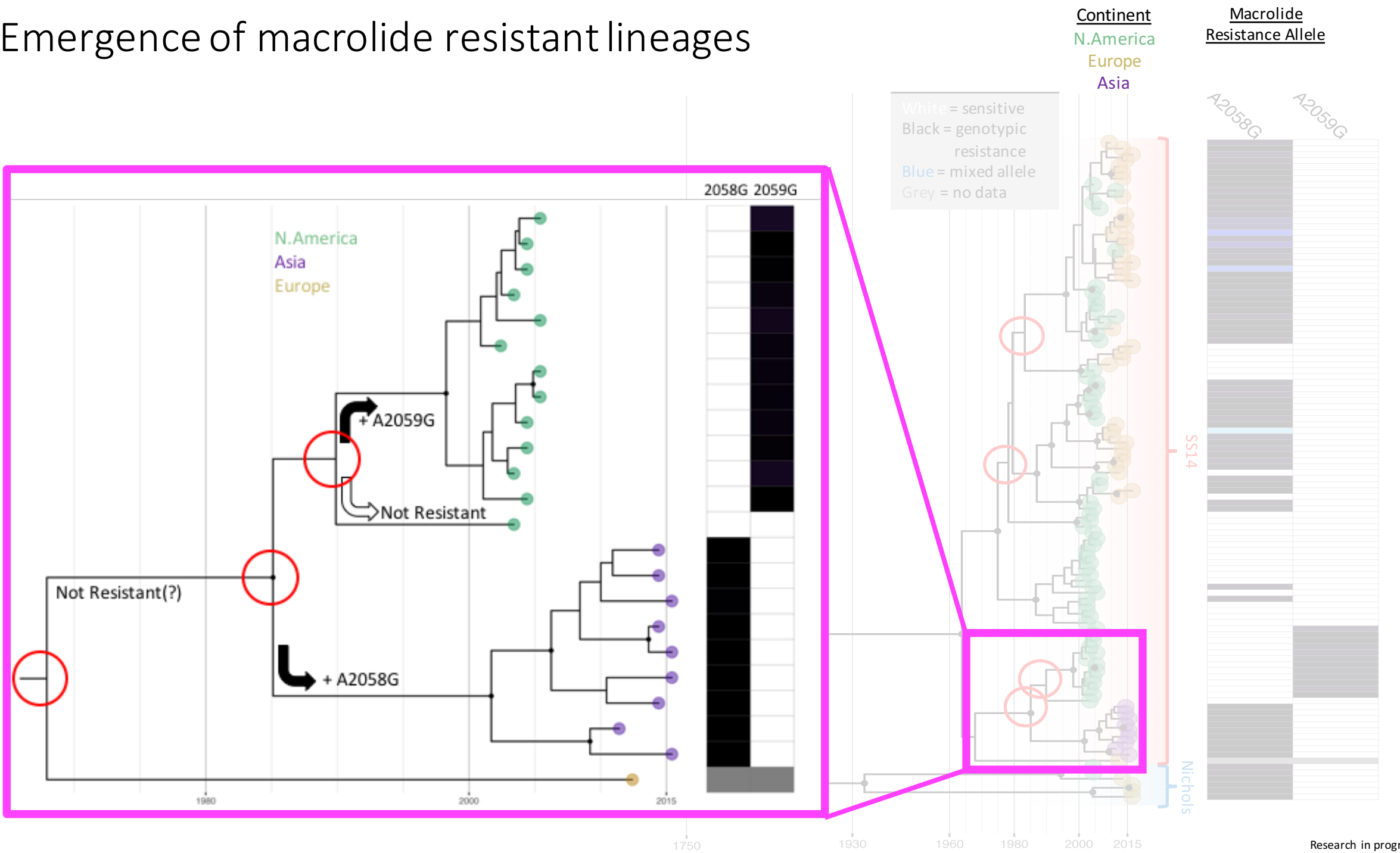
Emergence of macrolide resistant lineages



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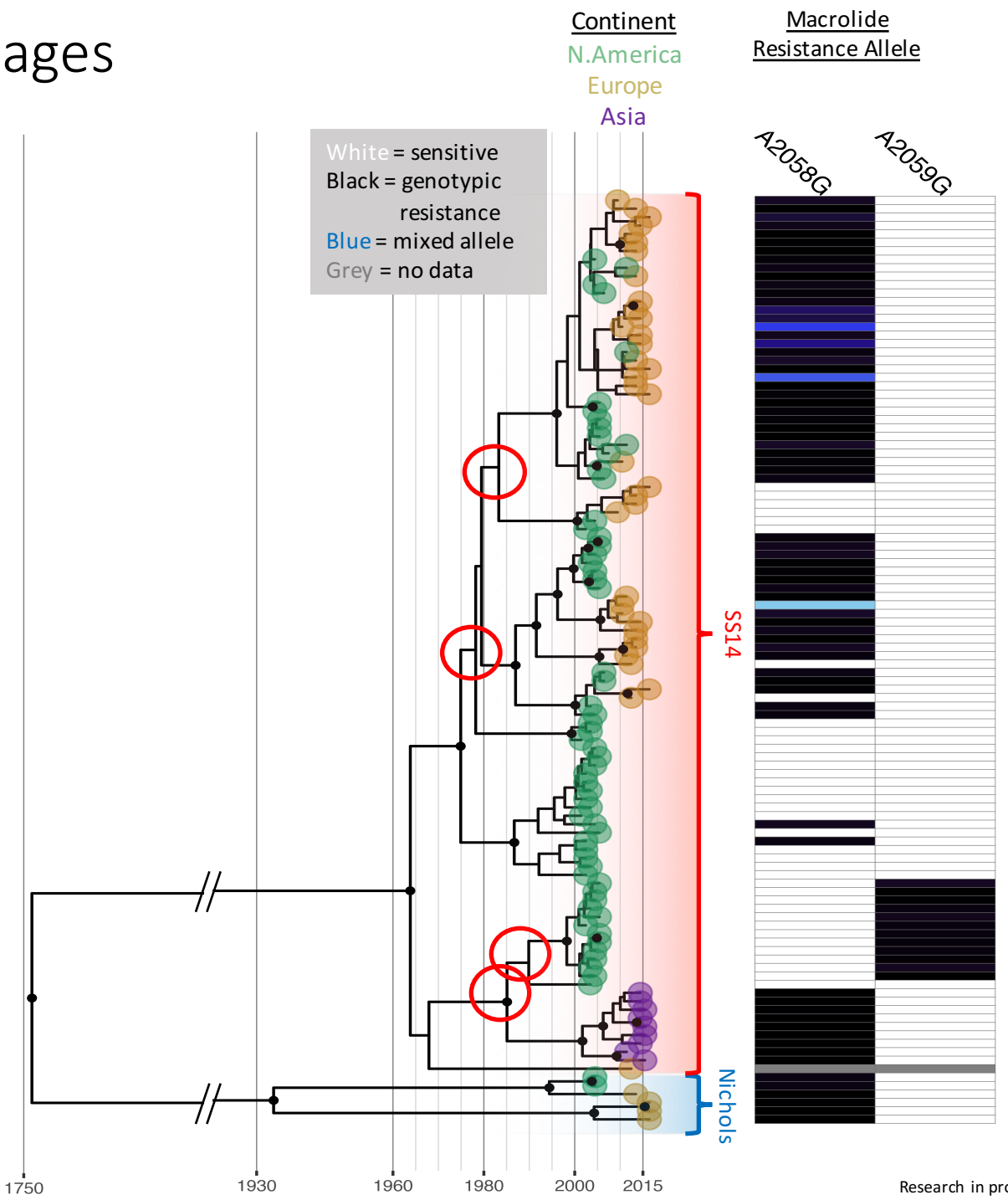
Emergence of macrolide resistant lineages

- Macrolide resistance has independently evolved and become fixed in lineages on multiple occasions
- Resistant lineages most likely evolved during the late 1980s/1990s
- Argues against recent expansion of SS14 due to macrolide resistance



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Conclusions

- Combining basic metadata with phylogenomic data can yield powerful insights into:
  - Lineage spread
  - Evolution of phenotypic traits (e.g. macrolide resistance)
    - Macrolide evolution has relevance beyond syphilis (e.g. WHO Yaws eradication campaign)
- Syphilis sequencing is now tractable at scale
  - We are conducting large scale sequencing of UK and global populations
  - Currently seeking collaborators

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- Sheila Lukehart

Ongoing collaborations
Public Health England
- Gwenda Hughes
- Helen Fifer
- Michelle Cole

Extra stuff: BEAST tree with 95% conf intervals on dates