GENOME WATCH

Putting a twist in syphilis vaccine development

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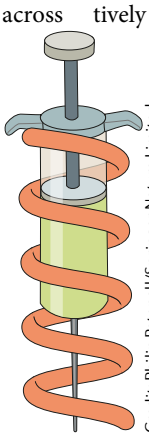
This Genome Watch highlights how population genomic strategies can aid in the development of an effective syphilis vaccine.

The worldwide increase in syphilis, caused by the sexually transmitted spirochete *Treponema pallidum* subsp. *pallidum* (TPA), has spurred the need for a vaccine. Difficulties in culturing TPA in vitro from clinical samples have limited our understanding of the global diversity of this host-adapted pathogen, which has further hampered vaccine development. During the past 6 years, several culture-independent enrichment techniques have partially addressed the problem of low bacterial loads against a background of highly abundant host DNA in clinical samples, and whole-genome sequencing has become possible directly from patient samples. Hybridization capture using DNA or RNA probes designed based on TPA genomes has become the most popular and efficient technique for this targeted genome sequencing. Three recently published studies used this technology for large-scale sequencing of TPA, which enabled the deep exploration of modern syphilis epidemics[1–3].

Population diversity is a key parameter for how successful vaccines will be. Genome sequencing revealed that two major TPA lineages, Nichols and SS14, co-circulate across multiple continents. The genetically homogeneous SS14 lineage was the dominant lineage in most sampled regions; however, both lineages exhibited similar phylodynamics and are responsible for current epidemics[1–3]. Furthermore, TPA populations circulating among patients in the twentieth century may have been different from the modern populations[1,3]. This has been linked to a population bottleneck in the late 1990s, followed by the expansion of modern sublineages in the 2000s. It has been suggested that this rapid expansion may have been due to the relaxation in sexual behaviour after the introduction of an effective antiretroviral therapy in the 1990s. This is relevant as some sublineages were found to be associated with specific sexual networks[3], which supports the observation that sexual behaviour is one of the most important factors in syphilis transmission. Overall, syphilis genomes exhibited very limited genetic diversity across time and space, which indicates a very low evolutionary rate[1–3]. Interestingly, a single highly discriminative locus, TP0548, used for multi locus sequence typing, was found to correlate well with TPA sublineages identified via phylogenomics[3]. This low population diversity of TPA highlights the possibility for the development of a universal vaccine. However, this has to be supported by further genomic studies from diverse populations.

Effective sample collection is required to improve genome surveillance efforts. Most TPA genomes published today originate from Europe, North America and Australia. To ensure the development of a globally effective vaccine, sampling in neglected continents, such as Africa, South America and Asia, must be made a priority. In addition, the majority of TPA genomes have been sequenced from swabs of syphilis ulcers owing to their relatively high bacterial load compared with the loads that can be found in blood samples. However, ulcer swabs can only be collected during a small time window at the beginning of the infection, whereas blood is usually collected from all patients for serological diagnosis through all stages of the disease. The extremely low pathogen loads combined with high host DNA loads in blood samples still represent a challenge for existing targeted genome sequencing techniques and, therefore, efforts should be made to overcome this problem.



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To further inform syphilis vaccine development, a greater understanding of the diversity of genes encoding immunogenic outer membrane proteins (OMPs) is needed. The unusual low surface density of OMPs, phase variation and gene conversion are the major reasons why TPA can escape the human immune system and persist in the host for many years. These mechanisms are likely to be the main reasons why the highest genetic diversity of TPA is hidden in paralogous, recombinant and repetitive regions. However, genes encoding those putative antigens are difficult to recover when using short reads, are often masked in the sequence alignments and hence are omitted from further analyses. Therefore, methods to recover these regions are needed to assist effective vaccine development efforts.

Finally, experimental validation of in silico predicted genes, coupled with functional annotation, is another crucial step for the selection of vaccine candidates. This is particularly timely as genetic manipulation of TPA has only recently become possible[4]. These toolkits pave the way for vaccine development and promise exciting times ahead for TPA research with clinical implementation.

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