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Invited Review

Dissecting malaria biology and epidemiology using population genetics and genomics

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ABSTRACT

Molecular approaches have an increasingly recognized utility in surveillance of malaria parasite populations, not only in defining prevalence and incidence with higher sensitivity than traditional methods, but also in monitoring local and regional parasite transmission patterns. In this review, we provide an overview of population genetic and genomic studies of human-infecting *Plasmodium* species, highlighting recent advances in the field. In accordance with the renewed impetus for malaria eradication, many studies are now using genetic and genomic epidemiology to support local evidence-based intervention strategies. Microsatellite genotyping remains a popular approach for both *Plasmodium falciparum* and *Plasmodium vivax*. However, with the increasing availability of whole genome sequencing data enabling effective single nucleotide polymorphism-based panels tailored to a given study question and setting, this approach is gaining popularity. The availability of new reference genomes for *Plasmodium malariae* and *Plasmodium ovale* should see a surge in similar molecular studies on these currently neglected species. Genomic studies are revealing new insights into important adaptive mechanisms of the parasite including antimalarial drug resistance. The advent of new methodologies such as selective whole genome amplification for dealing with extensive human DNA in low density field isolates should see genome-wide approaches becoming routine for parasite surveillance once the economic costs outweigh the current cost benefits of targeted approaches.

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1. Introduction

The renewed malaria eradication agenda has rejuvenated malaria control and elimination efforts across the globe, with many endemic countries observing a decline in malaria prevalence over the past 15 years (WHO, 2015). In concert with the declining prevalence, the local malaria epidemiology has shifted in many endemic regions, resulting in changes including increasingly unstable transmission and a rising proportion of non-falciparum species (Cotter et al., 2013). In these changing environments, surveillance of the parasite population is important to identify the most efficient intervention methods, monitor the efficacy of ongoing interventions, and identify high-risk areas such as those with emerging drug-resistant strains that render a significant risk of malaria resurgence. To complement traditional surveillance methods, which are largely based on measures of prevalence and incidence by light microscopy or rapid diagnostic test, molecular approaches have an increasingly recognized utility not only in defining prevalence and incidence with higher sensitivity (Cheng et al., 2015; Imwong et al., 2015; Waltmann et al., 2015) but also in the surveillance of local and regional parasite population structures to reveal transmission patterns (Barry et al., 2015; Daniels et al., 2015a; Ferreira and de Oliveira, 2015; Kwiatkowski, 2015). Parasite population genetics and genomics can reveal important features of underlying patterns of transmission, population migration and evolution that cannot be defined using traditional surveillance methodologies. In recent years, there has been an influx of malaria studies applying molecular epidemiology approaches to understand the genetic structure and diversity of *Plasmodium* populations in the context of malaria control and elimination. In this review, we provide an overview of the topic and a summary of molecular approaches that have been applied to study the genetic and genomic epidemiology of *Plasmodium* populations, highlighting recent advances in the field.

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2. Insights on transmission dynamics in *Plasmodium vivax* and *Plasmodium falciparum* using microsatellite genotyping

Although the cost of whole genome sequencing (WGS) continues to decline, targeted genotyping at highly polymorphic loci such as microsatellites, merozoite surface protein (*msp*)*1*, *msp2* and *glurp* or appropriately selected single nucleotide polymorphism (SNP) subsets remains a more economic, albeit more granular, approach to gauge parasite diversity, population structure and complexity of infection (COI). Microsatellites have been used extensively to define the transmission patterns of *P. falciparum* and *P. vivax*. The majority of population genetic studies in *P. falciparum* have used a consensus panel of markers established in 1999 (Anderson et al., 1999). Less accord has been achieved for *P. vivax*, although commonly applied marker sets include two panels established in 2007 (Imwong et al., 2007) and 2008 (Karunaweera et al., 2008). A number of *P. vivax* studies have also used a combination of short tandem repeats in variable surface proteins to fingerprint infections and assess COI (Koepfli et al., 2011a,b, 2013). Investigation of the allelic and haplotypic diversity at these highly polymorphic microsatellite loci has been extremely informative. Multiple-clone infections are a pre-requisite for cross-mating of different strains of *Plasmodium*. In high transmission settings, multiple-clone infections tend to be common, and *P. falciparum* populations are generally panmictic (highly admixed), exhibiting linkage equilibrium and high genetic diversity (Anderson et al., 2000; Mobegi et al., 2012). In lower transmission settings such as those found in many parts of Southeast Asia and South America, multiple-clone infections are less common and, as a result, *P. falciparum* populations display lower diversity, high levels of multilocus linkage disequilibrium and evidence of population structure, consistent with decreasing gene flow both within and between populations (Anderson et al., 2000; Anthony et al., 2005; Iwagami et al., 2009; Pumpaibool et al., 2009; Gray et al., 2013; Noviyanti et al., 2015). For *P. vivax*, however, the relationship between diversity and transmission intensity is less clear. Even in low transmission settings, population diversity remains high (Abdullah et al., 2013; Gray et al., 2013; Gunawardena et al., 2014; Liu et al., 2014; Goo et al., 2015; Wangchuk et al., 2016). Indeed, in accordance with findings from WGS studies (Neafsey et al., 2012; Hupalo et al., 2016; Pearson et al., 2016), several microsatellite-based studies comparing *P. falciparum* and *P. vivax* populations have demonstrated higher diversity in the latter (Ferreira et al., 2007; Gray et al., 2013; Orjuela-Sanchez et al., 2013; Jennison et al., 2015; Noviyanti et al., 2015). A number of factors may explain the consistently high *P. vivax* diversity observed in different endemic settings including relapse from the dormant liver stage (hypnozoite) reservoir, the earlier development of the transmissible gametocyte stage, imported infections and possible underestimation of the true incidence of infection on account of sub-patent infections. High levels of linkage disequilibrium and population structure provide some of the only hints of interrupted transmission, as observed in the *P. vivax* population in the pre-elimination setting of Sabah, Malaysia (Abdullah et al., 2013). The prevalence of multiple-clone infections may also be useful to define transmission intensity (Liu et al., 2014; Getachew et al., 2015; Goo et al., 2015; Noviyanti et al., 2015), but this relationship needs to be investigated further. Furthermore, consensus marker sets and minor allele calling methods are critical for effective comparability of the proportion of multiple-clone infections within and between sites (Havryliuk and Ferreira, 2009). Few studies have directly investigated how parasite population genetic patterns change over time with declining transmission (Nkhoma et al., 2013; Gatei et al., 2014; Chenet et al., 2015). However, with the current widespread use of microsatellite markers in multiple endemic sites with declining transmission, it is likely that many new studies will shed light on how parasite population dynamics are impacted.

A number of studies have now demonstrated the utility of microsatellite-based genotyping to identify features of both *P. vivax* and *P. falciparum* transmission of relevance to National Malaria Control Programs. These studies reflect a range of endemic settings including low transmission settings of South America; low, moderate and high transmission settings around the Asia-Pacific region; and higher transmission settings in Africa. In South America, a Bayesian modelling approach was used to investigate patterns of *P. vivax* gene flow at multiple sites in and around Iquitos, the capital city of the Peruvian Amazon. Here, high rates of unbalanced gene flow were observed, with Iquitos appearing to be the main reservoir of infection for surrounding regions (Delgado-Ratto et al., 2016). In the northwest of Ecuador, one of the last remaining malarious regions in the country, microsatellite genotyping demonstrated that the local *P. falciparum* population was sustained by multiple introductions from neighbouring countries and ancestral local parasites, with unstable transmission leading to frequent clonal expansions (Saenz et al., 2014; Saenz et al., personal communication). This dynamic mirrored the pattern observed in a recent study of *P. falciparum* in the pre-elimination setting of Panama, where SNP-based genotyping revealed highly clonal subpopulations that appeared to reflect epidemic expansions of vestigial infections and cases imported from Colombia (Obaldia et al., 2015). The northwestern region of Colombia remains one of the highest malaria-endemic regions in South America, presenting a considerable risk for imported malaria and resurgence in neighbouring countries. Nonetheless, a longitudinal study of the genetic diversity and structure of the *P. falciparum* population in Turbo, northwestern Colombia, between 2002 and 2009 demonstrated that ongoing interventions have indeed been successful in reducing local transmission (Chenet et al., 2015). With imported infections presenting a major challenge to malaria containment and elimination in South America, further investigations of local and cross-border transmission networks using methods similar to those applied by Delgado-Ratto and colleagues should strengthen surveillance efforts in the region.

Studies on parasite populations from Melanesia in the southwestern Pacific region, including investigations in Vanuatu, the Solomon Islands and Papua New Guinea (PNG), highlight the dedicated commitment to malaria control and elimination in the region. The islands of Melanesia present widely contrasting patterns of malaria epidemiology with varying proportions of co-endemic *Plasmodium* spp. and transmission intensities. They display a gradual west to east decline in transmission from some of the highest prevalence rates observed outside of Africa (PNG) to very low rates in pre-elimination settings (Vanuatu) (Gething et al., 2012). Previous studies of *P. falciparum* and *P. vivax* in the southwestern Pacific region have revealed a spectrum of population diversity and structure reflecting the underlying heterogeneity in transmission patterns within and between species across the region. Studies currently underway include an investigation using microsatellites over a 10 year period in Vanuatu, demonstrating a decline in COI in both *P. falciparum* and *P. vivax* isolates over the study period, consistent with declining transmission intensity as a result of concerted control efforts (Dowd et al., personal communication). The Solomon Islands has experienced comparable success to Vanuatu in reducing malaria incidence over two decades of intense control, with a 90% reduction in the rate of clinical cases: accordingly *P. falciparum* has almost disappeared from Central Province (Waltmann et al., 2015). This was further investigated by genotyping *P. falciparum* isolates from this province and comparing it with neighbouring provinces using both microsatellite and SNP markers (see Section 3). The results demonstrated very low *P. fal-*

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