Scientists discover maleness gene in malaria mosquitoes

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Anopheles gambiae male. Credit: T. Ant and S. Sinkins

Scientists, led by Dr Jaroslaw Krzywinski, Head of the Vector Molecular Biology group at The Pirbright Institute have isolated a gene, which determines maleness in the species of mosquito that is responsible for transmitting malaria. The research, published in the journal *Science*, describes identification and characterisation of a gene, named Yob by the authors, which is the master regulator of the sex determination process in the African malaria mosquito, *Anopheles gambiae*, and determines the male sex.

In insects, sex is commonly determined by a primary genetic signal that during the first hours of life activates a short cascade of genes, whose sex-specific products ultimately control whether an individual will develop as male or female. The molecular mechanisms underlying these developmental processes are surprisingly extremely variable, and in particular the primary sex-determining genes drastically differ in their nature between different groups of insects. Similar to humans, many insects possess a pair of sex chromosomes, with females carrying identical XX chromosomes and males XY chromosomes, the Y chromosome harbouring a dominant male-determining gene. The molecular identity of such maleness genes has remained enigmatic. Yob represents only the second known case in insects.

To identify Yob, researchers from Pirbright, with support from colleagues from the Liverpool School of Tropical Medicine, used high-throughput sequencing to sample all transcripts (genetic messages) produced in the *Anopheles gambiae* male and female embryos. After comparison of the sequencing data, they found, exclusively in males, fragments of transcripts corresponding to Yob. Further research showed that Yob is encoded on the Y chromosome, and that activity of Yob was

limited to males and was necessary to generate male-specific products of the sex determination pathway genes.

Researchers have identified male-specific mosquito RNA that is lethal when transferred to females, which spread malaria. Targeting female mosquitos in such a way could help reduce the spread of malaria. Credit: Carla Schaffer / AAAS

Unexpectedly, Yob transcripts are highly detrimental to females. When injected into mixed-sex early embryos of *Anopheles gambiae*, or another African mosquito species, Anopheles arabiensis, Yob kills females before they hatch from eggs, but leaves male development unaffected. Conversely, silencing normal embryonic Yob activity is lethal to males. These results indicate that, apart from determining maleness, Yob is pivotal for the control of another fundamental developmental process,

called dosage compensation, which balances levels of transcripts from genes located on the single X chromosome in males and on two X chromosomes in females.

"Our research may have far-reaching implications for the control of malaria. This preventable disease is the major cause of human suffering and an immense barrier to socioeconomic development, mainly in poor countries of sub-Saharan Africa, where nearly 200 million clinical cases and half a million deaths are reported every year. Malaria in that region is transmitted primarily by females of *Anopheles gambiae* and Anopheles arabiensis. Currently, application of insecticides to control mosquitoes remains the most efficient way of combating the disease, but with a rampant spread of resistance to chemicals in mosquito populations, the insecticides may soon become ineffective. Clearly, we urgently need alternative more sustainable mosquito control methods. Genetic strategies, such as those successfully used to control agricultural pests, have great potential. However, they require releases of male mosquitoes only, which represents an insurmountable obstacle to extending genetic control to malaria vectors, because no efficient methods to separate sexes in Anopheles currently exist. Now, the female-killing property of Yob gives us an invaluable tool for the engineering of male-only Anopheles strains suitable for malaria control in the future", said Dr Krzywinski.

More information: "A maleness gene in the malaria mosquito Anopheles gambiae," by E. Krzywinska et al. *Science*, DOI: 10.1126/science.aaf5605

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