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Smoke gets in your flies

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A new gene-association technique identifies metabolic genes that confer nicotine resistance to some *Drosophila* in the wild.

You can take the fruit fly out of North Carolina, but you can't take the North Carolina out of the fruit fly. *Drosophila* from North Carolina, where tobacco is traditionally grown, are more resistant to nicotine than *Drosophila* from California. Passador-Gurgel *et al*. identify *Drosophila* genes associated with nicotine sensitivity using a new gene-association technique called quantitative trait transcripts (QTT) in a recent article in *Nature Genetics*.

Although it was designed to identify genetic regions associated with continuous traits (a range of phenotypes), researchers often apply quantitative trait loci (QTL) mapping to binary disease states, in which individuals are either affected or unaffected. A recent variation of this technique called eQTL or genetical genomics associates the abundance of gene expression with a continuous trait. However, eQTL is commonly performed on the progeny of a single cross between inbred strains, a population lacking genetic variability. The authors designed QTT to address these shortcomings. They did microarrays on wild populations of *Drosophila* and correlated patterns of gene expression to a continuous trait using regression analysis.

Acute nicotine treatment stimulates *Drosophila*, but chronic exposure (24 hours) immobilizes and eventually kills them. The authors measured survival time following nicotine exposure in more than 200 genetically uniform *Drosophila* lines from North Carolina and California. The North Carolina lines showed greater variability in survival time than did the California lines, and 30% of the North Carolina lines survived longer than almost all of the California lines, suggesting that some *Drosophila* from North Carolina developed defenses against environmental exposure to nicotine.

QTT analysis identified transcripts encoding ornithine aminotransferase and alkaline phosphatase that together explained 30% of the variance in survival time. Ornithine is involved in detoxification through the urea cycle. Ornithine aminotransferase reduces ornithine to glutamate. Nicotine-resistant *Drosophila* showed elevated *ornithine aminotransferase* expression relative to nicotine-sensitive *Drosophila*. In nicotine-resistant *Drosophila*, nicotine treatment reduced *ornithine aminotransferase* expression, suggesting that ornithine metabolism might switch from glutamate production to detoxification in nicotine-resistant *Drosophila* exposed to nicotine.

Glutamate, which could be excitotoxic in the presence of nicotine, is better converted to GABA in nicotine-resistant relative to nicotine-sensitive *Drosophila*. Real-time PCR showed elevated expression of *Gad1*, the enzyme that converts glutamate to GABA,

and less reduction in *Gad1* expression following nicotine treatment in nicotine-resistant relative to nicotine-sensitive *Drosophila*. Regression analysis of mass spectrometry data showed correlations between survival time and levels of GABA and ornithine.

Alkaline phosphatase breaks down the pesticide lindane. Therefore, nicotine-resistant *Drosophila* may be well equipped to metabolize environmental toxins.

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1. Passador-Gurgel, G. , Hsieh, W. , Hunt, P. , Deighton, N. and Gibson, G. Quantitative trait transcripts for nicotine resistance in *Drosophila melanogaster*. *Nature Genetics* **39**, 264–268 (2007). | Article |