Extreme allelic heterogeneity at a *Caenorhabditis elegans* beta-tubulin locus explains natural resistance to benzimidazoles

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Benzimidazoles (BZ) are essential components of the limited chemotherapeutic arsenal available to control the global burden of parasitic nematodes. The emerging threat of BZ resistance among multiple nematode species necessitates the development of novel strategies to identify genetic and molecular mechanisms that underlie resistance. Efforts to detect helminth BZ resistance in parasitic nematodes is focused on three variant sites in the orthologs of the β-tubulin gene, *ben-1,* found to confer resistance in the free-living nematode *Caenorhabditis elegans*. Because of the limitations of laboratory and field experiments in parasitic nematodes, it is difficult to look beyond these three sites to identify additional mechanisms that might contribute to BZ resistance in the field. Here, we took an unbiased genome-wide mapping approach in *C. elegans* to identify the genetic underpinnings of natural resistance to the commonly used BZ, albendazole (ABZ). In agreement with known mechanisms of BZ resistance, we found that a majority of the variation in ABZ resistance among wild *C. elegans* strains is caused by variation in *ben-1*. We identified 25 distinct, low-frequency *ben-1* alleles within the *C. elegans* population, including many novel variants. Population genetic analyses indicate that these variants arose recently because of local selective pressures. Furthermore, we show that the common parasitic nematode β-tubulin allele that confers BZ resistance, F200Y, confers resistance in *C. elegans*. Importantly, we identified a novel β-tubulin-independent genomic region that is correlated with ABZ resistance in the *C. elegans* population, suggesting that multiple mechanisms underlie BZ resistance. Taken together, our results establish a population-level resource of nematode natural diversity as an important model for studying BZ resistance mechanisms.