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Natural variation and functional analyses provide evidence for coevolution between plant eIF4E and potyviral VPg

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Amino acid substitutions in the eukaryotic translation initiation factor 4E (eIF4E) result in recessive resistance to potyviruses in a range of plant species, including *Capsicum* spp. Correspondingly, amino acid changes in the central part of the viral genome-linked protein (VPg) are responsible for the potyvirus's ability to overcome eIF4E-mediated resistance. A key observation was that the physical interaction between eIF4E and the VPg is required for viral infection while eIF4E mutations causative of resistance prevent VPg binding and inhibit the viral cycle. In this study, polymorphism analysis of the *pvr2-eIF4E* coding sequence in a worldwide sample of twenty five *C. annuum* accessions identified ten allelic variants with exclusively non-synonymous variations clustered in two surface loops of eIF4E. Resistance and genetic complementation assays demonstrated that *pvr2* variants, each with signature amino acid changes, corresponded to potyvirus resistance alleles. Systematic analysis of the interactions between eIF4E proteins encoded by the ten *pvr2* alleles and VPgs of virulent and avirulent *Potato virus Y* (PVY) and *Tobacco etch virus* (TEV) strains demonstrated that resistance phenotypes arose from the disruption of the interaction between eIF4E and VPg, and that viral adaptation to eIF4E-mediated resistance resulted from the restored interaction with the resistance protein. Complementation of an eIF4E knock-out yeast strain by *C. annuum* eIF4E proteins further shows that amino acid changes did not impede essential eIF4E functions. Altogether, these results argue in favour of a coevolutionary arms race between *Capsicum* eIF4E and potyviral VPg.