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University of Connecticut

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Corresponding Faculty Member: Johann Peter Gogarten (gogarten@uconn.edu)



Paul R Bannister

Inteins in Actinophages -- Parasites of Parasites.

Paul R Bannister, Shelly Evi, Gabby Calfe, Adinai Chonweerawong, Carter S Gravina, Savannah Ameisha Greene, Catherine Jennings, Charles Joseph Principato, Alexandra C Vellekoop, Sophia Gosselin, J Peter Gogarten

Inteins, also known as protein introns, are self-splicing genetic elements found throughout all three domains of life and even within viruses. These elements are similar to introns; however, instead of splicing out at the RNA level, inteins are fully translated into a protein before they self-splice (leaving behind the intact host protein; the extein). This activity is conducted by the eponymously named self-slicing domain of the intein, but inteins also frequently contain a homing endonuclease domain. This second domain allows the intein to make a double-strand cut in an uninvaded allele, and then, during repair of the DNA, the intein is copied into the previously uninvaded allele.  
This homing activity allows inteins to spread rapidly throughout a population that possesses mechanisms for gene flow and recombination. Inteins tend to only invade highly conserved genes (1). This has led to two competing hypotheses. The first supposes that Inteins are solely selfish genetic elements, which invade highly conserved genes because their homing sites are more likely to be conserved, and that the intein is less likely to be selected out of the population. The second hypothesis posits that inteins are found in these conserved genes because they are not solely parasites, but instead provide some form of regulatory benefit by acting as an environmental sensor(2).  
In our efforts to investigate this question, we have conducted a wide-scale survey of presently unknown inteins within actinobacteriophages. By using a newly developed tool ICE-BLAST (iterative cluster expansion BLAST) we capture the large diversity of invaded exteins within the annotated protein sequences of PhagesDB.   
While it is already known that inteins are commonly found within phage terminase (3) proteins we show that inteins are much more widespread. We identified inteins in genes characterized as helicases, DNA methylase, proteins of no known function, tapemeasure protein, portal protein, ribonucleotide reductase, several terminase Phams, and in Pham 98880, whose members are often annotated as HNH Endonuclease. However, the intein’s homing endonuclease domains is not of the HNH but of the LAGLIDADG type, and the extein of this Pham is more than 95% identical to the intein-free Pham 14824, annotated as Cas4 family exonuclease, terminase, or HNH Endonuclease.   
By investigating the distribution of these inteins in relation to the exteins they invade, we show that these inteins display patterns of descent that are in line with the distribution of a horizontally transferred parasitic element (preliminary data) rather than an evolutionarily beneficial sensor.  
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2. Novikova O, Jayachandran P, Kelley DS, Morton Z, Merwin S, Topilina NI, Belfort M. 2016. Mol Biol Evol 33:783–799.  
3. Kelley DS, Lennon CW, SEA-PHAGES, Belfort M, Novikova O. 2016. mBio 7:e01537-16.