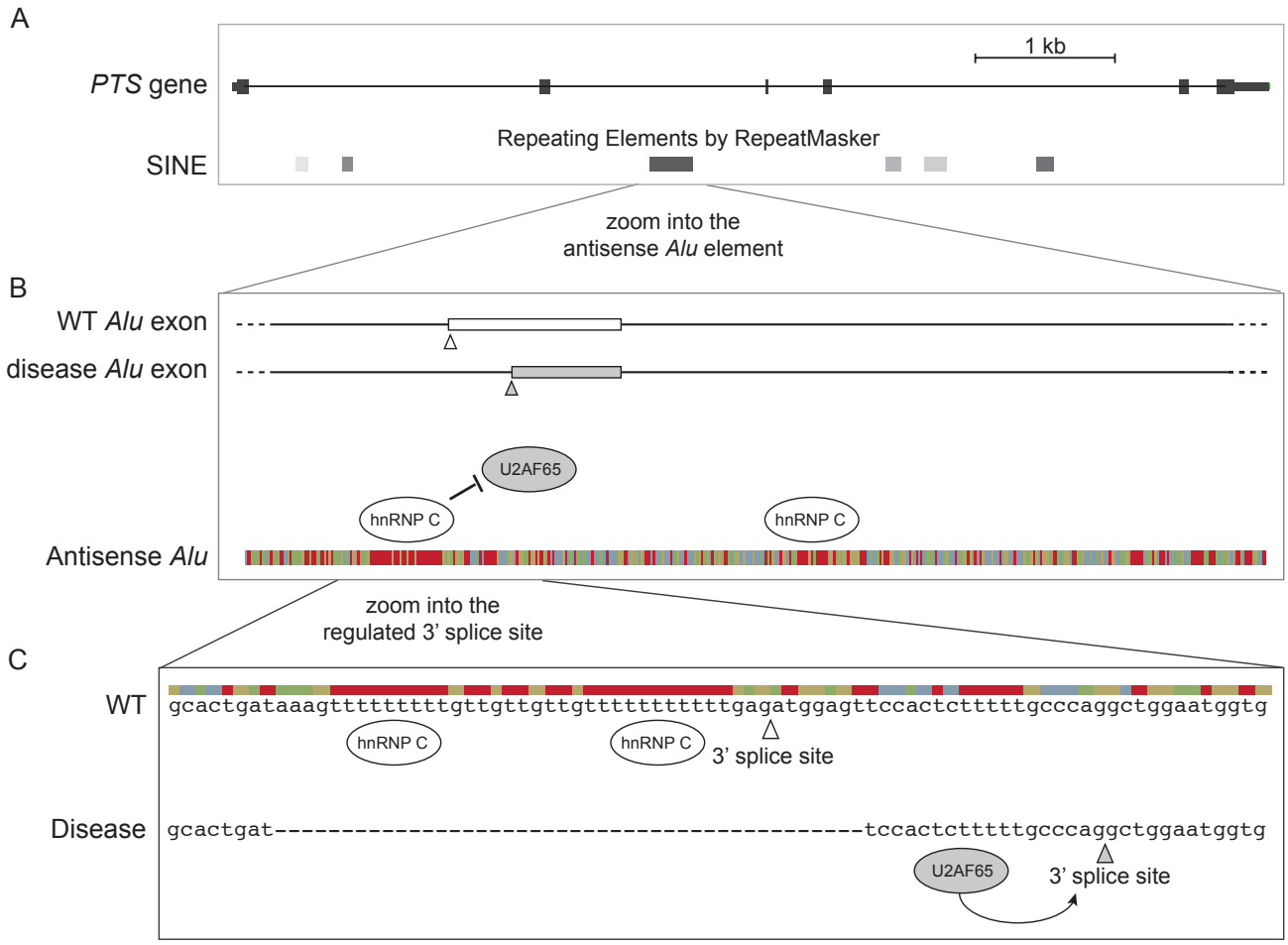

iCLIP revealed that hnRNP C represses the formation of new exons from *Alu* elements by competing with U2AF65 (Zarnack et al, *Cell*, 2013).

This figure shows why a mutation in the *Alu* element of the *PTS* Gene leads to hyperphenylalaninemia. It also demonstrates how iCLIP revealed the regulatory mechanisms that involve competitive or cooperative interactions between RNA and multiple RBPs.

(A) A view of the exon/intron structure of the *PTS* gene. The boxes below show the positions of short interspersed elements (SINE), which include *Alu* elements, as defined by Repeatmasker.

(B) The disease-relevant *Alu* element within the PTS gene is shown at greater resolution. The position of the two exons that can emerge from this *Alu* element are schematically indicated: the blank exon is rarely included in the WT cells, whereas the grey exon is part of the dominant isoform in disease. Below, the sequence is shown in a colour-coded fashion. The uridine tracts (in red) bind to hnRNP C, which represses binding of U2AF65.

(C) The two 3' splice sites that can lead to the formation of *Alu* exon are shown at nucleotide resolution. In WT cells, hnRNP C binds to the long uridine tracts to repress the binding of U2AF65, and therefore the 3' splice site marked by blank arrow is rarely used. In disease, the primary hnRNP C-binding site is deleted, and therefore U2AF65 can bind to the pyrimidine tract upstream of the 3' splice site that is marked by the grey arrow. This leads to stong inclusion of the grey exon that is shown in panel B.