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Type	Oral communication
Session	Molecular Evolution analysis
Title	Amino acid repeat length co-evolution in neural proteins
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Motivation

Homopolymeric amino acid repeats (AARs) have important roles in defining protein structure, function, and homo-/hetero-typic interactions, and can regulate specific phenotypes in a length-dependent manner. AARs undergo complex evolutionary dynamics by which their presence and length vary in ortholog proteins throughout phylogenesis.
While the cellular and molecular functions of AAR-bearing proteins are relatively well characterized, the functional relevance of these proteins to higher-order physiopathological processes at the organismal level is not clearly understood. We recently defined a higher-level functional mapping of polyQ proteins with roles in the nervous system and found significant enrichments of polyQ proteins in specific functional protein clusters related to major physiological processes and neuropsychiatric diseases (Vaglietti and Fiumara, NAR Genomics and Bioinformatics, 3(2):Iqab032, 2021). However, it is still unclear if this is the case for proteins bearing AARs other than polyQ.
AARs can mediate protein-protein interactions and their length variation can change the extension of the interaction surfaces. Our recent work indicates that the lengths of polyQ repeats in functionally related, physically interacting proteins can vary in a coordinated manner throughout phylogenesis (Vaglietti and Fiumara, 2021). It remains to be determined whether similar patterns of length co-evolution are also detectable for proteins containing other AARs.
To address these issues, we have now defined higher-level functional roles of proteins bearing AARs other than polyQ in the nervous system and studied the length co-evolution of their repeats throughout phylogenesis.

Methods

Towards this aim, we used a combination of bioinformatics approaches, developed in on our previous work, that allow the definition of the enrichment of proteins containing a given AAR in functional clusters of neural proteins, and the study of the length co-variation of AARs in protein pairs of interest (see Vaglietti and Fiumara, 2021).

Results

Extending our previous work on polyQ repeats (Vaglietti and Fiumara, 2021), we have tested the relative enrichment of proteins containing other AARs in functional clusters of proteins involved in major aspect of the physiology and pathology of the nervous system. Our analyses show that proteins containing different AARs, such as polyA, are differentially enriched in protein clusters related to specific aspects of the nervous system physiopathology.
Then, we investigated the evolutionary dynamics of AARs lengths in ortholog proteins in the taxon Primates. Specifically, we analyzed i) whether AAR length variability is different across functional clusters, ii) whether AARs in protein pairs belonging to functional clusters have overall length co-evolution rates higher than those found in random sets of functionally unrelated proteins, and iii) whether AARs in protein pairs belonging to networks of physically interacting proteins have overall length co-evolution rates higher than expected by chance in random sets of non-interacting proteins. Our findings indicate that, as for polyQ repeats, also some other AARs, such as polyA, display differential length variation in different functional protein clusters and significant patterns of length co-evolution in Primates.
These findings show that AAR length co-evolution in pairs and clusters of functionally related, physically interacting proteins occurs also for AARs other than polyQ, and have direct implications for our understanding of phenotypic variability and neuropsychiatric disease pathogenesis.

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