A novel N-terminal domain in PIK-related kinases: the FAT domain

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Phosphatidylinositol kinases are found in all eukaryotes and serve important functions in phosphatidyl-inositol (PI) signaling pathways. Recently, a new subfamily of the PI kinase superfamily involved in meiotic and V(D)J recombination, chromosome maintenance and repair, cell cycle progression and cell cycle checkpoint has emerged, called PIK-related. This family includes ATM, ATR, DNA-PK, ESR1, Rad3, TOR1, TOR2, FRAP, TEL1 kinases. These are large proteins (2000-4000 aa) that only share similarity in the ~300 aa kinase domain to classical PI kinases. Another group distantly related to PI kinases comprises the TRRAP proteins. They also share similarity to the PI kinase domain however they lack the catalytic residues and indeed none of them has been shown to possess kinase activity. It has previously been noted that the TRRAP and PIK-related proteins share a unique motif at the C terminus. Analysis of the remaining sequence has so far not been able to clearly define shared domains in the large N-terminal portions.

We here describe a novel homology domain spanning ~500 aa, N-terminal to the PI kinase domain in the PIK-related and TRRAP subfamilies. We call this domain FAT after representatives of the three main groups sharing the domain (FRAP, ATM, and TRRAP). This domain is only present in the FRAP, ATM and TRRAP subfamilies, it is not found outside these subfamilies and always coexists with the C terminal domain previously identified. It is possible that they fold together in a configuration that is necessary for proper function of the PI kinase domain, which is wedged in between the FAT and the C-terminal domains.

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