Pentameric assembly of the Kv2.1 tetramerization domain

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The Kv family of voltage-gated potassium channels regulate neuronal excitability. The biophysical characteristic of Kv channels can be matched to the needs of different neurons by forming homotetrameric or heterotetrameric channels within one of four subfamilies. The cytoplasmic tetramerization (T1) domain plays a major role in dictating the compatibility of different Kv subunits. The only Kv subfamily missing a representative structure of the T1 domain is the Kv2 family. We used X-ray crystallography to solve the structure of the human Kv2.1 T1 domain. The structure is similar to other T1 domains but surprisingly formed a pentamer instead of a tetramer. In solution the Kv2.1 T1 domain also formed a pentamer as determined with in-line SEC-MALS-SAXS and negative stain EM. The Kv2.1 T1-T1 interface involves electrostatic interactions including a salt bridge formed by the negative charges in a previously described CDD motif, and inter-subunit coordination of zinc. We show that zinc binding is important for stability. In conclusion, the Kv2.1 T1 domain behaves differently from the other Kv T1 domains which may reflect the versatility of Kv2.1, the only Kv subfamily that can assemble with the regulatory KvS subunits and scaffold ER-plasma membrane contacts.