When ‘UPS’ fails to deliver: a novel gene associated with the ubiquitin–proteasome system causes familial ALS

References

Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia


Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that causes progressive paralysis due to degeneration of upper and lower motor neurons in the brain and spinal cord. Death typically occurs between 2 and 5 years after symptom onset due to respiratory failure. There is no known cure, and treatment is limited to supportive care. Familial ALS (fALS) accounts for only about 10% of all cases, although sporadic cases are phenotypically indistinguishable from inherited ones. The most common causative mutations are found in superoxide dismutase 1 (SOD1), TARDBP and FUS (1), and these three genes along with several others, which have been reported as rare causes of ALS or ALS-like syndromes, account for approximately 30% of fALS.

Deng et al. were able to identify UBQLN2 mutations through analysis of a large ALS family in which the dominant inheritance pattern was indicative of X-linked transmission. After sequencing 41 genes in the candidate region, a unique mutation in UBQLN2 was identified, which is predicted to result in a proline to histamine substitution. Another 188 probands from families without male-to-male transmission were subsequently screened for UBQLN2 mutations. Four other mutations in four unrelated families were identified, all of which interestingly involved proline residues in a unique PXX repeat region of the gene.

A hallmark feature of ALS, and indeed of many neurodegenerative disorders, is the presence of pathologic protein inclusions in affected brain regions. Deng et al. made several careful observations about the aggregation pattern of ubiquilin 2 in pathological ALS cases. First, ubiquilin 2 appears to be a prominent component in the protein aggregates typically occurring in the spinal motor neurons of ALS patients. Inclusions immunoreactive for ubiquilin 2 were found in ALS cases caused by UBQLN2 mutations as well as in sporadic cases and in ALS caused by mutations in other genes. Second, inclusions that are immunoreactive for ubiquilin 2 are also almost always immunoreactive for ubiquitin and p62 and frequently also for TDP43 (the protein product of TARDBP), FUS and optineurin. In ALS/dementia cases (but not in cases of ALS without dementia), ubiquilin 2 immuno-positive inclusions are present in the hippocampus and sometimes, but not always, colabel with phospho-TDP43.

Ubiquilin 2 is a member of the ubiquitin-like protein family, comprising four members in the human genome. The structural organization of all members of the family is characteristic of proteins that deliver ubiquitinated proteins to the proteasome for degradation. The PXX repeat domain, where all of the mutations discovered to date are found (Fig. 2), appears to be a protein interaction domain, suggesting that perhaps misfolded proteins are not being appropriately delivered to the degradation machinery. Some preliminary in vitro experiments using a ubiquitin–proteasome reporter system indicate that mutant ubiquilin 2 does indeed impair the protein degradation pathway. The precise mechanism and downstream consequences of this dysfunction await further investigation. Although the exact role of ubiquilin 2 is still unclear, it seems likely that its association with the ubiquitin–proteasome pathway plays a role in disease pathogenesis.

The removal and clearance of misfolded or damaged proteins is critical for optimal cell functioning and has been implicated as having a role in multiple neurodegenerative disorders (2). The discovery of mutations in UBQLN2 provides a direct link between proteasome function and neurodegeneration, and may renew interest in discovering a means of modulating the ubiquitin–proteasome pathway as a therapeutic approach for ALS.

TL Petkau
Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada
e-mail: tpetkau@cmmt.ubc.ca.

Fig. 2. Schematic of the predicted structural and functional domains of ubiquilin 2, a 624 amino acid protein. A ubiquitin-like domain (UBL, aa.33–103) is predicted to bind the 55a subunit of the proteasome. A C-terminal ubiquitin-associated domain (UBA) is predicted to bind ubiquitinated proteins. Additional predicted structural and functional domains include four heat-shock-chaperonin-binding motifs (STI1) and 12 PXX repeats (aa.491–526). ALS- and ALS/dementia-linked mutations are clustered in the 12 PXX repeats.