TBK1 mutations in sporadic ALS

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Exome sequencing has revolutionised gene mutation discovery, focusing the hunt on disease-causing variants. A recent study in familial ALS (fALS) patients identified mutations in Tuba4A (a tubulin, thus implicating axon dysfunction) as a needle in the haystack (Smith et al 2014,). They looked at 363 fALS cases, with a replication cohort of 272 cases. But no other mutations were immediately obvious. This suggests that the identification of other coding mutations in novel genes in fALS is going to be challenging.

So, given the paucity of clearly pathogenic novel exonic variants in fALS, what are the chances that new mutations could be found in a cohort of sporadic ALS patients (sALS), who by definition have no family history of ALS? The chances ought to be slim, but the sheer size of the latest exome study published in Science was key to identifying a number of novel variants. Cirulli et al looked at a cohort of 2874 sALS and a replication cohort of 1318 ALS cases, some of which were familial. The most significant finding was an over representation of missense and loss of function variants in TANK-binding kinase 1 (TBK1). TBK1 phosphorylates many targets, perhaps most interestingly proteins involved in autophagy, such as OPTN and SQSTM1, both of which are also mutated in some ALS cases. Autophagy is a major mechanism of rubbish disposal that may go awry in neurodegenerative diseases leading to aggregates of TDP-43 in ALS, Lewy bodies in PD and amyloid plaques in AD, and is currently an area of intense research. TBK1, OPTN and SQSTM1 are also all implicated in a second pathway, NFkB, which is involved in inflammation, which is also broadly implicated in ALS.

The authors do not go into more detailed functional studies regarding TBK1 (figure 2 summarises mutations they found in well-known ALS genes, while figure 3 is a pathways/interactions diagram). They do, however, show that another less significant hit from their study, NEK1, interacts in vitro with known ALS genes (VAPB and ALS2).

Clearly a lot more functional work is needed to identify how these TBK1 variants contribute to disease, and TBK1 inhibitors, which are already in existence, may be useful tools to begin this process. Furthermore, the huge amount of data generated by Cirulli et al will serve as an important resource for current researchers and for future, larger studies of ALS, which will identify the missing genes in the interaction networks that underlie motor neuron degeneration.

Smith BN, Ticozzi N, Fallini C, et al. Exome-wide rare variant analysis identifies TUBA4A mutations associated with familial ALS. Neuron. 2014 Oct 22;84(2):324-31

Elizabeth T. Cirulli[1],* Brittany N. Lasseigne[2],* Slavé Petrovski[3] et al Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. Science. Published online Feb 19th 2015.