SORLA-FIX

CSF sSORL1 levels as a potential biomarker for identifying pathogenic SORL1 variants

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Aims, research questions and working hypothesis
SORL1 is a protein critical to the endolysosomal pathway, a key process for maintaining brain health. It facilitates the trafficking of cargo from endosomes to the Golgi or cell surface. When functioning properly, SORL1 is cleaved at the cell surface in a soluble form, known as sSORL1. However, variants that strongly impair *SORL1* disrupt its localization to the cell surface, resulting in reduced levels of sSORL1 in the interstitial fluid. We hypothesize that CSF sSORL1 levels are reflective of the pathogenicity of the variant, serving as an indicator of their impact on protein function.

Means/methods implemented by the consortium
Using a method called Domain Mapping of Disease Mutations (DMDM), we identified high-risk variants associated with Alzheimer's disease and separated missense variants according to priority levels: high priority (HPV), moderate priority (MPV), low priority (LPV), no priority (NPV), and protein truncating variants (PTV). To confirm their effects, we measured sSORL1 concentrations in CSF of these carriers using ELISA and comparing levels among controls (n = 25), AD patients (n = 43) and the different prioritized *SORL1* variant carriers (HPV = 7, MPV = 2, LPV = 1, NPV = 9 and PTV = 5). We validated these findings using Western blotting as an independent method and further confirmed them in vitro by transfecting cells with high-risk variants to assess reductions in sSORL1 shedding.

What are the outcomes of the project?
While sSORL1 levels are variable across individuals, the majority of carriers of high and Moderate priority and PTVs showed reduced sSORL1 levels, indicating a possible impairing effect on SORL1 function.

Significance and impact of the work on the field
These findings provide preliminary evidence that *SORL1* variants impairing SORL1 function can be identified by their reduced levels in CSF.

Next steps and future challenges
We will optimize this ELISA assay by analyzing CSF samples from an independent dataset of SORL1 variant carriers representing diverse priorities (HPV = 11, MPV = 10, LPV = 4, NPV = 3 and PTV = 4). When successful, use of this assay may support *SORL1* variant pathogenicity in future clinical settings.