Human prion diseases are rare, fatal, degenerative disorders of the central nervous system (CNS) which can arise sporadically, be genetically inherited due to autosomal dominant mutations in the *PRNP* gene encoding the prion protein (PrP), or acquired through infection e.g. by meat infected with bovine spongiform encephalopathy (BSE). They are caused by misfolding of PrP into scrapie prion protein (PrP^{Sc} or prion), a pathological isoform rich in β-sheet structure, which is detergent-insoluble, partially protease-resistant, and can self-replicate by inducing misfolding of native PrP. Sporadic Creutzfeldt-Jakob disease (sCJD) is the most common prion disease, that affects 1 to 2 cases per million people each year worldwide. While progress has been made in understanding the molecular basis of the different disease subtypes and the mechanisms that cause brain damage, effective treatments and early pre-symptomatic diagnostic and prognostic tools are still lacking. To address this problem, PRIONOMICS unites a team of world-leading experts in prion research, neuropathology, omics, biomarker development, and bioinformatics from seven different countries (including external collaborations). This interdisciplinary team will use unique and already existing CJD patient cohorts, already existing and novel omics data complemented by cutting-edge bioinformatics to identify the underlying mechanisms that lead to the development and progression of CJD. We will put strong emphasis on identification of dysregulated pathways involved in age at onset and/or disease progression rate. The potential targets and identified pathways will be validated using human organoids. By combining information from human omics-data and mechanistic data from organoids, PRIONOMICS aims to develop new blood-based biomarkers for persons at risk and therapeutic drug targets for CJD. PRIONOMICS places a strong emphasis on involving patients in the research process and making the results accessible to the public.