C9orf72

C9orf72 (chromosome 9 open reading frame 72) is a protein that in humans is encoded by the gene C9orf72.

The human C9orf72 gene is located on the short (p) arm of chromosome 9 open reading frame 72, from base pair 27,546,546 to base pair 27,573,866 (GRCh38). Its cytogenetic location is at 9p21.2.

The protein is found in many regions of the brain, in the cytoplasm of neurons as well as in presynaptic terminals. Disease-causing mutations in the gene were first discovered by two independent research teams, led by Rosa Rademakers of Mayo Clinic and Bryan Traynor of the National Institutes of Health, and were first reported in October 2011.

The mutations in C9orf72 are significant because it is the first pathogenic mechanism identified to be a genetic link between genetic frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS).

Pérez-Millan et al. studied 102 presymptomatic C9orf72 mutation carriers, 52 symptomatic carriers: 42 suffering from FTD and 11 from MND, and 75 non-carriers from the Genetic Frontotemporal dementia Initiative (GENFI). All subjects underwent T1-MRI acquisition. We used FreeSurfer to estimate the volume proportion of WM in the brainstem regions (midbrain, pons, and medulla oblongata). We calculated group differences with ANOVA tests and performed linear and non-linear regressions to assess group-by-age interactions.

A reduced WM ratio was found in all brainstem subregions in symptomatic carriers compared to both noncarriers and pre-symptomatic carriers. Within symptomatic carriers, MND patients presented a lower ratio in pons and medulla oblongata compared with FTD patients. No differences were found between presymptomatic carriers and non-carriers. Clinical severity was negatively associated with the WM ratio. C9orf72 carriers presented greater age-related WM loss than non-carriers, with MND patients showing significantly more atrophy in pons and medulla oblongata.

They find consistent brainstem WM loss in C9orf72 symptomatic carriers with differences related to the clinical phenotype supporting the use of brainstem measures as neuroimaging biomarkers for disease tracking [1)].

Results indicate that the total levels of TDP-43 in the serum are decreased especially in FTD patients with the C9orf72 repeat expansion or FTD-MND phenotype, both subtypes strongly associated with TDP-43 type B brain pathology. Serum-based measurement of TDP-43 could represent a useful tool in indicating C9orf72 repeat expansion and FTD-MND-related TDP-43 neuropathology for future diagnostics and intervention studies [2)].

1)

Pérez-Millan A, Borrego-Écija S, van Swieten JC, Jiskoot L, Moreno F, Laforce R, Graff C, Masellis M, Tartaglia MC, Rowe JB, Borroni B, Finger E, Synofzik M, Galimberti D, Vandenberghe R, de Mendonça A, Butler CR, Gerhard A, Ducharme S, Le Ber I, Santana I, Pasquier F, Levin J, Otto M, Sorbi S, Tiraboschi P, Seelaar H, Langheinrich T, Rohrer JD, Sala-Llonch R, Sánchez-Valle R; Genetic FTD

Initiative, GENFI. Loss of brainstem white matter predicts onset and motor neuron symptoms in C9orf72 expansion carriers: a GENFI study. J Neurol. 2022 Nov 29. doi: 10.1007/s00415-022-11435-x. Epub ahead of print. PMID: 36443488.
2)

Katisko K, Huber N, Kokkola T, Hartikainen P, Krüger J, Heikkinen AL, Paananen V, Leinonen V, Korhonen VE, Helisalmi S, Herukka SK, Cantoni V, Gadola Y, Archetti S, Remes AM, Haapasalo A, Borroni B, Solje E. Serum total TDP-43 levels are decreased in frontotemporal dementia patients with C9orf72 repeat expansion or concomitant motoneuron disease phenotype. Alzheimers Res Ther. 2022 Oct 11;14(1):151. doi: 10.1186/s13195-022-01091-8. PMID: 36217158.