

Neurodegenerative Disease & Movement Disorders

A clinical perspective into early stages of neurodegenerative disease

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Advances in therapeutical strategies for neurodegenerative diseases would reduce the burden related to these diseases. To test effectively compounds for diseases such as Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD), or Alzheimer’s disease (AD) bring therapy to individuals as early as possible, there is an urgent need for the establishment of standards and networks for identification and qualification of biological marker candidates in early stages of neurodegeneration. Biomarkers are needed not just for pre-clinical diagnosis but also to monitor drug safety, to identify individuals who are most likely to respond to specific treatments after stratification of presymptomatic conditions and to quantify the benefits of treatments. In this prospective, genetic markers appear more useful in ALS/FTD: 19 disease genes have been reported to be associated with typical ALS or atypical motor neuron diseases with or without associated frontotemporal dementia (ALS-FTD). Mutations in four genes, namely *SOD1*, *TARDBP*, *FUS*, and *C9orf72*, account for ~50% of all FALS cases and ~10% of SALS. Given the relatively high mutational frequency, a robust genotype-phenotype correlation can be drawn for these genes. Conversely, pathogenic mutations in the other 15 ALS-associated genes (*ALS2*, *SETX*, *SPG11*, *VAPB*, *ANG*, *FIG4*, *OPTN*, *ATXN2*, *VCP*, *UBQLN2*, *SIGMAR1*, *CHMP2B*, *PFN1*, *ERBB4*, and *HNRNPA1*) are collectively responsible for less than 5% of cases. Usually those variants are found in isolated pedigrees, often with atypical ALS phenotypes and are private mutations, thus making a clear genotype-phenotype correlation extremely difficult (Renton et al., 2014). The recent discovery of *C9orf72* gene as the main cause of ALS and FTD definitively consolidated the hypothesis that the two diseases belong to the same phenotypical, neuropathological, and genetic spectrum, opening new prospective in pre-clinical diagnosis. Even before this momentous discovery, however, similar neuropathological features and common mutations in several other genes have been described in both diseases. TDP-43 immunoreactive ubiquitinated inclusions are in fact present in >50% of all FTD cases, while a *FUS* pathology similar to ALS6 is also observed in atypical FTD, basophilic inclusion body dementia, and neuronal intermediate filament inclusion disease. Not

surprisingly, *TARDBP* and *FUS* mutations, originally identified in ALS cases, have been subsequently found in bvFTD patients with or without motor neuron signs. Conversely, other genes initially identified in FTD pedigrees have subsequently been associated to ALS, with or without dementia. Amyotrophy of the limbs has been described in patients with FTD-parkinsonism carrying mutations in the *MAPT* gene. *CHMP2B* mutations have been described in bvFTD patients showing an insidious change in personality and behavior, memory loss, apathy, aggressiveness, stereotyped behavior, disinhibition, dysgraphia and dyscalculia, as well as in ALS cases. Lastly, mutations in the *VCP* gene, originally identified as causative for an uncommon type of FTD associated with inclusion body myopathy and Paget's disease of the bone, have been later found in ALS patients. The discovery of more causative genes in SALS is due mainly to GWAS: we have established the largest association study in ALS to date and undertaken a GWAS meta-analytical study combining 3,959 newly genotyped Italian individuals (1,982 cases, 1,977 controls). We analyzed a total of 13,225 individuals, 6,100 cases and 7,125 controls for almost 7 million single nucleotide polymorphisms (SNPs) and we identified a novel locus with genome-wide significance at 17q11.2 (rs34517613 $P = 1.11 \times 10^{-8}$; OR 0.82) that was validated when combined with genotype data from a replication cohort ($P = 8.62 \times 10^{-9}$; OR 0.833) of 4,656 individuals. Furthermore, we confirmed the previously reported association at 9p21.2 (rs3849943 with $P = 7.69 \times 10^{-9}$; OR 1.16). Finally, we have estimated the contribution of common variation to heritability of sporadic ALS as ~12% using a linear mixed model accounting for all SNPs (Fogh et al., 2013). In both ALS and FTD liquor markers appear insignificant when compared to their role in AD: the adequate definition of amyloid-beta, tau and phosphotau in the cerebrospinal fluid (CSF) overcomes the value of any genetic marker as mutations in one of three genes (APP, PSEN1, and PSEN2) reported as causal in AD (Frisoni et al., 2010). In the present perspective, ALS/FTD and AD represent complementary models to define the early stages of neurodegeneration. The development of neuroimaging techniques, both structural (magnetic resonance imaging; MRI) and functional largely have contributed to our understanding of structural and functional changes in both diseases: the definition of early stages of neurodegeneration represents a critical target for future research. Informations gained from both genetics and CSF biomarkers may ideally complement each other with specific neuroimaging evidence (Agosta et al., 2010).

References

Agosta F., Chiò A., Cosottini M., De Stefano M., Falini A., Mascalchi M., Rocca M.A., Silani V., Tedeschi G., Filippi M. The present and the future of neuroimaging in amyotrophic lateral sclerosis. *AJNR Am J Neuroradiol*, 2010, 31, 1769-1777;

Fogh I., Ratti A, Gellera C, Lin K, Tiloca C, Moskvina V, Corrado L, Sorarù G, Cereda C, Corti S, Gentilini D, Calini D, Castellotti B, Mazzini L, Querin G, Gagliardi S, Del Bo R, Conforti FL, Siciliano G, Inghilleri M, Saccà F, Bongioanni P, Penco S, Corbo M, Sorbi S, Filosto M, Ferlini A, Di Blasio AM, Signorini S, Shatunov A, Jones A, Shaw PJ, Morrison KE, Farmer AE, Van Damme P, Robberecht W, Chiò A, Traynor BJ, Sendtner M, Melki J, Meininger V, Hardiman O, Andersen PM, Leigh NP, Glass JD, Overste D, Diekstra FP, Veldink JH, van Es MA, Shaw CE, Weale ME, Lewis CM, Williams J, Brown RH, Landers JE, Ticozzi N, Ceroni M, Pegoraro E, Comi GP, D'Alfonso S, van den Berg LH, Taroni F, Al-Chalabi A, Powell J, Silani V; the SLAGEN Consortium Collaborators. *Hum Mol Genet*. 2013 Nov 20. [Epub ahead of print] PMID: 24256812

Frisoni G.B., Fox N.C., Jack C.R., Scheltens P., Thomppson P.M. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol* 6, 67-77, 2010

Renton A.E., Chiò A., Traynor B.J. State of play in amyotrophic lateral sclerosis. *Nat Neurosci* 17, 17-23. 2014