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ABSTRACT BOOK

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Detection Of Tardbp Gene Mutations In Frontotemporal Dementia (Ftd) Greek Patients

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Introduction: Frontotemporal Dementia (FTD) can be either familial (30-50%) or sporadic, and is as common as Alzheimer's in people <65 years old. Among the many genes involved in the disease is the TARDBP gene, which encodes the TAR DNA-binding protein 43 (TDP-43) and exists in up to 6 different isoforms in humans, due to alternative splicing. It is involved in various cellular processes, particularly in regulating gene expression and maintaining RNA integrity. TARDBP gene mutations could result in ubiquitin-positive aggregations (mainly 25kDa carboxy-terminal fragments) and mislocalization from the nucleus to the cytoplasm that possibly can leads to FTD.

Patients and methods: In 20 well-ascertained FTD patients, EDTA blood was collected after obtaining their informed consent within the context of the BRAIN PRECISION funding. DNA isolation was performed with the High Pure PCR Template Kit (Roche). Specific primers were designed for DNA amplification and sequencing of the amplicons of 6 TARDBP exons. Then cycle sequencing (Big Dye Terminator v3.1) and electrophoresis of the purified products in the SeqStudio genetic analyzer (Thermo ABI) was executed. Results were analyzed with bioinformatics software Chromas, NovoSNP, Franklin and Varsome.

Results: In 3 samples (A903, A910, and A987), a homozygous variant was found in an intronic region of exon 1 in NG_007375.3(TARDBP):g.207C>T, while in sample A975 showed a

heterozygous variant respectively. In sample A975 was found a synonymous variant (GCT>GCC) in the coding region of exon 2 (chr1:11013925, rs61730366, p.Ala66(=), c.198T>C) in NM_007375.4 sequence), possibly classified as benign. In sample A975, a point mutation (TARDBP:c.584T>A) was identified in exon 5 at chr1:11020469, causing a substitution from glutamic acid to valine (p.Val195Glu) possibly a missense variant of uncertain significance (VUS).

Moreover, in sample A975, a frameshift mutation (g.13048_13049insGfs) was observed in exon 5 of the NM_007375.4 sequence.

Conclusions: Further functional studies are required in order to characterize the pathogenicity of these DNA alterations.