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Supplemental Digital Content 2

Haplotype Analysis: Methods and Results

To investigate whether the three *TARDBP* p.Ser292del variation carriers are descendants of a common founder, allele sharing study was performed with seven microsatellite markers (D1S2663, D1S450, D1S244, D1S2736, D1S2667, D1S2740, D1S228) flanking 6.7 Mb around the TARDBP gene. Microsatellite alleles were typed by electrophoresis on the ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA) using PCR fragments obtained with fluorescently-labeled primers. Primer pairs were those reported in the uniSTS database (http://www.ncbi.nlm.nih.gov/unists/). Different dilutions of the PCR products were further mixed with deionized formamide and the GeneScan 600 LIZ Size Standard (Applied Biosystems). Resulting electropherograms were analyzed using the Peak Scanner software v1.0 (Applied Biosystems). Alleles were defined by direct inspection of the electropherograms. The results are shown in the following table.

Table. Genotypes of *TARDBP* flanking microsatellites in two siblings (II-3, II-5) with FTLD and a control carrying the p.Ser292del variant.

Marker	Genomic position (kb)[a]	Subject's genotype[b]		
		II-3	II-5	Control
D1S2663	7,257	**186**-198	**186**-196	**186**-188
D1S450	9,585	**247**-247	**247**-257	**247**-255
D1S244	10,574	287-**287**	287-**287**	283-**287**
D1S2736	10,615	**117**-117	**117**-117	115-123
TARDBP	11,082	**del**-wt	**del**-wt	**del**-wt
D1S2667	11,487	**248**-262	**248**-254	**248**-266
D1S2740	11,921	82-**94**	92-**94**	92-**94**
D1S228	13,986	**113**-113	**113**-113	**113**-119

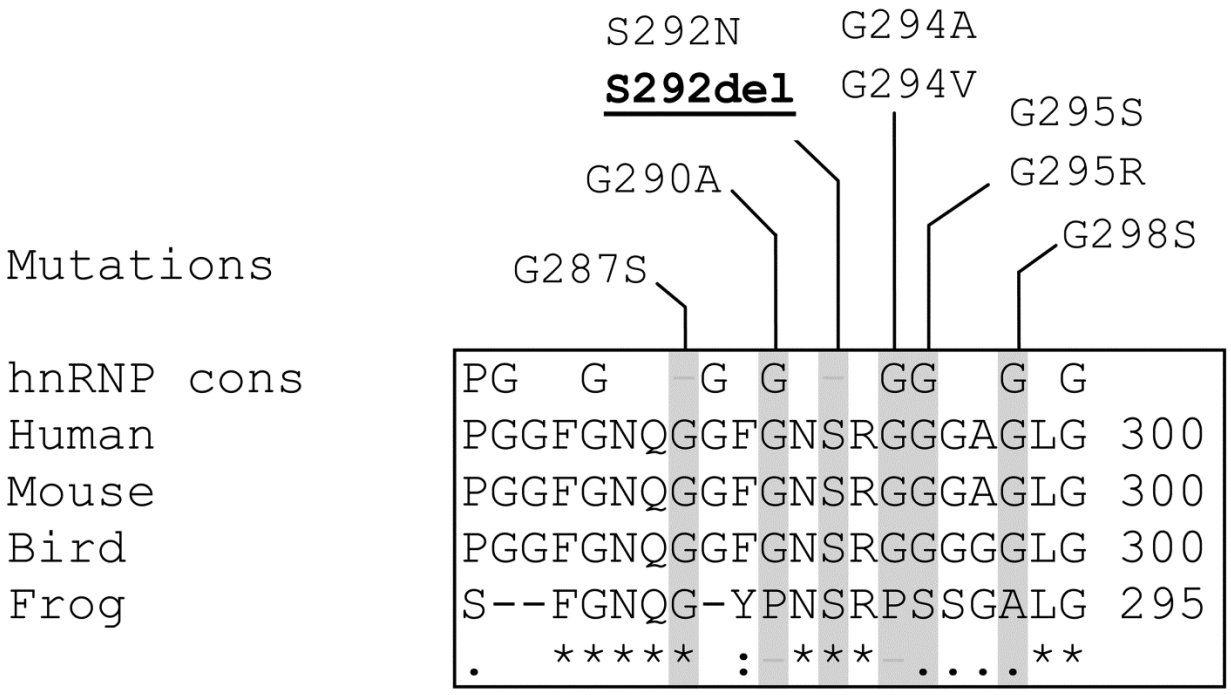
[a]Genomic position relative to Human genome build 37.2.

[b]Alleles that are shared between the FTLD family and the control are in bold.

FTLD indicates frontotemporal lobar degeneration.

Supplemental Digital Content 3

Figure. Conservation of amino acid residues affected by human *TARDBP* variants. The conservation of amino acid residues is shown in comparison to human heterogeneous nuclear ribonucleoproteins (hnRNP) A1 and A2 (fully conserved residues are shown) and to TDP-43 in different species. Human sequence variants are shown according to Lagier-Tourenne et al.,[1] protein access codes used in alignment are in the order of appearance P09651.5, AAB60650.1, Q13148.1, NP_663531.1, NP_001026049.1 and NP_989054.1.



Reference

1. Lagier-Tourenne C, Polymenidou M, Cleveland DW. TDP-43 and FUS/TLS: emerging roles in RNA processing and neurodegeneration. *Hum Mol Genet*. 2010;19:R46-64.

Supplemental Digital Content 1

Supplemental References

S1. Kaivorinne AL, Kruger J, Kuivaniemi K, et al. Role of MAPT mutations and haplotype in frontotemporal lobar degeneration in Northern Finland. *BMC Neurol*. 2008;8:48.

S2. Kruger J, Kaivorinne AL, Udd B, et al. Low prevalence of progranulin mutations in Finnish patients with frontotemporal lobar degeneration. *Eur J Neurol*. 2009;16:27-30.

S3. Sreedharan J, Blair IP, Tripathi VB, et al. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science*. 2008;319:1668-1672.

S4. Buratti E, Brindisi A, Giombi M, et al. TDP-43 binds heterogeneous nuclear ribonucleoprotein A/B through its C-terminal tail: an important region for the inhibition of cystic fibrosis transmembrane conductance regulator exon 9 splicing. *J Biol Chem*. 2005;280:37572-37584.