journALS

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A comprehensive, uniform analysis of three decades of genetics research in ALS and FTD

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Overview

We present journALS, a soon-to-be launched web application designed to assess the clinical significance of all previously reported ALS- and FTD-associated genetic variants. Data is presented from 1,028 manually screened genetic studies. This primary corpus contains 3,112 reported variants in 363 genes. For each variant, detailed phenotype data including sex, age of onset and family status were gathered, in addition to variant information such as zygosity and *de novo* status. Variants were annotated with large publicly available datasets in addition to ALS-specific datasets and are analysed uniformly and agnostically in accordance with the American College of Medical Genetics guidelines; assessing each variant for pathogenicity, penetrance, prevalence, and phenotypic and geographic heterogeneity.

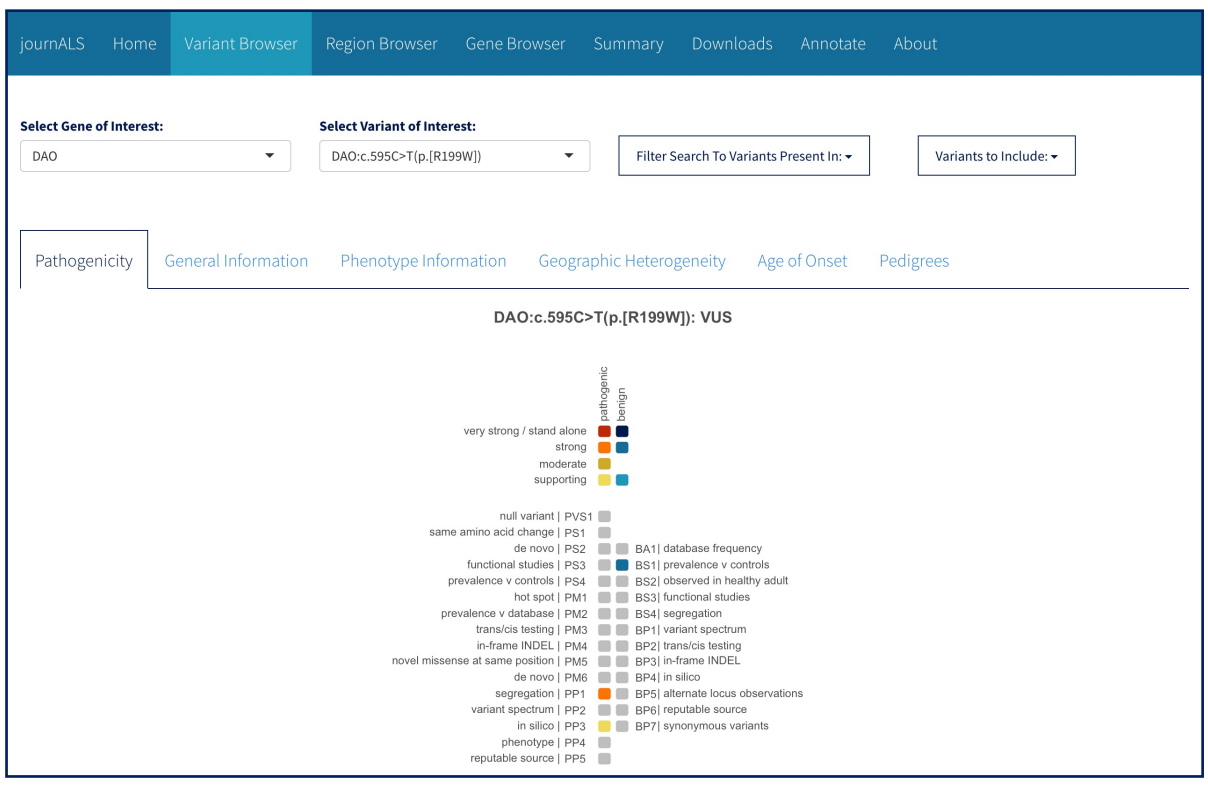

Figure 1: journALS Screenshot
ACMG criteria are viewed for *DAO*:c.595C>T(p.[R1999W]). Even though the variant has been found to strongly segregate in a pedigree (PP1) and *in silico* tools predict pathogenicity (PP3), there is also strong benign evidence as the variant is more common in controls than in cases (BS1).

Results

112 pathogenic (P) and likely pathogenic (LP) variants are confirmed in 21 genes (Table 1), with 10% of variants classified as benign or likely benign; and greater than 89% classified as variants of uncertain significance. Globally, pathogenic variants are identified in 38% of familial ALS patients and 7% of sporadic ALS patients; compared to 37% of familial FTD cases and 4% of sporadic FTD cases (Figure 2).

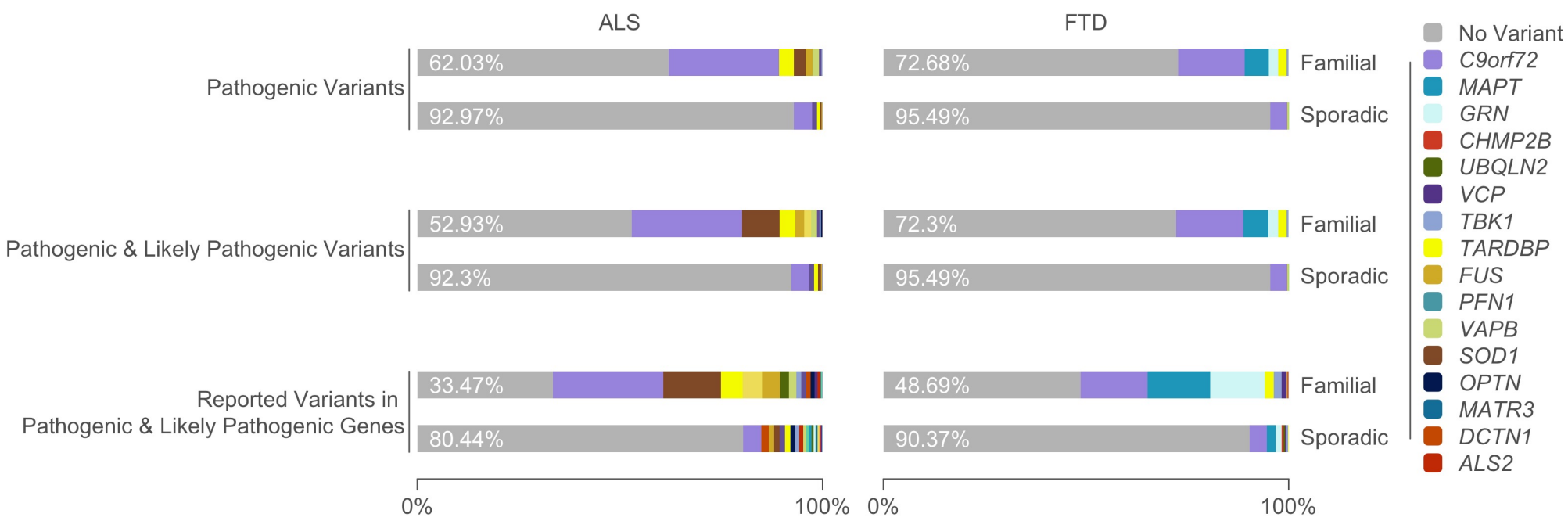

Figure 2: Global Proportion of ALS and FTD Variant Carriers
For ALS and FTD the percentage of carriers of P variants, P and LP variants, and any variant in genes carrying P or LP variants are presented. The written percentage indicates the percentage of cases carrying no variant.

Table 1: Genes Carrying Pathogenic of Likely Pathogenic ALS or FTD Variants

Genes carrying pathogenic variants
C9orf72,FUS, GRN, MAPT,SETX, SOD1, TARDBP, TBK1,VAPB
Additional genes carrying likely pathogenic variants
ALS2, CHMP2B, DCTN1, ERLIN1, ERLIN2, MATR3, OPTN, PARK7, PFN1, SIGMAR1, UBQLN2, VCP

Conclusion

Our analysis finds pathogenic or likely pathogenic variants in 21 genes out of 363 cited in the literature. Our results support a reorientated view of several ALS and FTD genes and genetic variants for which the published evidence depends heavily on only a single domain. However, there are also reasons why our analysis of high penetrance, pathogenic variants may not identify a truly causative gene. Some papers omit key details such as segregation evidence which is necessary for characterisation within our pipeline. Additionally, ALS genes recently identified through genome-wide association and exome burden studies may not have a particular identifiable pathogenic variant.

As precision treatments targeting specific ALS-causing mutations in specific patients are becoming an increasingly important therapeutic paradigm, distinguishing truly pathogenic ALS and FTD variants from benign genetic variation is now essential; journALS is a tool to achieve this.

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