ALS in Turkey: Results from recent genetic studies

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Screening for common ALS genes
(Sanger sequencing and Fragment length analysis)

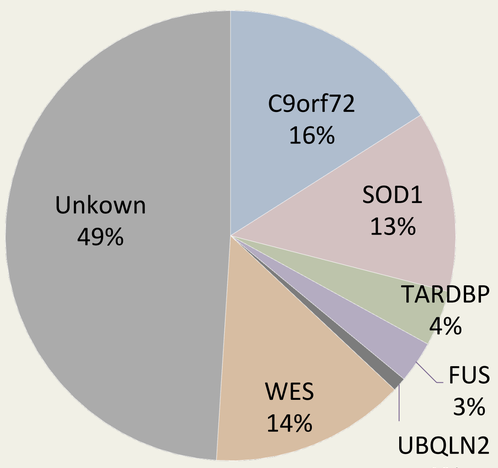
- **sALS and fALS** — C9orf72
- **fALS with dominant inheritance** — SOD1, TARDBP, FUS, UBQLN2 (X-linked)
- **Cases with consanguinity** — SOD1-D90A, SOD1-N86S

Analysis of rare ALS genes & Searching for novel ALS genes

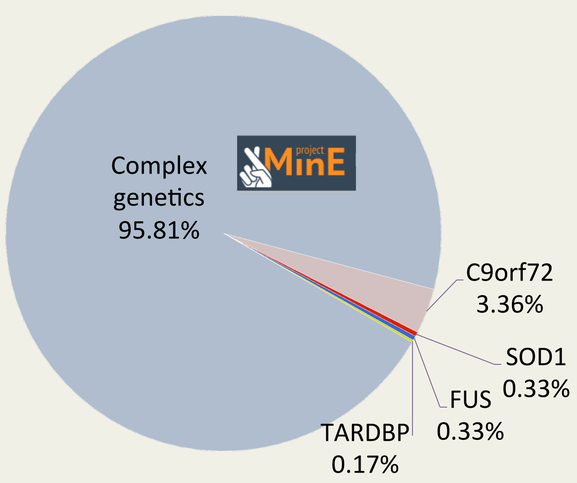
- **Whole Exome Sequencing in consanguineous families**
  - Differential diagnosis in cases with juvenile onset or atypical ALS
  - Searching disease modifiers in families with low or incomplete penetrance
- **Whole Genome Sequencing in sALS**
  - Novel gene identification & Functional Studies

Turkey, with its wealthy historical background and unique geography forms a natural bridge between Europe and Asia. The coastal areas at the Mediterranean Sea and extensive rural parts bordering the Near Eastern countries and the Black Sea make Turkey a rich genetic pool with a high ethnic heterogeneity. In contrast with other European populations, in which family sizes have been decreasing steadily in the last 50 years, Turkey is still very dynamic, with high birth rates and traditionally large kindreds consisting of several living generations and an impressive number of offspring. Because close consanguineous marriages are still part of the Turkish culture, exceeding 60% in the eastern parts of the country, the number of autosomal recessively inherited forms of diseases is in excess of what is to be expected. In this study, we report the results of our systematic research on the molecular basis of ALS in Turkey.

229 fALS (162 families)



734 sALS

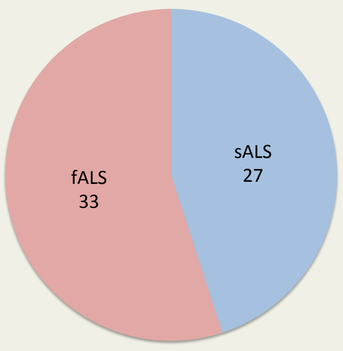


C9orf72

26 families with 33 affected individuals and six yet asymptomatic gene carriers
27 apparently sporadic cases

Age of onset
range: 32-80
mean: 55±9,6

Site of onset
limb: 19
bulbar: 10
mixed: 1
cognitive dysfunction: 6

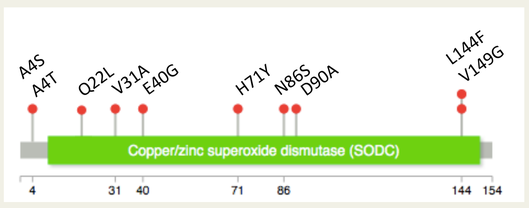


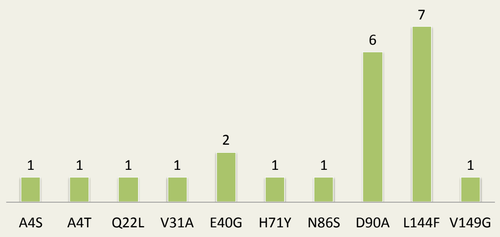
Age of onset
range: 40-71
mean: 53±8,4

Site of onset
limb: 18
bulbar: 3
mixed: 3
cognitive dysfunction: 3

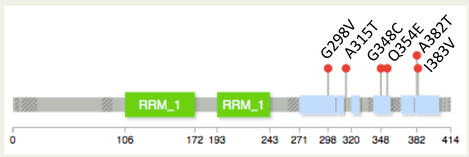
SOD1

10 different mutations in 22 cases

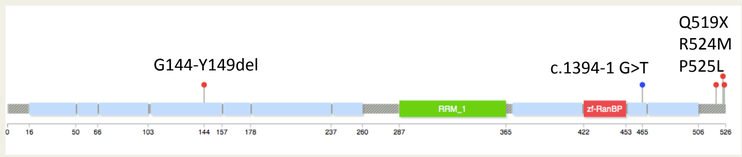




TARDBP



FUS



Whole Exome Analyses

Exome analysis in 55 pedigrees with either dominant inheritance pattern or first-degree consanguinity, revealed distinct and rare mutations in 23 families. In most of the cases where consanguinity and juvenile disease-onset is present, we have identified mutations in genes that are not primarily associated with ALS. Although the patients were initially diagnosed with ALS, the results showed that making a differential diagnosis can be very hard due to the varying and overlapping phenotypes in the spectrum of motor neuron diseases.

	Gene	DNA change	Protein change	# of patients	Age of onset of index	Phenotypes of patients
AD	MPZ#1	c.293G>A	p.Arg98His	3	43	Charcot-Marie-Tooth
	ANG#1	c.208A>G	p.Ile70Val	1	52	ALS
	VCP#1	c.572G>C	p.Arg191Pro	2	58	ALS with dementia
	ERBB4#1	c.3286C>T	p.Arg1096Cys	3	47	ALS
	LRSAM1#1	c.578G>A	p.Cys193Tyr	2		Charcot-Marie-Tooth 2P
	TRPV4#1	c.943C>T	p.Arg315Trp	2	8	Scapuloperoneal Spinal Muscular Atrophy
	TRPM7#1	c.4445C>T	p.Thr1482Ile	2	19	ALS
	SQSTM1#1	c.822G>C	p.Glu274Asp			
AR	ERLIN1#1	c.281T>C	p.Val94Ala	4	15	Slow progressive ALS/ Hereditary Spastic Paraplegia
	C19orf12#1	c.194G>T	p.Gly65Val	1	9	Neurodegeneration with Brain Iron Accumulation 4
	C19orf12#2	c.194G>T	p.Gly65Val	1	10	
	C19orf12#3	c.32C>T	p.Thr11Met	1	24	
	DNAJB2	c.757G>A	p.Glu253Lys	1	30	Distal Spinal Muscular Atrophy
	IGHMBP2#1	c.638A>G	p.His213Arg	1	9	Spinal muscular atrophy with respiratory distress
	SYNE1#1	c.22930C>T	p.Gln7644Ter	2	21	Young-onset ALS
	SYNE1#2	c.23524C>T	p.Arg7842Ter	4	17	
	ACADS#1	c.1108A>G	p.Met370Val	1	25	Short-cahin Acyl-Coa dehydrogenase deficiency
	SPG11#1	c.6224A>G c.7155TC>G	p.Asn2075Ser p.Tyr2385Ter	2	23	SPG11-based ALS
	SPG11#2	c.7132T>C c.2250delT	p.Phe2378Leu p.Phe750Leufs*3	2	14	
	OPTN#1	c.293T>A c.873dupC	p.Met98Lys p.Gly291fsX6	2	31	ALS
	OPTN#2	c.1075delAA	p.359 del AA	3	32	
	OPTN#3	c.1075delAA	p.359 del AA	2	43	
	DJ1#1	c.133C>T	p.Gln45Ter	3	24	ALS-Parkinsonism-dementia
	PLEKHG5#1	c.2120C>A	p.Pro707His	1	14	Young-onset ALS
	PLEKHG5#2	c.1648C>T	p.Gln550Ter	2	20	

Project MinE: Whole Genome Analyses

Within the framework of Project MinE, currently we are analyzing the results of 313 ALS patients and 113 controls. So far, we identified several rare mutations in genes with low penetrance like *VCP, ERBB4* and *ANG*.

In the long run, the collected data will pave the way to establish a Turkish population-specific database.

The epidemiology of ALS in Turkey has features representing the pattern seen in Caucasian populations; however, it has also specific aspects, such as the more complex nature of the disease in molecular and clinical terms. The rich spectrum of mutations reflects both the different genetic background and the heterogeneous nature of the Turkish population, broadening the phenotype associated with ALS (Özoğuz et al., 2015).

Acknowledgements
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References
Özoğuz et al., 2015. The distinct genetic pattern of ALS in Turkey and novel mutations. *Neurobiology of Aging*, 36, 1764.e9-1764.e18.