Fused in Sarcoma Amyotrophic Lateral Sclerosis (FUS-ALS) Is One of the Most Severe and Aggressive Types of Genetic ALS[1]

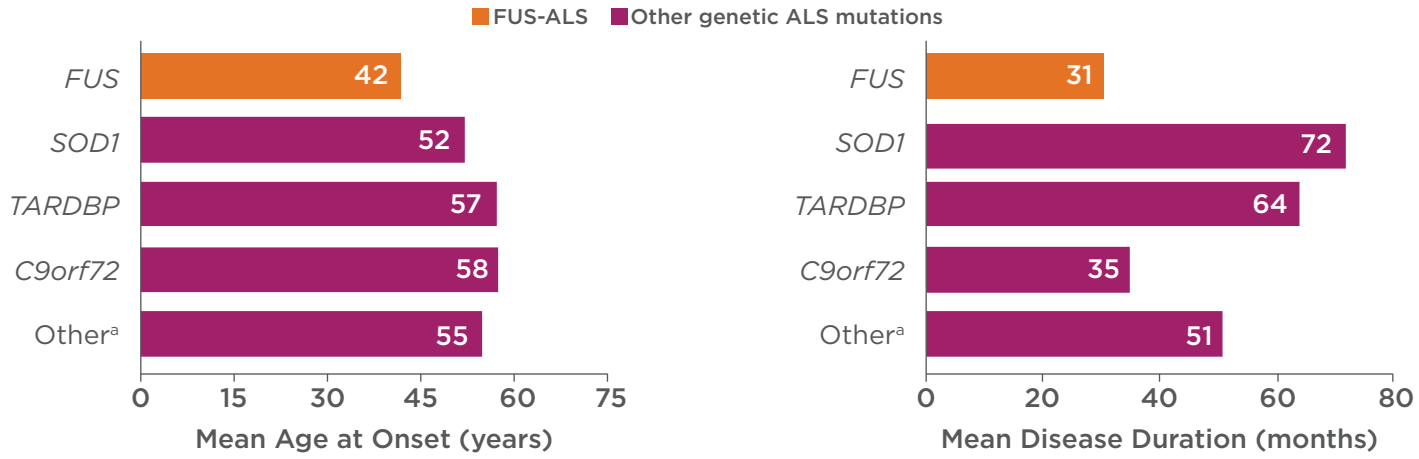
ALS is a neurodegenerative disorder that occurs due to loss of upper and lower neurons, leading to progressive paralysis and death.[1]

FUS variants are 1 of the 5 most common causes of genetic ALS[2]

Genetic ALS: ALS due to a genetic variant in patients with and without a family history of the disease makes up >10% of all cases of ALS.[2]

People living with FUS-ALS are generally younger at disease onset and have a shorter duration of survival than people living with other forms of genetic ALS.[1,3,4] More than 60% of people living with FUS-ALS are <45 years of age.[5] In addition to being severe and aggressive, FUS-ALS patients may also present with frontotemporal dementia.[1,6] The mean survival of patients with FUS-ALS is 31 (±25, standard deviation) months following symptom onset (Figure 1).[1]

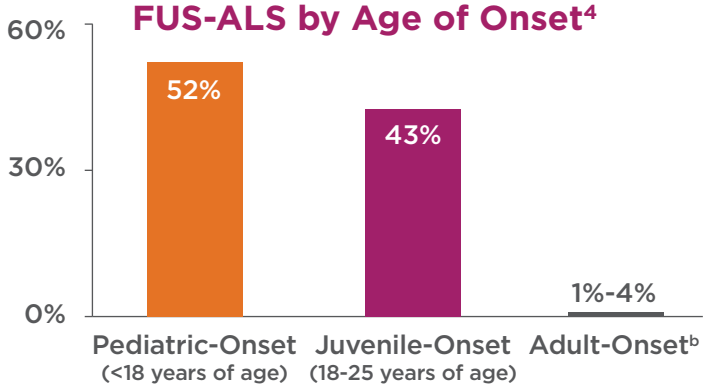
Figure 1: Age of Onset and Disease Duration by Known Variants Associated With Genetic ALS[1]



FUS variants are the leading cause of juvenile- and pediatric-onset ALS (Figure 2).[4] In patients with pediatric-onset FUS-ALS, disease onset generally occurs during adolescence.[4] Patients with FUS-ALS have a mean age of onset of 42 years.[1]

The type of *FUS* variant can affect the severity and rate of disease progression, as well as the age of disease onset.[7]

Figure 2: Percentage of People Living With ALS Diagnosed With FUS-ALS by Age of Onset[4]



[a]Other is an average of less prevalent mutations that are known to cause genetic ALS. Mutations include *CCNF*, *UBQLN2*, *KIF5A*, *ANG*, *PFN1*, *ATXN2*, *VAPB*, *OPTN*, *SQSTM1*, *NEK1*, *SETX*, *TBK1*, *TUBA4A*, *FIG4*, *MATR3*, *VCP*, *SPG11*, *hnRNPA1*, and *ALS2*.[1] [b]FUS-ALS accounts for ~1% of ALS cases with no known family history and 4% of cases with a known family history.[4]

1. Connolly O, et al. *J Pers Med.* 2020;10(3):58. 2. Salmon K, et al. *Brain*. 2022;145(4):1207-1210. 3. Sharma A, et al. *Nat Commun.* 2016;7:10465. 4. Picher-Martel V, et al. *J Child Neurol.* 2020;35(8):556-562. 5. Shang Y, Huang EJ. *Brain Res.* 2016;1647:65-78. 6. Ling SC, et al. *Neuron.* 2013;79(3):416-438. 7. Naumann M, et al. *Ann Clin Transl Neurol.* 2019;6(12):2384-2394.

Early Diagnosis and Treatment Are Critical for People With Fused in Sarcoma Amyotrophic Lateral Sclerosis (FUS-ALS)[1]

A diagnosis of FUS-ALS can be delayed from months to years due to variability in clinical presentation, lack of biomarkers, and paucity of genetic testing[2,3]

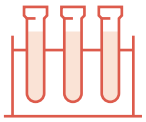
Consensus guidelines published by the American Neurological Association regarding ALS genetic testing and counseling recommend that all persons with ALS be offered genetic testing with an ALS gene panel that includes screening for *FUS* variants.[4]

A diagnosis of ALS may be delayed a median of ~9-24 months.[3]

ALS may be misdiagnosed in up to 68% of cases due to the variability in clinical presentation and lack of biomarkers.[3,5]

Genetic testing rates in ALS often don't reflect the true burden of genetic variants in ALS.[6]

A genetic test is required to confirm a diagnosis of FUS-ALS because the initial symptoms are nonspecific.[2,3]



Genetic testing may shorten the time it takes to diagnose, provide insight into the type of ALS, inform treatment choices, and provide opportunities for people to participate in research or clinical trials.[1,7-9]

Earlier care and treatment by a collaborative multidisciplinary team is associated with a modest improvement in quality of life and survival[10]

People with FUS-ALS should be managed with a collaborative multidisciplinary team of healthcare professionals (HCPs), which may include[2,10]

- Neurologists
- Nurses
- Pulmonologists
- Speech therapists
- Physical and occupational therapists
- Respiratory therapists
- Nutritionists/dietitians
- Psychologists
- Social workers
- Genetic counselors

None of the Food and Drug Administration (FDA)–approved treatments available for ALS specifically target FUS or its associated underlying disease pathology.[11-16]

1. Salmon K, et al. *Brain*. 2022;145(4):1207-1210. 2. Siddique N, Siddique T. In: *GeneReviews®*. University of Washington, Seattle; 1993-2021. March 23, 2001. Updated September 28, 2023. Accessed January 29, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1450/ 3. Longinetti E, Fang F. *Curr Opin Neurol*. 2019;32(5):771-776. 4. Roggenbuck J, et al; ALS Genetic Testing and Counseling Guidelines Expert Panel. *Ann Clin Transl Neurol*. 2023;10(11):2074-2091. 5. Richards D, et al. *J Neurol Sci*. 2020;417:117054. 6. Vajda A, et al. *Neurology*. 2017;88(10):991-999. 7. Zhang L, Hong H. *Pharmaceutics*. 2015;7(4):542-553. 8. Roggenbuck J, et al. *Genet Med*. 2017;19(3):267-274. 9. Klein CJ, Foroud TM. *Mayo Clin Proc*. 2017;92(2):292-305. 10. Chen JJ. *Am J Manag Care*. 2020;26(9 suppl):S191-S197. 11. Chia R, et al. *Lancet Neurol*. 2018;17(1):94-102. 12. Hergesheimer R, et al. *Expert Opin Pharmacother*. 2020;21(9):1103-1110. 13. FDA approves new treatment option for patients with ALS. US Food and Drug Administration. September 29, 2022. Accessed January 28, 2024. https://www.fda.gov/news-events/press-announcements/fda-approvesnew-treatment-option-patients-als/ 14. Yadav A, et al. *J Neuroinflammation*. 2021;18(1):238. 15. Kusaczuk M. *Cells*. 2019;8(12):1471. 16. Qalsody. Package insert. Biogen MA Inc. Updated April 2023. Accessed January 12, 2024. https://www.biogencdn.com/us/pdfs/qalsody-prescribing-information.pdf/