SHORT NOTE

ALSOD: The Amyotrophic Lateral Sclerosis Online Database

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Abstract

More than 100 point mutations spanning the 153 amino acid SOD1 sequence have been identified in individuals with ALS. In 1999 the Amyotrophic Lateral Sclerosis Database (ALSOD) was generated to store these mutations along with ALS patient information to facilitate the identification of a correlation between the SOD1 genotype with the ALS phenotype. Here we report our ongoing development and redesign of the ALSOD database and its automated procedures. The significant new features have improved ALSOD, helping link the mutations of the SOD1 gene to the hypothetical three-dimensional protein structural rearrangement, and the resulting ALS phenotype. Additionally, ALSOD now provides a more comprehensive knowledge base for ALS, detailing genetic, proteomic, and bioinformatics information associated with the disease. ALSOD can be accessed at http://alsod.iop.kcl.ac.uk/als/.

Key words: ALSOD, amyotrophic lateral sclerosis, database, SOD1, genetics

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disease of motor neurons, that results in relentlessly progressive weakness and death from respiratory failure, usually within three years. The only reliably reproducible risk factors are increasing age, being male, or having a family history of ALS (present in approximately 2–13% of cases). In 12–23% of those with a family history and about 2–7% of all cases, mutations are found in the SOD1 gene (1). However, despite a decade and a half of research, the mechanism by which SOD1 mutations cause ALS remains unknown. In 1999 the ALSOD database was put in place to store clinical and genetic information, to help identify correlations between ALS genotype and ALS phenotype (2). More than 100 different point mutations spanning the 153 amino acid SOD1 sequence are now stored in ALSOD with corresponding clinical information.

In this paper we report our ongoing development of the ALSOD database and its automated procedures. These significant new features have improved ALSOD, helping to link the genetic mutations of the SOD1 protein to the hypothetical 3-D structural rearrangements caused by the mutation, and the resulting patient phenotype.

An overview of ALSOD v2.0

Since the release of ALSOD v1.0 in 1999, ALSOD has significantly grown and been utilized by institutes across the world. In total, 50 users from four different continents (Asia, North America, Europe and Australia) have registered with ALSOD to add data to the database. From these 50 users, 17 institutions have submitted ALS mutational information to ALSOD, and 10 institutions have submitted ALS patient information to the database.

ALSOD mutational information update

In the last nine years the number of mutations recorded for the SOD1 gene has nearly doubled to 122. Those reported in ALSOD consist of 107 exon substitutions, two intron substitutions, four deletions, three insertions, five non-pathological variants, and one set of compound mutations. Nearly all submissions have come from the research teams.
ALSOD patient information update

There are clinical details for 97 individuals with familial SOD1 mutations in ALSOD representing 12 different countries and three continents (Asia, Europe and North America). These include 55 males and 42 females. Ethnicity is reported as Asian, Indian, Latino-American, or White, with the majority being White (70). The mean age of onset for the 86 subjects with the required data is 47.2 years (range 14–72 years). The site of onset is recorded as lower limb in 59 individuals, upper limb in 24, and bulbar in three individuals.

The ALSOD website

The website is now located at http://alsod.iop.kcl.ac.uk/als and has been broken down into 12 sections making it easier to find the relevant data quickly. By selecting the case summary section, a user can quickly retrieve all of the mutational data and patient information entered for their gene of interest. A further development to the website is the addition of a data download page permitting the free download of all of the patient and mutational data in ALSOD.

Significant changes have been implemented on the ALSOD website so the database can be searched to look for a specific type of mutation (compound, insertion, deletion, substitution or non-pathological variant) in an ALS gene of interest (SOD1, ALS2, VAPB or NEFH). For each mutation the DNA position mutated, original DNA sequence, mutated DNA sequence, original amino acid, mutated amino acid, intron/exon location, zygosity, and a link to hypothetical mutant structure, can be identified. Since the last release the ALSOD team have collaborated with the Motor Neuron Database Team (MNDB) at University College London (UCL), to develop a structural protein model for each mutation. Each SOD1 mutant sequence is mapped on to the Protein Database (PDB) coordinates of all of known crystallized SOD1 structures, and a series of tests are run to predict how the amino acid substitution affects the tertiary structure of the SOD1 protein.

Future plans for ALSOD

Over the next few months ALSOD will be expanded to incorporate mutational data and patient information for additional genes that have been linked to ALS (e.g. TDP43 and DCTN1). More graphical and statistical summary web pages will be developed, further improving the appearance and functionality of the ALSOD website.

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References