Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease that causes a loss of the nerve cells that control movement [1]. There is progressive weakness leading to death due to respiratory failure. In Australia, at any one time, about 2000 people are living with ALS, and about 400,000 people diagnosed with ALS worldwide. The cause of ALS is still unclear.

The majority of ALS is sporadic (SALS), however, about 10% of all ALS patients are familial (FALS) with an autosomal dominant pattern of inheritance [2], which means the second generation only needs to get the abnormal gene from one parent to inherit the disease. Current theories of ALS pathogenesis include genetic risk factors, stress to cells due to oxygen free radicals, abnormal proteins within cells. Among these theories, the effect of genetic risk factors has attracted a lot of attention.

The recognition of genetic risk factors in ALS came from observing epidemiological aggregation of ALS in families. Nonetheless, these genetic risk factors are varied [3] with many elements interlinking to form the clinical picture of ALS, and no single element solely responsible.

Studies based on FALS have achieved important outcomes. So far, over 20 Mendelian genes in ALS have been identified. Mendelian genes are genes passed from parents to their children. These genes are major risk genes for ALS. Examples include TARDBP (also called TDP-43), the gene for “TAR DNA binding protein”; FUS, which is the gene name from ‘Fused-in-sarcoma’; DAO, which is the gene for D-amino acid oxidase. SOD1, the gene of “Superoxide dismutase 1” and OPTN, the gene for Optineurin.

Although some of ALS risk genes have been identified, how these Mendelian genes can impact the development of this disease is still under investigation. Improved techniques in genetics, molecular study and cell biology have resulted in an initial understanding of potential mechanisms, however further research is still required.

TARDBP is the gene name of the TAR DNA binding protein 43 (TDP-43). TARDBP mutations are also linked with cell death in ALS. Mutations in TARDBP can be found in about 4% of FALS patients. There is very small percentage of SALS patients also carrying the mutated TARDBP gene form.

FUS was identified after TARDBP. There are about 4% ALS patients carrying mutations in the FUS gene. It is understood that FUS is a small molecule that goes to the cell nucleus to function [4] and FUS mutations can cause motor neuron degeneration.

SOD1 is the gene name of “Copper zinc superoxide dismutase 1”. It was discovered in 1993. The function of SOD1 is to metabolise superoxide radicals. Mutations in SOD1 gene can
affect SOD1 function and also cause cell death in motor neurons. Mutations in SOD1 gene are responsible for about 20% of familial cases of ALS [5].

OPTN is a relatively newly identified risk gene in ALS and was initially identified in Japanese families. OPTN negatively regulates certain cellular molecular pathways. Mutations in OPTN can prevent it from functioning normally, causing cellular pathways being operated abnormally (over operated for example) which may have involvement in the disease process.

The discovery of the many causative genes for ALS indicates this disease is not associated with a single clinically inducing entity. Genetic factors contribute to some of the pathogenesis of ALS. Understanding the mechanisms behind ALS development, particularly from a genetic perspective can contribute great lengths and options in the design of new and better targeted therapeutics for treatment of patients.

2. Broom, W.J.; Greenway, M.; Sadri-Vakili, G.; Russ, C.; Auwarter, K.E.; Glajch, K.E.; Dupre, N.; Swingler, R.J.; Purcell, S.; Hayward, C., et al., 50bp deletion in the promoter for superoxide dismutase 1 (sod1) reduces sod1 expression in vitro and may correlate with increased age of onset of sporadic amyotrophic lateral sclerosis. Amyotroph Lateral Sc 2008, 9, 229-237.