1. Raziskovalna organizacija (*Research organisation)*:

Univerza v Ljubljani,
Medicinska Fakulteta, Inštitut za patologijo (Faculty of Medicine, Institute of Pathology)

2. Ime in priimek mentorja (*Name and surname of a mentor*):

Damjan Glavač

3. Področje znanosti iz šifranta ARRS (*Primary research field*):

3 - Medicinske vede, 3. 01 Temeljna medicina in 3. 03 Nevrobiologija
3 – Medical Sciences, 3. 01 Basic medicine and 3. 03 Neurobiology

4. Kontaktni e-naslov mentorja (*Contact of a mentor)*:

Oddelek za molekularno genetiko, Korytkova 2, 1000, Ljubljana
Telefon : 01 543 7180, E-pošta : damjan.glavac@mf.uni-lj.si

5. Kratek opis programa usposabljanja (*Short description of the program)*:

SLO
Amiotrofična lateralna skleroza je nevrodegenerativna bolezen, za katero je značilna selektivna izguba zgornjih in spodnjih motoričnih nevronov. Degeneracija nevronov vodi do postopne atrofije skeletnih mišic in smrti zaradi dihalne nezadostnosti, običajno 2-5 let od pojava simptomov bolezni. Na novo zbolita letno 2 posameznika na 100.000 prebivalcev, najpogosteje okoli 55. leta starosti. Približno 10% vseh primerov bolezni je družinskih, večina bolnikov pa ima sporadično obliko bolezni, ki se fenotipsko ne razlikuje od družinske oblike, kar pomeni, da verjetno obstaja skupen proces, ki vodi do smrti nevronov.
Razvili bomo novo večnivojsko molekularnogenetsko metodologijo, ki vključuje analizo na nivoju genoma, transkriptoma (kodirajočega in nekodirajočega) in epigenoma (metilacija DNA).
Z uporabo sekvenciranja nove generacije bomo prvič izvedli obsežno molekularnogenetsko analizo slovenskih bolnikov z amiotrofično lateralno sklerozo (ALS). V raziskavo bomo vključili približno 200 bolnikov z ALS in približno enako število zdravih kontrol. Z genetsko analizo bomo ugotavljali prisotnost mutacij/polimorfizmov v genih, ki so jih do sedaj v največ študijah povezali z boleznijo in vključujejo ALS2, ANG, ATXN2, C9orf72, DAO, DCTN1, FIG4, FUS, NEFH, OPTN, SETX, SOD1, SPG11, TAF15, SIGMAR1, CHMP2B , PFN1, ERBB4, HNRNPA1, MATR3, CHCHD10, UNC13A, PRPH, SQSTM1, SPAST, ELP3, LMNB1, TARDBP, UBQLN2, VAPB, VCP. Z analizo RNA po celotnem transkriptomu bomo ugotavljali spremenjeno izražanje na nivoju mRNA, dolgih nekodirajočih RNA in miRNA med bolniki z ALS in kotrolno skupino.To nam bo omogočilo, da na nivoju RNA odkrijemo določene nove potencialne gene povezane z nastankom bolezni ali nove molekularne označevalce na nivoju nekodirajočih RNA, predvsem miRNA. Z ugotavljanjem spremenjeno izraženih nekodirajočih RNA se odpira tudi možnost raziskovanja tarčnih genov teh RNA kot potencialnih genov vključenih v razvoj bolezni. Spremenjen nivo metilacije DNA, ki ga bomo raziskovali, je tudi lahko biološki označevalec, ki vpliva na nastanek in potek bolezni ter zdravljenje.
Rezultati te raziskave bodo omogočili širši vpogled v molekularnogenetske mehanizme amiotrofične lateralne skleroze, ki je zaenkrat neozdravljiva bolezen. Odkritje novih molekularnih označevalcev bolezni na nivoju DNA, epigenetike ali kodirajočih in nekodirajočih RNA predstavlja potencialno možnost za zgodnejšo diagnostiko bolezni ali za oblikovanje molekulskih tarč za prihodnje zdravljenje.

ANG

Amyotrophic lateral sclerosis is neurodegenerative disease characterized by the selective loss of upper and lower motor neurons. This neuronal degeneration leads to a progressive skeletal muscle atrophy and death by respiration failure after 2-5 years from onset of symptoms. The disease, presenting in middle age, has an incidence of 2 per 100,000 persons per year. The familial ALS forms represent only 10% of cases, majority of cases are sporadic forms, which are mostly phenotypically indistinguishable from familial forms, suggesting the existence of common pathways at the basis of neuronal death.

We will develop a new multilevel molecular-genetic methodology which includes analysis at the genome, transcriptome (coding and non-coding) and epigenome (methylation) level.

Using next generation sequencing we will perform first comprehensive molecular genetic analysis of Slovenian patients with amyotrophic lateral sclerosis (ALS). In the study we will include about 200 patients with ALS and approximately the same number of healthy controls. Genetic analysis will enable us to detect genetic mutations/polymorphisms in genes that have been up to now most frequently associated with the disease. We will analyse genes including ALS2, ANG, ATXN2, C9orf72, CRYM, DAO, DCTN1, FIG4, FUS, LUM, NEFH, OPTN, SETX, SOD1, SPG11, TAF15, SIGMAR1, CHMP2B , PFN1, ERBB4, HNRNPA1, MATR3, CHCHD10, UNC13A, PRPH, SQSTM1, SPAST, ELP3, LMNB1, TARDBP, UBQLN2, VAPB, VCP.

With RNA analysis through the entire transcriptome we will search for differential expression on the level of mRNA, lncRNA and miRNA between patients and controls. This will allow us to detect at the level of mRNA potencial novel genes associated with the disease or novel molecular markers among ncRNAs, specialy miRNAs. Differentially expressed ncRNAs enable also research of target genes of these ncRNAs as potential genes in association with disease. Changes in the level of DNA methylation could also serve as biological marker that influence development and treatement of disease.

Results of this research will enable a wider insight in molecular-genetic mechanisms of amyotrophic lateral sclerosis, which is incurable for the time being. The discovery of new molecular markers of the disease on the DNA level, epigenetic or coding and non-coding RNAs represents potential for earlier diagnostic and for designing new molecular targets for future treatment.