Discovery of microRNA – related mutations in human ALS patient genomes

Acronym: miRNAgenetics

Principal Investigator: Eran Hornstein

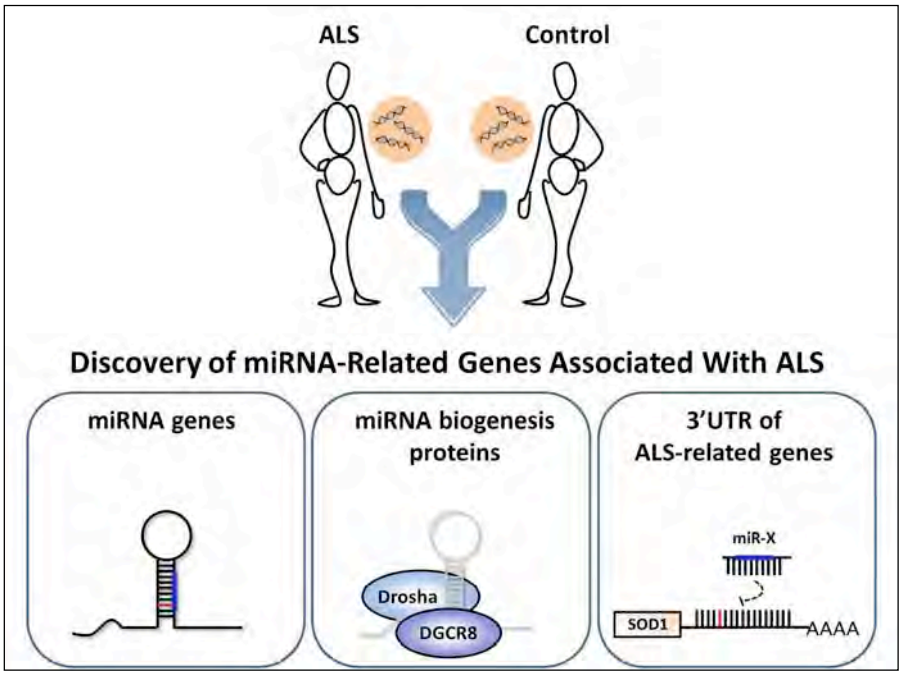
Grant: 80 000€

Duration: one year

Summary of the research project

Recent advances in next generation sequencing bring to reality a new era in molecular medicine, providing unprecedented opportunities to discover new underlying causes for human diseases. We are utilizing sequencing technologies to investigate the genetics of microRNA (miRNA) in ALS.

Our previous studies demonstrated that miRNA activity is essential for motor neuron survival, miRNA malfunction causes spinal motor neuron disease; that Dicer activity is dysregulated in ALS and that global down regulation of miRNAs is observed in human ALS.



We propose to unveil novel miRNA gene mutations in human ALS. Identification of such mutations - in miRNA genes or their partners – has high potential to drive breakthroughs in understanding ALS pathogenesis, by providing insights into degeneration pathways in ALS motor neurons. Because miRNAs are highly drugable, the data obtained within the proposed FTL project could lead to further evaluation of new therapeutic targets and drug leads.

To identify ALS - associated genetic mutations in miRNA -related genes, in large independent cohorts of ALS patients and controls. We will strengthen preliminary observations by increasing the statistical power, scale and accuracy of our human genetics results.

1. We employ a new approach, in silico capture, to analyze selected regions of interest from whole - genome sequencing relative to data analyzed by DNA capture and sequencing. We will study two additional cohorts by independent in silico capture.

   These datasets are gained under term of collaboration from Ammar Al-Chalabi (King's College London) and John Landers (UMASS med.). UK cohort constitutes of ~500 ALS genomes and 150 unaffected controls, whereas the UMASS med. cohort constitutes of ~300 ALS genomes and 80 unaffected controls.

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A bioinformatics pipeline is already established for detection of single nucleotide variance and for meta-analysis of polymorphic variants in the four independent populations.
In total our project will have data of more than >2,200 ALS patients.

2. We will use Fluidigm access arrays for testing the best 50 SNPs from the discovery cohorts in additional independent cohorts of 1000 Caucasians ALS patient DNA samples and 1000 relevant controls from the repositories of Robert H. Brown Jr., UMASS and / or Coriell Institute for Medical Research.
3. We will verify polymorphic nucleotides in ALS patient genomes, by Sanger sequencing.

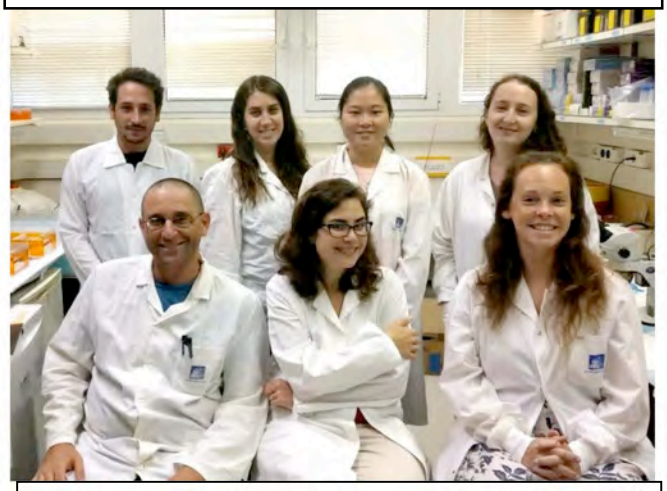
This project is carried out at the

Department of Molecular Genetics, Weizmann Institute of Science, Rehovot,Israël.

The team of researchers working on the project:

Chen Eitan and Pr Eran Hornstein on the right

Pr Eran Hornstein, Revital Ravid, Irit Reichenstein, Chen Eitan



Upper row from left to right:
Aviad Siany, Raquel Fine, Jing Liang, Irit Reichenstein
Lower row from left to right:
Dr. Iddo Magen, Revital Ravid, Chen Eitan