DelCAA-HD

Delineating the role of HTT Cis-Variants in the pathogenesis of Huntington disease (delCAA-HD)

Huntington disease (HD) is a fatal brain disorder with no cure or treatment that can alter the development of the disease. Several clinical trials in HD have recently failed. It is well known that HD is always caused by an increased size of a repeat in the letter code CAG of the DNA in the hunting-tin gene. There is an inverse correlation between the size of the CAG repeat and the age when typical motor symptoms appear in HD, which also defines the age when clinical diagnosis is given to an individual with the altered huntingtin gene. However, the age of clinical diagnosis can only be explained by the size of the CAG repeat to around 50%. Several large studies investigating the genome in detail of thousands of individuals with HD have revealed that there are other important genetic variants that can to some extent explain the age of clinical diagnosis in HD. These variants are mainly within the CAG repeat of the huntingtin gene and are called cis-variants. Importantly, these variants have not been considered in the characterization of clinical cohorts of individuals with HD including in the development of clinical trials aiming to halter disease development. Also, the impact of the genetic variants on the pathological effects in the brain is not known. Here we propose to fill an important and urgent gap in the knowledge of clinical genetics in HD. We will determine the role of cis-variants in the huntingtin gene identified in large genetic studies in the development of HD (delCAA-HD) using a combination of three clinical cohorts and novel animal and cellular models of HD. The results will lead to improved diagnostic assay accuracy, more accurate information for genetic counselling and enhanced understanding of HD that will facilitate further clinical trials.

The delCAA consortium is composed of five international leading research laboratories, each with recognized and complementary expertise in various aspects of HD. This transnational collaboration will be crucial to successfully achieve the aims of this project.

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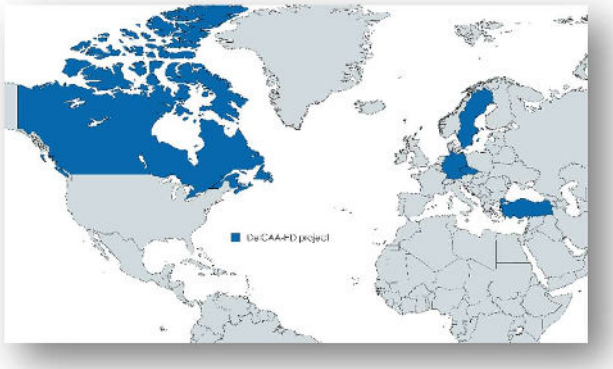

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