SUJET DE THESE ED 614 & 615

Sujet de thèse

Informations sur l'équipe	
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Informations sur le sujet	
Titre du sujet	Population-based study to compare Amyotrophic Lateral Sclerosis incidence, mortality rate and phenotype between European and Hispanic populations (France - Ecuador)
Mots clés	Epidemiology, Amyotrophic Lateral Sclerosis, incidence, phenotype, ethnic groups, ancestries
Présentation détaillée du projet doctoral *(1 page maximum)*	The beam of evidence about the heterogeneity on ALS incidence, mortality and phenotype between human populations is based on different clues: - A meta-analysis of ALS incidence (Marin et al. Int J Epid 2017), (considering data of about 13,150 ALS cases reported worldwide), based on population based studies with multiple sources for case ascertainment - gold standard methodology for descriptive epidemiology - showed that subcontinent was the main source of incidence heterogeneity. While standardized incidence of ALS appeared homogeneous in populations of European origin in Europe, North America and New Zealand (pooled ALS standardized incidence of 1.81 (95%CI 1.66-1.97)/ 100,000 person years of follow up (PYFU)), incidence in Eastern Asia (Japan, China) has been found significantly lower 0.83 (95%CI 0.42-1.24)/100 000 PYFU), as in South Asia (Iran, 0.73 (95%CI 0.58-0.89)/ 100 000 PYFU). - A meta-analysis of ALS phenotypic and survival characteristics (Marin et al. Eur J Epid 2016) (considering data of about 12,700 ALS cases reported worldwide) highlighted the phenotypic heterogeneity of ALS at time of onset [age, sex ratio (SR), bulbar onset], age at diagnosis, occurrence of comorbidities in the first year after diagnosis, and outcome (survival). Subcontinent was also a major explanatory factor for the variability of the ALS phenotype. Some markers of ALS phenotype were homogeneously distributed in western countries (SR, mean age at onset/diagnosis) but their distributions in other subcontinents were remarkably different. Other markers presented variations in European subcontinents (familial ALS, bulbar onset) and in other continents. As a consequence, ALS outcome strongly varied, with a median survival time from onset ranging from 24 months (Northern Europe) to 48 months (Central Asia). - Reports form mixed populations in the United Kingdom and the USA, constantly showed lower incidence and prevalence in non-Whites populations (Hispanics, Asian, African American) as compared with Whites (Rechtman et al. 2015). Also, mortality studies reported consistently that ALS mortality was lower among Hispanics and African American people as compared with White people. Lastly, a mortality study in Cuba found that ALS adjusted mortality rate was considerably lower in the mixed population: 0.55

	(95%CI 0.40-0.72) than in whites (0.93/100,000 PYFU; 95%CI 0.83-1.03) and blacks (0.87/100,000 PYFU; 95%CI 0.62-1.17) (Zaldivar Neurology 2009). ALS is considered as a complex genetic disease caused by multiple susceptibility genes interacting with a variety of environmental risks. European populations share common ancestral origins and, depending on the degree of relatedness, are likely to share a variety of rare "at-risk" genes, combinations of which may increase susceptibility to disease. Conversely, admixed populations, containing a much wider variety and different combinations of at-risk alleles, might experience a lower overall risk of developing the disease. At this stage, it is necessary to determine the variability of ALS incidence, mortality and phenotype between European (Limousin territory, France) and Hispanic populations (Ecuador, including ethnically mixed and admixed populations) using homogeneous and standardized methodology. This will be done through this pilot study that might pave the way of key results in the field.
Objectif et contexte *(300 mots max)*	Recent original investigations and systematic reviews lead researchers to postulate the heterogeneity of ALS incidence, mortality and phenotype between human populations. Difference in ALS occurrence and clinical characteristics could be related to difference in case ascertainment, health care system access and variability of study design. Nevertheless, these variations could be related to differences in terms of determinants of incidence and phenotype such as: (i) environmental risk factors, (ii) type and frequency of ALS genetic mutations and (iii) genetic ancestral origin of the populations and level of admixture. **The general aim of this Phd program is to determine the variability of ALS incidence, mortality and phenotype between European (France) and Hispanic (Ecuador) populations in relation to ancestral origin, level of admixture, type and frequency of ALS genetic mutations and environment.** The specific aims of this project are: 1) To describe and compare: - ALS incidence rates - ALS mortality rates - ALS phenotype (clinical characteristics, comorbidities) Between European (France) and Hispanic (Ecuador) populations. 2) To relate variations in ALS incidence, mortality and phenotype with - Ancestral origin and level of admixture of the populations (data from population genetics analysis using ancestral markers) - Type and frequency of ALS genetic mutations - Environmental factors Given the fact that ALS is a rare disease, the sample size of our study remains relatively modest (180 subjects in Limousin and 120 subjects in Ecuador), we acknowledge the potential limitation of statistical power of this program. This study is nevertheless a first original and innovative step that will need to be replicated and extended to other geographical areas.
Résultats attendus *(300 mots max)*	The study might have an important impact in ALS:

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	- Providing preliminary elements on the potential influence of genetic factors, especially populations ancestries, along with ALS genetic mutations on ALS heterogeneity. - Assessing how population ancestral origin modifies the risk of developing ALS, which may provide important insight of the pathogenic mechanisms. - Improving our understanding of the ALS variation in different populations and providing clues about potential gene-environmental determinants and the risk of developing the disease. - Leading to important advances in the knowledge of the mechanisms of ALS that might impact the innovation in therapeutic approaches. - By giving insight in ALS mechanism, this research might open new areas of investigations for the other neurodegenerative disorders (Parkinson's and Alzheimer's diseases). - Besides, the project will lead to the establishment of a new ALS register: in Ecuador (Tropical country characterized by and admixed population). This will promote high epidemiological, clinical investigations and improve ALS care in this country.
Références bibliographiques *(10 max)*	1. Marin B, Boumédiene F, Logroscino G, Couratier P, Babron M-C, Leutenegger AL, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. Int J Epidemiol. 2017 Feb 1;46(1):57–74. 2. Marin B, Logroscino G, Boumédiene F, Labrunie A, Couratier P, Babron M-C, et al. Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. Eur J Epidemiol. 2016 Mar;31(3):229–45. 3. Rechtman L, Jordan H, Wagner L, Horton DK, Kaye W. Racial and ethnic differences among amyotrophic lateral sclerosis cases in the United States. Amyotroph Lateral Scler Front Degener. 2015 Mar;16(1–2):65–71. 4. Zaldivar T, Gutierrez J, Lara G, Carbonara M, Logroscino G, Hardiman O. Reduced frequency of ALS in an ethnically mixed population: a population-based mortality study. Neurology. 2009 May 12;72(19):1640–5.
Financement doctoral	*Sous réserve de financement*

Informations sur le candidat

Profil et compétences recherchées	Les compétences indispensables portent sur le domaine de la méthodologie de la recherche, de l'épidémiologie et des biostatistiques. Le doctorant qui sera recruté devra à terme maitriser également les caractéristiques cliniques de la SLA et devra donc être ouvert à ces aspects. Un candidat avec un master dans le domaine de la santé publique (épidémiologie) est souhaité. La maitrise de la langue espagnole serait un plus.

Diffusion

Souhaitez-vous que le sujet soit déposé sur le site de l'ABG par le collège doctoral ?	Oui

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Document à compléter en français et/ou en anglais