Implementation of a Latin American network for the investigation of the genetic landscape of childhood epileptic encephalopathies: report of preliminary results

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Introduction: Childhood epileptic encephalopathies (CEEs) are a heterogeneous group of epilepsies characterized by progressive development of psychomotor dysfunction associated with severe epilepsy. Recently, rare *de novo* mutations have been found in patients with CEEs. Since it is well known that allele frequency for rare variants may significantly vary across populations from different ethnic backgrounds, it is possible that the frequency of the mutations causing CEEs may also vary. In order to investigate the issue, we have established a Latin American research network for the investigating of the genetic landscape of CEEs.

Materials and Methods: This is a project involving the BRAINN and the International League Against Epilepsy (ILAE). Neurology services from different countries in Latin America have been contacted over the past year. A common clinical protocol has been established which includes inclusion and exclusion criteria for patient enrolment. Data will be obtained from patients with all types of CEEs (West, Otahara, Lennox-Gastaut, Dosse, Dravet syndrome and others). DNA extraction will be performed in each country and samples will be shipped to the molecular genetics laboratory at UNICAMP for molecular testing performed by whole exome sequence.

Results: From November 2016 to October 2017 we were able to directly contact 17 collaborative centers (CCs) from eight Latin American countries (Peru, Mexico, Argentina, Chile, Colombia, Honduras, Nicaragua and Dominican Republic). More than 80% (14/17) of the CCs were receptive to the proposal by answering to our messages, and around 70% (12/17) of the CCs remain in current active communication with us (3 CCs from Peru, 2 from Argentina, 4 from Chile, 1 from Colombia, 1 from Honduras, and 1 Dominican Republic). Six CCs are still waiting for institutional approval for international collaboration or to better explore local capacities for DNA extraction. Seven CCs already submitted the projects to the local ethics committee, of which until now, two were approved. Currently, around 20 patients with CEEs have already been selected for DNA extraction in the respective countries. In addition, we developed a program, including videos and on-site training, aiming to establish a centralized DNA extraction facility in Honduras (led by researchers from the UNAH) to centralize extraction in all Central America and Caribbean countries.

Discussion: The results obtained so far in the consolidation process of the regional research network have been successful. Mostly, the initiative has been well accepted; however, several factors have delayed the work, such as: **i)** few centers for the studies of epilepsies in Latin America; **ii)** difficulties to identify local capacities to perform DNA extractions mainly in Central America and Caribbean countries; **iii**) use of extraction methods different from the one required for next-generation sequencing; **iv**) significant delays in institutional and local ethics committees for approval of the project. Strategies to solve these problems have been implemented successfully in most cases.

Conclusion: A systematic evaluation of CEEs has never been performed in Latin America, which have negative implications in the ability to make the diagnosis and manage these patients. On the research side, due to the high heterogeneity and population admixture, we are likely to identify additional mutations/candidate genes in the Latin American population, thus contributing to the ILAE global efforts to better understand and to offer better treatments to severe epilepsies worldwide.

References: [1] Gonsales MC et al., Arq Neuropsiquiatr 73(11): 946-958, 2015; [2] McTague A et al., Lancet Neurol 15(3): 304-316, 2016.