Neurogenetics in Peru: clinical, scientific and ethical perspectives

Mario Cornejo-Olivas¹ · Keren Espinoza-Huertas¹ · Mario R. Velit-Salazar^{1,2} ·
Diego Veliz-Otani¹ · Indira Tirado-Hurtado¹ · Miguel Inca-Martinez¹ ·
Gustavo Silva-Paredes¹ · Karina Milla-Neyra¹ · Victoria Marca¹ ·
Olimpio Ortega¹ · Pilar Mazzetti^{1,3}

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Abstract Neurogenetics, the science that studies the genetic basis of the development and function of the nervous system, is a discipline of recent development in Peru, an emerging Latin American country. Herein, we review the clinical, scientific and ethical aspects regarding the development of this discipline, starting with the first molecular diagnosis of neurogenetic diseases, to family and population-based genetic association studies. Neurogenetics in Peru aims to better explain the epidemiology of monogenic and complex neurodegenerative disorders that will help in implementing public health policies for these disorders. The characterization of Peru and its health system, legal issues regarding rare diseases and the historical milestones in neurogenetics are also discussed.

Keywords Bioethics · Neurogenetics · Peru · Public policies

Neurogenetics in Latin America

Neurogenetics studies the genetic basis of the nervous system, exploring its function and development for a better understanding of neurological disorders (Trelles and De los Angeles 1989; Vaillant 2000). Roughly, 80 % of the transcriptome is expressed in the human brain (Hawrylycz et al. 2012), where resident cell types show specific neuroanatomical distributions and molecular signatures that can be associated with neurodegenerative and neuropsychiatric disorders (Lotan et al. 2014; Miller et al. 2010). The development of novel genomic technologies, large-scale genome databases and global collaborations have revolutionized our understanding of the molecular basis and diagnostic and therapeutical approaches in many neurological disorders, especially within highly polygenic disorders (McCarroll et al. 2014).

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✉ Mario Cornejo-Olivas
mario.cornejo.o@incngen.org.pe

Keren Espinoza-Huertas
keren.espinoza.h@incngen.org.pe

Mario R. Velit-Salazar
mario.velit.s@upch.pe

Diego Veliz-Otani
diego.veliz.o@incngen.org.pe

Indira Tirado-Hurtado
indirath20@gmail.com

Miguel Inca-Martinez
miguel.inca.m@incngen.org.pe

Gustavo Silva-Paredes
gus7772000@yahoo.es

Karina Milla-Neyra
akmillaneyra@gmail.com

Victoria Marca
mvmarca@yahoo.com

Olimpio Ortega
olimpio12@hotmail.com

Pilar Mazzetti
pilar.mazzetti.s@incngen.org.pe

¹ Neurogenetics Research Center, Instituto Nacional de Ciencias Neurológicas, 1271 Ancash Street, Barrios Altos, Lima, Peru

² School of Medicine, Cayetano Heredia University, Lima, Peru

³ School of Medicine, Universidad Nacional Mayor de San Marcos, Lima, Peru

Many countries worldwide have at least one neurogenetics division that offers clinical assessment and molecular diagnostics and produces research in the field. The rising number of affected individuals with neurogenetic disorders promoted the development of the field in many Latin American countries over the last few decades. The largest Latin American countries, Brazil (www.ufrgs.br/genetica/hcpa/neurogenetica), Mexico (www.innns.salud.gob.mx) and Argentina (neurogenetica.weebly.com), have implemented both clinical and research centres, mostly linked to human genetics and neurology departments at the main universities, national institutes and health care centres. Other countries, despite technological and economic limitations, have developed neurogenetics centres due to the emergence of several thriving niches (Table 1).

Mapping of the *HTT* gene, causative of Huntington disease (HD), and further characterization of its mutation was accomplished through studies involving Venezuelan kindreds in a US-Venezuela collaborative research project (Group THsDCR 1993). The prevalence of spinocerebellar ataxia (SCA) type 2 or SCA2 in Holguín, Cuba, is considered the highest worldwide (Velazquez-Perez et al. 2011) and has led to the development of a multidisciplinary healthcare and research centre in this town. Clinical guidelines for the integral management of SCA2 families, including genetic counselling and presymptomatic testing, have also been developed in this region (Velazquez Perez et al. 2009). SCA10 has been so far described in Mexico and South America (Alonso et al. 2007; Teive et al. 2011) and is felt to be of American Indian ancestry (Almeida et al. 2006). The well-known high prevalence of autosomal dominant Alzheimer disease due to *PSEN1* mutations in Colombia has allowed a prolific scientific research on this disorder (Acosta-Baena et al. 2011). In this context, Peru has been working in the field for almost 20 years, through the Neurogenetics Research Centre at *Instituto Nacional de Ciencias Neurológicas* (INCEN), the only centre in the country focusing its clinical and research activities on monogenic and complex neurological disorders.

Peru, an emerging Latin American country

Peru is located in the central-western coast of South America. The main spoken language is Spanish, and its population is characterized by a mixed ethnic background with predominance of Amerindian and European ancestries with a smaller contribution of Asian and African ones (Sandoval et al. 2013). Of the 31.1 million inhabitants estimated by 2015, 23.3 % live in rural areas (www.inei.gob.pe/). There are heterogeneous levels of health indicators along the country with a significant percentage of the population suffering from the social, political and economic inequities that still characterize the country, mainly in rural areas. These factors contribute to a continuous migration to urban areas, mainly to

the capital city Lima, where at least one third of the population resides (INDEPA 2010; Valdez et al. 2013).

In the last decade, Peru has experienced a consistently growing economy, reduced poverty and broad support for democracy, which constitute critical social determinants of health. The current life expectancy is about 75 years, varying with socioeconomic and geographic settings (www.inei.gob.pe/). Peru has been classified by the World Bank as an upper-middle income economy; nevertheless, its gross domestic product is below its Latin American peers (www.worldbank.org/). The health expenditure in Peru is only 5.3 % of the gross domestic product, among the lowest in South America (Yamada and Castro 2010), and around one third of the population still lack health insurance (Posso et al. 2015).

There are few laws protecting patients affected with genetic diseases in Peru, which are mostly unregulated. In 2011, a law titled “National Interest and Preferred Care Treatment for patients with Rare and Orphan Diseases” was promulgated, ranking 399 orphan diseases into four groups, according to their impact, difficulties for screening or diagnosis, financial and social burden, treatment, quality of life and family risk (Hernandez-Vasquez et al. 2014). Funding for the entire “very high priority” group was arranged, leaving the remaining groups dependent on budget availability. Only one of the eight most frequently followed diseases at the Neurogenetics Research Centre was placed in the “high priority group”, five were placed in the “very low priority” group, and regrettably two diseases, inherited neuropathies and familial early-onset Parkinson disease, are not even listed. This apparent disparity may be explained by the absence of national research studies that would otherwise adjust the indicators used for this prioritization of funding.

Neurogenetics in Peru is closely tied to research in HD, since the first report of this disorder, back in 1950, documenting a HD family with nine affected members from the southern regions of Peru (Saavedra 1950). Since 1983, there have been reports of a high incidence of HD in a valley south of Lima, suggesting that the region could be the primary HD cluster in Peru (Cuba 1986). International and local researchers have visited this valley and collected samples from families over the past 30 years (Torres et al. 2008), raising great expectations for potential treatments, which have been unfulfilled once they exceeded the scope of their studies. On the other hand, the large number of HD cases reported in this valley drew journalists’ attention, the reports of whom generated stigma towards the affected individuals and the region (Loayza 2005). As a result, many affected families have limited socialization with local and surrounding regions. This highlights the importance of carefully considering cautious and ethical approaches (including an appropriate informed consent process for research), when disclosing any information about rare and severe disorders in any given population or community.

Table 1 Neurogenetics centres in Latin America

Country	Latin American neurogenetics centres	Founded in	Services
Argentina	Consultorio y Laboratorio de Neurogenética del Centro Universitario de Neurología JM Ramos Mejía, Buenos Aires	2008	C, G, T, R
Argentina	Instituto de Neurociencias Buenos Aires (INEBA), Buenos Aires	2004	C, G, T, R
Brazil	Rede Neurogenética - Serviço de Genética Médica, Hospital de Clínicas Porto Alegre (HCPA), Porto Alegre	na	G, R
Brazil	Laboratório Neurogene, Florianópolis	1995	G
Chile	Consulta de Neurogenética - Clínica Las Condes (CLC), Santiago	2008	C
Chile	Laboratorio de Biología Molecular y Citogenética de la Red de Salud UC CHRISTUS, Santiago	2010	G, R
Colombia	Grupo de Neurociencias de Antioquia, Universidad de Antioquia (UdeA), Medellín	na	R
Costa Rica	Área de Neurogenética del Centro de Investigación en Neurociencias (CIN), Universidad de Costa Rica (UCR), San José	1999	T, R
Cuba	Centro para la Investigación y Rehabilitación de las Ataxias Hereditarias (CIRAH), Holguín	2000	C, G, T, R
Cuba	Departamento de Neurogenética - Instituto de Neurología y Neurocirugía (INN) Prof. Dr. José Rafael Estrada González, La Habana	1980	C, G, T, R
Ecuador	Unidad de Movimientos Anormales y Bioestadística-Servicio de Neurología - Hospital Carlos Andrade Marín, Quito	1996	C, R
Guatemala	Instituto para la Investigación Científica y la Educación Acerca de las Enfermedades Genéticas y Metabólicas Humanas (INVEGEM), Santa Lucía Milpas Altas	2010	C, G, T, R
Mexico	Laboratorio de Neurogenética - Instituto Nacional de Neurología y Neurocirugía (INNN) Manuel Velasco Suárez, México, D.F.	1967	C, G, T, R
Peru	Neurogenetics Research Center - Instituto Nacional de Ciencias Neurológicas (INCN), Lima	1995	C, G, T, R
Uruguay	Policlínica de Neurogenética de enfermedad de Parkinson y movimientos anormales - Departamento de genética - Facultad de Medicina de la Universidad de la República, Montevideo	na	C, G, T, R

The table compares some of the neurogenetic centres in Latin America according to services available. Most of them were generally founded over the last three decades. This information was recovered by a website research internet using the words “neurogenética” and the name of each Latin American country

C clinical assessment, G molecular genetics diagnosis, T teaching, R research, na not available

It was not until 1995 that the Neurogenetics Research Centre at INCN in Lima, Peru, was established as the first unit devoted to providing healthcare for neurogenetic disorders in the country. This centre is still the only one dedicated to research and clinical care of patients affected with neurogenetic disorders, mainly HD, myotonic dystrophy, hereditary ataxias, inherited neuropathies and many other neuromuscular disorders. Individuals with common neurodegenerative diseases like Parkinson and Alzheimer's disease, including other dementias, are also followed at the centre for research purposes. Currently, the only two specialists working in the field have attended roughly 400 consultations, each, per year; appointments are made at least 2 months in advance. There have been a growing number of appointments over the last 5 years, most notably in consultations for HD (Table 2). Neurogenetic consultations are only available in the capital city; yet, around 30 % of patients assessed at the centre live in nearby cities and provinces (Fig. 1). It is highly likely that a considerable number of patients affected in an advanced stage of their disease and those living far from the capital city (especially if they cannot afford transportation and consultation fees) are still waiting and in need of a specialized consultation.

The biggest challenge in genetic counselling is transmitting accurate and comprehensive information to enable families in choosing a course of action, allowing them to cope with the psychological, clinical and socioeconomic consequences of genetic disease (Kang 2013). Since formal training programmes in genetic counselling are still unavailable in Peru, counselling is offered by neurologists with growing expertise in human genetics at the Neurogenetics Research Centre. The implementation of presymptomatic diagnosis for neurogenetic disorders is still unavailable since it requires a multidisciplinary team including psychologists, psychiatrists and medical geneticists, high levels of confidentiality and an office or area solely dedicated to presymptomatic consultations, all of which are currently non-existent at the centre (Rodrigues et al. 2012). In other neighbouring countries such as Argentina, the presymptomatic diagnosis of HD and other late-onset neurological disorders are handled by neurologists

and clinical geneticists with supporting DNA testing (Penchaszadeh 2013). The role of genetic counselling includes more than just communicating complex medical information to families, it also involves considering the consequences associated with unintentionally revealing the risk of disease in relatives or offspring with a genetic disorder (Counseling AHCog 1975).

The Neurogenetics Research Centre in Peru began working on molecular genotyping for monogenic disorders since 2000, using a thermal cycler donated by the Japanese embassy, which allowed by first time the molecular diagnosis of HD in Peru. Since then, we have followed up on more than 300 HD families, over 14 years, collecting DNA samples and clinical data, allowing the study of many aspects of HD in Peru. Over the past 5 years, the molecular diagnosis of Kennedy disease, Fragile X syndrome and DYT1 dystonia, among others, have also become available. In other Latin American countries, laboratory testing for neurogenetic disorders such as fragile X and spinal muscular atrophy has been carried out as early as 1999 in Argentina (Penchaszadeh 2013) and 2003 in Brazil (Horovitz et al. 2013). Certified molecular diagnosis for neurogenetic disorders requires methods that guarantee an optimized sensitivity and specificity for each test. The equipment and reagents needed, however, are expensive, causing its low availability due to the low prioritization of these disorders by the government. Hence, some laboratories in Peru have implemented alternative, less costly, in-house methods that do not require the use of sophisticated equipment; however, they are probably less accurate.

The clinical and molecular data collected for almost two decades at the Neurogenetics Research Centre have provided much insight into many aspects of some neurogenetic disorders, including the existence of a high incidence of HD at southern Lima, including many late- and early-onset HD phenotypes (Cornejo-Olivas et al. 2015). Other initial studies using this data described the normal allele distribution of unstable microsatellites in the *HTT* gene and other unstable microsatellites (Tirado-Hurtado et al. 2014). Also, observational studies allowed the description of the relative frequency of dominant ataxias, with an unexpectedly high frequency of SCA10 and a low frequency of Machado-Joseph disease (MJD/SCA3) in the Peruvian population (Cornejo-Olivas et al. 2013a).

The large number of DNA samples and linked clinical data from Parkinson's Disease (PD) cases has allowed the Neurogenetics Research Centre to become the Peruvian site for the Latin American Research consortium on the Genetics of Parkinson's Disease (LARGE-PD), the first large-scale repository of PD samples in Latin America. Since 2007, the enrolment of both cases and controls from Peruvian Amerindian and mestizo populations has allowed for research in the genetics of PD and other complex neurodegenerative disorders (Foundation 2014). Population stratification is a

Table 2 Number of appointments by disorder at the Neurogenetics Research Centre, INCN, Lima, Peru (2010–2014)

	2010	2011	2012	2013	2014
Huntington disease	29	87	176	312	334
Hereditary ataxias	24	63	61	12	130
Myotonic dystrophy	24	34	42	63	40
Parkinson disease	24	10	20	6	58
Fragile X syndrome	1	3	1	15	17
Myopathies	18	29	26	17	22
Other	14	77	102	253	146
Total	134	303	428	678	747

Fig. 1 Proportion of appointments per disease group by macroregions at the Neurogenetics Research Center 2010–2014. The figure shows that the majority of patients followed at the Neurogenetics Research Center, INCN, in Lima, Peru, come from the capital city and nearby provinces,

while a smaller portion of the appointments are from eastern parts of Peru. Note that Huntington's disease represents the largest number of appointments across all regions

major concern in population-based genetic association studies of complex diseases, since it can lead to spurious associations between genetic polymorphisms and the studied trait (Cardon and Palmer 2003). This problem is especially relevant for highly admixed populations, such as Peruvians, but can be controlled and corrected by accounting for the genetic ancestry of cases and controls. Furthermore,

population genetics studies can give insights about the origin of mutations with clinical relevance such as the *HTT* expansion (Tirado-Hurtado et al. 2014) and LRRK2-R1441G for PD (Comejo-Olivas et al. 2013b). Therefore, the development of population genetics of Amerindian and admixed Peruvian populations has become very much needed in neurogenetics research.

Describing the genetic variability of indigenous populations poses its own ethical concerns, as the group's beliefs and traditions must be considered throughout the entire study (Stephens et al. 2007). When working with indigenous groups, the relevance of the study from the own community worldview should be recognized, as their understanding of health and disease might differ from the Western perspective. The potential implications of the study's results for the community should be addressed, especially potential harms, such as discrimination and stigmatization that might arise from revealing the community's name (Brief and Illes 2010).

Perspectives

Neurogenetic disorders require integral lifelong healthcare management. A multidisciplinary team of clinicians, basic scientists, psychologists, social workers and administrative staff should work together to address the specific needs of affected individuals and their families taking account of social and cultural mediators. Establishing formal genetic counseling training programmes and the participation of physicians, nurses and other healthcare professionals will have a high positive impact on healthcare for affected individuals and families. A fully integrated service, encompassing clinical assessment and diagnosis, molecular genetic testing by international standards for accreditation, genetic counselling and follow-up consultations would assist in performing both clinical and translational activities. Finally, improving the current infrastructures with cutting-edge technologies, collaborative research networks and continuous education is required to improve research in neurogenetics in Peru.

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Compliance with ethical standards This article does not contain any studies with human or animal subjects performed by any of the authors.

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