Title	**Contribution of mitonuclear mismatch to disease in Latin-American admixed patients.**
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Non-G2MC collaborators.	Arslan Zaidi, PhD. University of Pennsylvania, United States. Matthieu J. Miossec, PhD. University of Oxford, United Kingdom.
Future funding	A 3-year version of this proposal has been presented for the 2022 Chile's Fondecyt funding competition. Results will be communicated by the end of the year.

Introduction. Many cellular processes depend on tightly regulated mitonuclear interactions that have been optimized by the coevolution of the nuclear and mitochondrial genomes. For thousands of years, the major continental groups of humans evolved in isolation and adapted to their local environments. However, in Latin America, due to the "Columbus Exchange" occurring only 529 years ago, the African, European, and indigenous populations came into close proximity and started mixing, effectively forcing mitonuclear coevolution to test novel combinations of nuclear and mitochondrial genotypes that previously never existed together. The impact of this "mix and match" has not been evaluated in humans, but in many other organisms, mitonuclear mismatch (MNM, i.e., differences between the nuclear and mitochondrial ancestries) leads to altered mitochondrial function and reduced viability.
We are interested in describing the contribution of MNM to disease. MNM could serve as a proxy to understand diseases involving mitonuclear interactions, such as neurodegenerative, immunological and developmental disorders. In Latin-American admixed individuals, the mitochondrial DNA (mtDNA) is predominantly of indigenous origin, but their nuclear genome contains a gradient of indigenous, European, and African ancestries. Therefore, because offspring inherit the nuclear genome from both parents, but mtDNA only from the mother, the combination of parental nuclear ancestries and fixed mtDNA ancestry can lead to changes in MNM and the manifestation of disease phenotypes. For diseases in which the usual search for individual causal or modifier genes has been unfruitful, considering mitonuclear interactions is a novel strategy.

Vision. To draw attention to the underexplored complexity of Latin-American genomes.

Aims.

1. To characterize MNM in healthy Latin-American admixed trios (mother, father, offspring), and intergenerational changes in MNM (child-mother).
2. To compare MMN of a cohort of Chilean patients suspected of neurological, immunological or mitochondrially-related diseases to MNM of healthy individuals.

Impact. Latin-American and other admixed populations are underrepresented in global, clinical genomics research. Uncovering the effects of mitonuclear mismatch in this population will contribute to (1) propelling Latin-American genomic medicine, and (2) establishing MNM as a bona fide contributing genetic mechanism to disease.

Executive plan. This is a data analysis-centric project achievable within the restrictions imposed by the current worldwide health situation. For aim 1, we will use genotype data of the mother and offspring of 156 Latin-American admixed trios (mother, father, offspring) generated by the 1000 Genomes Project Phase 3. For aim 2 we will reuse whole exome data from ≥45 Chilean patients that have been generated as part of another research initiative within our group (kindly provided by Dr. Repetto, Dr. Poli and Dr. Pérez-Palma).
We have no previous experience managing large genomic datasets within a cloud environment; thus, we anticipate that we will spend half of the first year perfecting this analytical strategy. Simultaneously, we will advance data analysis within our own servers, thus not limiting progress.
As a 12-month pilot project, we expect to successfully provide a fully replicable and reproducible repository of methods, fined-tuned to work with Latin-American genomic data, as well as to share our experience in using cloud-based tools for the analysis of large and free-to-use genomic datasets. Year 2 is included to illustrate how the project continues after the pilot.

	Year 1				**Year 2**			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Aim 1: MNM in health (G1K trios)								
Data acquisition and curation	X	X						
Fine-tuning local ancestry estimation	X	X	X					
Aim 2: MNM in Chilean cohort								
Alignment and variant calling	X	X						
Local ancestry estimation		X	X					
Other activities								
Statistical analyses			X	X	X			
Launch of the project's repository of methods				X				
Communication of preliminary results				X				
Preparation of manuscripts			X	X	X	X	X	X
Scientific meetings				X		X		X
Training of students	X	X	X	X	X	X	X	X

Budget. Presented as item, justification and amount in USD/year,

Personnel		
Salary + benefits for a full-time bioinformatics research assistant (45h/week)	The assistant will be in charge of data management, fine tuning and execution of primary and secondary bioinformatic pipelines, troubleshooting, and the creation of a shareable repository for the project's	27,000

	methods. They will focus on transparency, replicability and reproducibility of the results.	
Salary PI part-time (10h/week)	The PI will oversee the project and focus on dissemination of results.	6,000
Materials and supplies		
Maintenance of local computational infrastructure	We host a computer cluster. Users of the facility are expected to contribute proportionally to computing usage.	5,000
Cloud storage and cloud computing fees	The 1000 Genomes Project data for aim 1 is large, but it has been made available via cloud services to facilitate data exploration and manipulation without the need of local infrastructure to handle it. Although we have the computational infrastructure, we would like to gain experience in cloud computing using large genomic datasets and transfer the know-how to future researchers. Fees are based on usage of the cloud infrastructure, so we cannot anticipate a specific cost, but they are usually low according to the providers.	2,000
Support for local/country involvement		
Community engagement	Infographics for the project in Spanish and English. Video capsules. Seminars.	2,000
Hands-on workshop on statistical methods for the study of demographic processes shaping genetic variation in Latin America (if COVID-19 restrictions allow).	Dr. Zaidi has agreed to participate as a guest speaker for the Annual Meeting of the Genetics and Genomics Society of Chile. Airfare + per diem for a 7-day visit, including the main workshop, one seminar, and one lecture at Universidad del Desarrollo.	2,500
Travel and meeting support		
Attendance at an international meeting or on-site training, for example ASHG, ESHG, G2MC. (if COVID-19 restrictions allow).	Membership + airfare + per diem for a 5-day international trip.	3,000
	Total requested	**47,500**