PROPOSAL ABSTRACT

Contribution of intergenerational mitonuclear mismatch to disease in Latin-American admixed patients.

Background: 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 Native American 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.
MNM could serve as proxy to understanding diseases involving mitonuclear interactions, such as neurodegenerative, immunological and developmental disorders. In Latin-American admixed individuals the mitochondrial DNA (mtDNA) is predominantly of Native American origin, but their nuclear genome contains a gradient of Native American, European, and African ancestries. Therefore, because offspring inherit the nuclear genome from both parents, but the mtDNA only from the mother, the combination of parental nuclear ancestries and fixed mtDNA ancestry, can lead to increased MNM and the manifestation of disease phenotypes. We are interested in describing the contribution of MNM to disease. For diseases in which the usual search for individual causal o modifier genes has been unfruitful, considering mitonuclear interactions is a novel strategy.

Hypothesis: Intergenerational MNM changes contribute to the variable expression of disease phenotypes in Latin-American admixed patients.

Aims and methodology: This project chiefly aims to discover whether MNM contributes to disease in admixed populations. Using bioinformatics, we will infer global and local ancestry to compare the characteristics of MNM and intergenerational changes in MNM (ΔMNM) between healthy and diseased groups of Latin-American admixed individuals. MNM is defined as the fraction of nuclear ancestry not matching the mtDNA ancestry. For example, an individual with 55% European (EUR), 40% Native American (NAM) and 5% African (AFR) nuclear components, with NAM mtDNA haplogroup B, would have MNM of 60% (EUR+AFR). ΔMNM will be defined as $(MNM_{offspring} - MNM_{mother}) / MNM_{mother}$. For the first time we will generate and leverage existing genomic datasets to describe the distribution of ΔMNM in Latin-American admixed healthy and diseased cohorts. Aims: (1) We will characterize the distribution of ΔMNM in healthy Latin-American admixed individuals using data from 156 trios generated by the 1000 Genomes Project. (2) We will compare the distribution of ΔMMN of a Chilean cohort of 45 rare disorders patients (unaffected mother, affected offspring) to ΔMNM of healthy individuals. (3) We will describe the contribution of paternal nuclear mitochondrial alleles to the expression of congenital defects in the offspring of 33 cases of maternally inherited 22q11.2 deletion syndrome. We expect that the distribution of ΔMNM will be characteristic of each cohort and informative of diseased status.

Relevance: This proposal combines population and clinical genomics in a novel study of mitonuclear mismatch as contributor to disease. 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) propel Latin-American genomic medicine, and (2) establish MNM as a bona fide contributing genetic mechanism to disease.

This is a data analysis-centric project achievable within the restrictions imposed by the current worldwide health situation.