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THE HUMAN VARIOME PROJECT COUNTRY NODE OF ARGENTINA IN THE FIRST TWO YEARS OF ACTIVITY: PAST, PRESENT AND FUTURE

EL NODO ARGENTINO DEL PROYECTO VARIOMA HUMANO EN LOS PRIMEROS DOS AÑOS DE ACTIVIDAD: PASADO, PRESENTE Y FUTURO

Solano A.R.[1,2]*, Garrido M.[3], Mele P.G.[1], Podestá E.J.[1], Reichardt J.K.V.[4]

[1] Instituto de Investigaciones Biomédicas (INBIOMED), Facultad de Medicina, Universidad de Buenos Aires-CONICET, Ciudad Autónoma de Buenos Aires, Argentina.

[2] Genotipificación y Cáncer Hereditario, Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno" (CEMIC), Ciudad Autónoma de Buenos Aires, Argentina.

[3] President of Innocence Project Argentina, Florida, Vicente López, Buenos Aires, Argentina.

[4] Australian Institute of Tropical Health and Medicine, James Cook University, Cairns, Queensland, Australia.

Corresponding author:
Ángela Rosaria Solano
asolano@cemic.edu.ar

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ABSTRACT

The Human Variome Project (HVP) is an international effort aiming systematically to collect and share information on all human genetic variants. It has been working for years in collaboration with local scientific societies by establishing systems to collect every genetic variant reported in a country and to store these variants within a database repository: LOVD (Argentinian chapter: ar.lovd.org). Formally established in 2017 in the Argentinian Node, up to June 2019 we collected more than 25,000 genetic variants deposited by 17 different laboratories. Nowadays the HVP country nodes represent more than 30 countries. In Latin America there are four country nodes: Argentina, Brazil, Mexico and Venezuela; the first two interacted recently launching the LatinGen database. In the present work we want to share our experience in applying the HVP project focusing on its organization, rules and nomenclature to reach the goal of sharing genetic variants and depositing them in the Leiden Open Variation Database. Contributing laboratories are seeking to share variant data to gain access all over the country. It is one of our goals to stimulate the highest quality by organizing courses, applying current nomenclature rules, sponsoring lectures in national congresses, distributing newsletter to serve the Argentinian genomics community and to stimulate the interaction among Latin America countries.

Key words: Data sharing, Argentinian chapter of LOVD, Human Variome Project (HVP)-Argentina

RESUMEN

El Proyecto Varioma Humano (HVP) es un esfuerzo internacional que tiene como objetivo recopilar y compartir sistemáticamente información sobre todas las variantes genéticas humanas. Hemos estado trabajando durante tres años en colaboración con sociedades científicas locales, mediante el establecimiento de sistemas para recolectar todas las variantes genéticas reportadas en el país y almacenarlas dentro de la base de datos LOVD (capítulo argentino: ar.lovd.org). En el año 2017 fue establecido formalmente el Nodo Argentino del HVP, habiéndose recolectado más de 25.000 variantes genéticas depositadas por 17 laboratorios diferentes hasta junio de 2019. Hoy en día existen al menos 30 nodos del HVP, correspondientes a diferentes países. En América Latina hay cuatro nodos: Argentina, Brasil, México y Venezuela; Los dos primeros interactuaron recientemente lanzando la base de datos LatinGen. En el presente trabajo queremos compartir nuestra experiencia en la aplicación del proyecto HVP centrándonos en su organización, reglas y nomenclatura para alcanzar el objetivo de compartir variantes genéticas y depositarlas en la base de datos de variaciones abiertas de Leiden (LOVD). Es uno de nuestros objetivos estimular la más alta calidad mediante la organización de cursos, aplicación de las reglas de nomenclatura actuales, patrocinio de conferencias en congresos nacionales, distribución de boletines informativos para la comunidad de genómica argentina, y estimulación de la interacción entre los países de América Latina.

Palabras clave: Compartir datos, Nodo argentino de LOVD, Proyecto Varioma Humano (HVP)-Argentina.

INTRODUCTION

The Human Variome Project (HVP) (Burn and Watson, 2016) is a world-wide organization working to facilitate the collection, curation and interpretation of information on human genetic variation, as well as the free and open sharing of this information. To facilitate these goals, the HVP has created country nodes to support data sharing and facilitating the process of depositing genetic variants. A few reports have been published that shed light on aspects critical for the role of genetics in the current complex situation (Al Aama *et al.*, 2011; Patrinos *et al.*, 2011; Smith and Vihinen, 2015).

The Node of Argentina of the Human Variome Project was launched in November 2017 with the support of the Minister of Health Prof. Dr. Jorge Lemus and his Vice Minister Néstor A. Pérez Baliño, who were very enthusiastic in writing the letters for proposing at the BRCA challenge/UNESCO the creation of our node. A few professionals from different areas joined their experiences in starting the activity and all of them are listed in our web page: https://humanvariomeprojectargentina.org.ar/. We are running through the generous activity of volunteers who donate their work to manage the activities.

We are proud of the recent formal registration of our node as a Non-Profit Association at the "Inspección General de Justicia", an achievement reached with the assistance of our legal expert, Dr. Manuel Garrido, which will allow us to pursue formal activities with legal requirements.

It is necessary to put in context the current technical and practical situation in the region to explain the Argentinian HVP.

In the past few years the analyses of genetic variants have increased since current technologies allowed to expand sequencing, including in Latin America. Recent reviews (Dutil *et al.*, 2015; Jara *et al.*, 2017) have revealed significant genetic variants heterogeneity among the different countries and in the methodologies and criteria used for selecting patients which are often restricted by the modest available budgets and constrained human resources needed for clinical interpretation. In fact, the initial available data reveals the heterogeneous spectrum of pathogenic variants among the regions and/or countries. This information may improve clinical management and, therefore, improve patient outcomes. In addition, the need for data to support policies for genetic testing in different international regions is what makes this a fundamental contribution through this publication. The reports include a wide variety of methodologies, reflecting the enormous revolution in sequencing technologies over a short time span. Therefore, cautious interpretation of the results is imperative. The publications reviewed revealed a lack of common and recurrent variants in the region. Additionally, there are some Amerindian founder variants for countries like Brazil, Colombia, Mexico, Peru (Ossa and Torres, 2016) and Chile (Alvarez *et al.*, 2017). Applications for Recommended System Status can be made at any time to the ISAC via the ICO (Smith and Vihinen, 2015).

In fact, there was a premonition back in 2008 by Sir John Burn (Burn and Watson, 2016): "The HVP attracted widespread support within the academic community with more than a thousand affiliates at the last count. The underlying concept was to move toward a more formalized curation system based on data shared between country nodes. It was recognized that this would be necessary because of the significant differences between different jurisdictions in terms of data protection legislation, public perception of genetics, research infrastructure, and diagnostic service provision". In the experience of the Argentinian node, we are delighted for the opportunity to put into practice this farsighted philosophy and practice of genetic work, and the extraordinary possibility to extend it to all our colleagues working in genetics in the country.

SEQUENCING TECHNOLOGIES IN LATIN AMERICA, CONTRIBUTION OF THE NODES

Genetic analyses in Latin America (LA) have increased exponentially in the last few years, albeit not as much as in the rest of the world, the role of our country node is essential as it uniforms the nomenclature by curating the variants reported to be sent to the database (Leiden Open Variation Database, LOVD, in our case), seeks for education in genetics for clinicians and laboratory professionals, stimulates academic activities, all of them to improve the quality of clinical genetic information, as the most important areas.

In our experience an important role of the Argentinian node is to stimulate regional activities, since there is much stimulus to promote the creation of nodes in other countries and, hopefully, gain interactivity among the working groups. An interesting example can be found in the *BRCA1/2* gene sequencing, the main focus.

Among the most frequently analyzed genes are the *BRCA1* and *BRCA2* genes. The information collected thus far is not sufficient to discern the spectrum of genetic variants in the different regions and/or countries. Furthermore, it is becoming important as it may improve clinical practice and subsequently benefit patient outcomes. In addition, the need for data to support

policies for testing in different international regions is a fundamental strength of the present communication. The different publications included reports with a wide spectrum of methodologies (Alemar *et al.*, 2016; Kehdy *et al.*, 2015; Weitzel *et al.*, 2013), reflecting the fast evolution in sequencing technologies and, thus, a cautious interpretation is imperative to avoid the eventual missing of variants due to the limitations of the methods. Overall results showed very few common variants in Latin America, although the substantial differences in the methodologies are a limitation. In a recent publication of the results published from sixteen laboratory groups in Brazil (Palmero *et al.*, 2018), only five performed full sequencing of both *BRCA1/2* genes (Alemar *et al.*, 2017; Carraro *et al.*, 2013; Fernandes *et al.*, 2016; Maistro *et al.*, 2016; Silva *et al.*, 2014); the other studies include sequencing selected exons, analyzing only the *BRCA1* gene and other various assays.

European ancestry is most prevalent in Argentina (Cardoso *et al.*, 2018; Solano *et al.*, 2012; Solano *et al.*, 2017; Solano *et al.*, 2018), Brazil (Palmero *et al.*, 2018) and Uruguay (Delgado *et al.*, 2011) and the sequencing results of novel and few recurrent variants are consistent with heterogeneity from this admixture. Very importantly, a warning for not blindly importing panels of hotspot genetic variants if not tested before in the local context of regional spectrum of variants. In fact, this contributes to the best interpretation of the genetic results as a crucial part of our educational function, always necessary as described and discussed for Argentina (Solano *et al.*, 2017). It echoes similar findings in Brazil (Alemar *et al.*, 2016) and confirmed the lack of usefulness in the recent compilation of publications (Palmero *et al.*, 2018). There are some Amerindian founder variants identified in countries like Brazil, Colombia, Mexico, Peru (Ossa and Torres, 2016) and Chile (Alvarez *et al.*, 2017), reflecting the local contribution to the genetic spectrum from the native populations, a very important population and epidemiological disclosure.

Even in the recent survey "worldwide snapshot" (Toland *et al.*, 2018), the authors did not receive relevant data from LA (the data in the publication does not represent Latin America; it only includes two laboratories: one each for Argentina and Brazil). The sample surveyed does not represent the actual technological situation in the region and specifically neither of the two Latin American countries both with an HVP country node, that could be of utility to validate the reported data; the rest of the countries were not included in the survey, which consists of an Excel spreadsheet of 65 fields, so the conclusions are extremely limited when it comes to this region. A rescue for this omission was written by 9 laboratories (Argentina, Brazil, Chile, Colombia, Costa Rica, Guatemala, Mexico and Uruguay) with an author from the original study who open the survey for Latino America and we sent for publication in November 2019.

A more realistic overview can be obtained by reviewing databases in the case of Argentina, with 25,064 variants deposited at LOVD, by 17 laboratories from five cities in the country. A brief description of genetic testing in Argentina was recently summarized (Cotignola *et al.*, 2019).

All these technical limitations highlight the importance and the utility of the policies effective worldwide through the leadership of HVP country nodes, including data sharing and practices (Smith and Vihinen, 2015).

ACADEMIC ACTIVITIES OF THE ARGENTINIAN NODE OF THE HUMAN VARIOME PROJECT

As published (Smith and Vihinen, 2015): "the HVP Consortium works collaboratively to define international standards and guidelines that describe best-practice methodology in each of the areas, which can then be utilized in the implementation of specific systems and processes."

In pursuing the optimal translation of these practices into our professional local community, we organized in Argentina both local meetings and a few international meetings documented in our webpage, www.humanvariomeprojectargentina.org.ar/, as follows:

- Prof. Dr. Johan den Dunnen from the Leiden Open Variation Database, Netherlands participated at the "XLVI Argentine Congress of Genetics and IV Regional Conference SAG-NOA" (Catamarca, Argentina, October 1st-4th, 2017, www.sag.org.ar). He also lectured at "Centro de Educación Médica e Investigaciones Clínicas (CEMIC), October 6th, 2017" resulting very fruitful interaction with the experts present from the most specialized Institutions in hereditary cancer in Argentina.
- Organized by the "Sociedad Argentina de Investigación Clínica" (SAIC) held in Buenos Aires, Argentina, Prof. Dr. Juergen K.V. Reichardt participated, at both levels, interacting with the Community, on November 12th 2017, and the day after at the Annual Congress of SAIC (https://www.saic.org.ar) as speaker at the Symposia of the Node. The interest of the community in the genetic concepts and the application in health was remarkable, the clarity of Dr. Reichardt was key for the excellent interaction.
- At the International Congress of Genetics (ICG) in Foz do Iguaçu, Brazil, September 10th to 15th, 2018, the Chair of the Node of Argentina, Dr. Angela R. Solano lectured in a Symposium with the participation of three other Latino American scientists.

- Held in Buenos Aires on November 22nd and 23rd, 2018, the Workshop of the Node of Argentina of the Human Variome Project was a very interactive meeting. The workshop was a success and it is remarkable the interest and enthusiasm of the participants sustained by lectures which updated data including practical implications and application of programs in clinical cases in their own notebooks, skills to be reinforced as they are very critical nowadays due to the permanent advances and the necessity of an updated knowledge through life-long learning.

The importance of the meeting was reinforced by the recognition of Prof. Dr. Johan den Dunnen as Honor Guest for the City Hall of the City of Buenos Aires, on November 21st. For this occasion Dr. den Dunnen gave an impressive presentation on "International Standards for Genetics Nomenclature", held at the Golden Room of the main Palace of the City Hall.

The Argentinian Node was invited to participate of the activities of the Ecuador network for genetics and genomics (Red de Genética y Genómica, ReGG: https://www.yachaytech.edu.ec/en/regg/) (founded by one of us, JKVR) a year ago to promote research, training, offer continuing education, share expertise, equipment, advice and assessment in Ecuador. This association is made up of two universities, four research institutes and the Secretariat for Science and Technology (SENESCYT; the equivalent of the Science and Technology Ministry in Ecuador).

ReGG has held monthly meetings and also held its first annual meeting in April 2019 in Quito, Ecuador (www.yachaytech.edu.ec/en/noticia/first-regg-annual-reunion/). This meeting brought together national and international speakers and paved the way for a bright future for genetics and genomics in Ecuador amongst its 150 participants. It is anticipated that the annual meeting will continue and serve as a conduit for national and regional collaboration as well.

The common activities in Latin American countries will be hopefully shared at LatinGen (www.latingen.org), launched with the colleague from Brazil including the Chair of the Node of Brazil of the Human Variome Project, Dr. Iscia Lopes-Cendes. The aim is to support data-sharing in LA by fostering collaboration and integration among projects in different countries, as follows:

- a) To facilitate the centralization and integration of public databases already established in LA.
- b) To stimulate and support new initiatives by providing technical assistance (bioinformatics expertise) to implement public databases in LA.
- c) To support education and training in the field of human genetic variation in LA.

As it is summarized in the web page of the Argentinian Node: "Latin America and the Caribbean region make up one of the largest areas of the world, and this region is characterized by a complex mixture of ethnic groups sharing Iberian languages. The area is comprised of nations with different levels of social development. This region has experienced historical advances in the last decades to increase the minimal standards of quality of life; however, several factors such as concentrated populations in large urban centers and isolated poor communities still have an important impact on medical services. Latin American researchers have greatly contributed to the development of genetics and historic interethnic diversity and the multiplicity of geographic areas are unique for the study of gene-environment interactions".

DATA SHARING AND GENETIC DEVELOPMENT

As a round-up concept for this work: data sharing is an international initiative from clinical, medical, and basic research laboratories to systematically identify and document genetic variants (including pathogenic and benign genomic variants) worldwide. Data is provided as gene and/or disease-specific collections, and also as country-specific data, and this effort sustains the country-specific variants listing in the LOVD, for us: ar.lovd.org; we succeeded in improving the translational research strategies and clinical decision-making processes nationally, regionally and beyond. The challenge is ongoing and we look forward to accelerate the production of results taking advantage of the enormous progress in the era of rapidly advancing technologies. Actually, the most critical part may be the decision to be a depositor of all variants detected, an attitude that in some laboratories still is a matter of some hesitation, and the good news is that many new laboratories are incorporated daily into this data sharing effort.

Finally, we mention the updates and alerts about new sand challenges in the worldwide genetics and genomics community, published in the weekly newsletter of the Global Alliance for Genetics and Health (GA4GH; www.ga4gh.org). An important disclosure a few months ago was a description about the current landscape of the direct to consumers (DTC) laboratories: DTC laboratories are enterprises engaged in sequencing DNA of a client sample sent following the instructions of a kit that can be bought at the pharmacies and paid by the consumer, without the necessity of a medical order. The danger arises of its application in diagnostics (press release, March 6th, 2018, www.ga4gh.org). A very important matter for the professionals involved is the writing of reports with clinical importance for patients, from

which medical decisions will be supported, including diagnoses, treatments, surgeries, etc.

REMARKS AND CONCLUSIONS

The role of the Argentinian node of the HVP is to support the activities in genetics and genomics in every province of Argentina, and we are looking forward to increasing the contribution from all local laboratories involved in gene sequencing. Furthermore, we hope that our work may serve as an inspiration to other countries in the region that still do not have their own nodes, and we are always happy to share our experience to make the implementation of the countries nodes easier and faster.

The launching of the LatinGen database with our colleagues from Brazil is very promising to stimulate the interaction of the region and to join efforts in the genetic development of Latin America countries.

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