IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 7th IRDiRC Diagnostics Scientific Committee meeting

Teleconference
31 October 2014

Organization

Organized by: Scientific Secretariat
Teleconference

Participants

Dr Kym Boycott, Ottawa, Canada, co-chair
Prof Michael Bamshad, Seattle, USA, co-chair
Prof Han G. Brunner, Nijmegen, Netherlands, co-chair
Prof Xavier Estivill, Barcelona, Spain
Prof Gert Matthijs, Leuven, Belgium

Dr Barbara Cagniard, Scientific Secretariat
Dr Sophie Höhn, Scientific Secretariat

Apologies

Prof Johan den Dunnen, Leiden, Netherlands
Prof Milan Macek, Prague, Czech Republic
Prof Woong-Yang Park, Seoul, Korea
Prof Pak-Chung Sham, Hong Kong, China
Prof Hendrik Stunnenberg, Nijmegen, Netherlands
Prof Jun Wang, Shenzhen, China

Agenda

- Variant Data Sharing for Clinical Interpretation and Discovery
- Case-based Matching for Gene Discovery
- Solving the Unsolvable Rare Diseases – Beyond the Exome
- Model Systems to Support Variant Interpretation

REPORT

The purpose of this teleconference was to discuss the draft white paper on recommendations regarding long-term funding priorities to present to the Executive Committee. This paper is based on discussions held in the last teleconference of this committee (7 October 2014) and in an informal meeting in San Diego, during the ASHG 2014 meeting. It was decided to ask for either 6 or 12 M Euros for each project, based on the funding of European projects.

Variant Data Sharing for Clinical Interpretation and Discovery

- Data generated in diagnostics labs are missing. It should be specified that, although IRDIRC is mostly related to research, both research and diagnostic data are necessary as there is a lot of activity in Diagnostic laboratories.
- Integration of existing platforms mentioned in the white paper is indeed necessary. Fact-finding to determine if such initiatives already exist would be good (EBI, etc.). ClinVar should be acknowledged in the white paper.
- Companies building software for diagnostic or for variant interpretation should include a tool facilitating automated reporting to urge user to file variants into databases.
- Need for quantitative data about disease variant and population controls variant data.

Case-based Matching for Gene Discovery

- "Background" and "Gap/Need" paragraphs are fine.
- More concerted effort and better and more sustainable infrastructure/resources are necessary as it will take years to implement.
- Part of the research project is to determine what is considered identifiable data and thus what level of data needs to be consented for sharing.
- Ideally, there would be a repository that contains the raw data that could be reprocessed. There are 2 major obstacles:
    - Changing the culture of sharing, at least in the US.
    - There is a lack of data sharing policies. Many institutions are still ignorant about their ability to share data and are thus conservative and consider that they cannot share data.

Solving the Unsolvable Rare Diseases – Beyond the Exome

- Project aims to target a certain set of refractory recognizable syndromes, including the ones listed in the document, where we know that, multiple groups have attempted to determine the molecular pathogenesis and been unsuccessful.
- Approaches would be developed which could be use more broadly for some of the more difficult diseases.
- Development of WGS and RNA-seq approaches to investigate refractory RD.
- Complementary approaches such as metabolomics might be included.

- Development of tools for analyzing and interpreting non-coding variants.
- Development of novel approaches to detect mosaicism.
- Creative approaches are best and thus the list of "infrastructures/research needed" need not be exhaustive.

Model Systems to Support Variant Interpretation

- The purpose is the development of effective animal models for interpreting RD gene variants. Approach to the problem could include:
    - (1) platform-driven (small group of 5-6 labs that would analyze variants being agnostic to gene-pathway mechanisms)
    - (2) a more collaborative approach (many different labs with different expertise; much more difficult to coordinate).
- We are looking for the next generation of disease modeling; the key word is wide applicability.
- Deliverable would be that they need to show applicability to a wide-range of conditions with a moderate throughput and a time-scale realistic for diagnostic purpose (3 months maximum).
- Platform would not need to also provide mechanistic readout or lead for therapies as it is too complicated, but it would be a bonus if the assay might be generalized to drug screening.
- Possible approach: allocation of 3M Euros each to 4 platforms (Zebrafish, C. elegans, Yeast, Drosophila) to enable the proof of concept. Each platform should integrate minimum number of centers needed to ensure the deliverable is met. Important point would be focused expertise with no requirement for multiple partners.