IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 6th IRDiRC Diagnostics Scientific Committee meeting

Teleconference
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Organization

Organized by: Scientific Secretariat
Teleconference

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Agenda

1. Case-based matching for gene discovery
    a. Phenotype and genomic datasets
    b. Matchmaker exchange type efforts – pilots and beyond
2. Variant Data sharing for clinical interpretation and discovery
    a. Integration of existing platforms (dbGAP, ClinVar, EBI)
    b. Education on importance of sharing
3. Model systems to support variant interpretation (Model WG)
    a. Expertise driven (advantage – increase RD research in basic labs; disadvantage – coordination intensive)
    b. Platform driven (agnostic – possibly for genes of unknown function)
4. Other topics

REPORT

The purpose of this teleconference was to start discussing recommendations regarding long-term funding priorities to present to the Executive Committee, keeping in mind the Diagnostics Scientific Committee's (DSC) goal, which is to help enable the identification of most genes by 2020. These recommendations will be compiled in a white paper, which can be used as the basis of future funding calls by any of the IRDiRC funders (i.e. European Commission).

1. Case-based matching for gene discovery

The matching of unsolved cases has a very immediate impact on gene discovery. The first recommendation was made based on the value of case-based matching for gene discovery in research and clinical settings:

a. Phenotype and genomic datasets

Case matching is based on phenotype and genotype datasets. These datasets need to be standardized.

b. Matchmaker exchange type efforts

To facilitate both phenotypic and genotypic data exchange, the Matchmaker Exchange initiative, co-lead by IRDiRC and the Global Alliance for Genomics and Health, has been developing an Application Program Interface (API) to allow these resources to communicate with one other. It is currently connecting PhenomeCentral in Canada to GeneMatcher in USA (Centers for Mendelian Genomics, Johns Hopkins University). It is a pilot but it is moving slowly given there is no dedicated funding. The Data Working Group (WG) of the Global Alliance has offered to provide support of the API. It is early days and no matches have been identified from this pilot API to date. It is necessary to show that it is successful to expand it. It needs additional funding for infrastructures. A very immediate need is to show that Matchmaker works (i.e. following up on some of the potential hits and whether they are actually validated).

As there are so many databases, there is also an urgent need to standardize how matching between databases will happen. Standard operating procedures are required.

2. Variant data sharing for clinical interpretation

It is of key importance to push the scientific community to share their variants to solve their unsolved cases and establish the causality of variants. This is why the second recommendation was made on variant data sharing for clinical interpretation and discovery based on:

a. Integration of existing platforms

A lot of variants are of unknown clinical significant variance. Integration of what databases that already will help diagnose rare disease patients. Funding is needed to help the scientific community export their local databases into worldwide accessible databases.

b. Education on importance of sharing

It is important that the scientific community understand the value of sharing and the value of the data in their local database.
Meetings or workshops could be organized for investigators with variants to come together and to point out the value of sharing. Such a session could be organized during the European Society of Human Genetics which will take place in Glasgow on June 6-9, 2015.
Scientific journals could be encouraged to declare that all variants must be submitted to a database with publication; submission to a database could become mandatory prior to publication.

3. Model systems to support variant interpretation

The third recommendation was made on the use of model systems to support variant interpretation. Two approaches could be undertaken:

a. Expertise driven

The WG on Model Systems had brought forward a proposal for some network type calls where clinician scientists with genes would be connected to model organism researchers in the world with expertise in gene pathways, and give them some seed money to look at the function of that particular gene in the context of disease.
This case by case model is more complicated than a platform driven model. It represents a coordination challenge. However, its advantage is that it increases rare disease research in basic laboratories.

b. Platform driven

The alternative to an expertise driven model would be some systematic analysis of specific variants that have been detected in rare disorders using a wide scope of model systems to move things quite quickly in the analysis of the clinical consequences of those variants.
This larger scale agnostic platform would also be useful for genes of unknown function.
The ideal model would be the combination of a. and b.

Other topics

- Does IRDiRC accept sponsors and charity to expand its funding? For example, private industry funders (i.e. Illumina) could want to fund standard and guidelines, with a commercial interest. IRDiRC could decide that this money could be used for guidelines. Topic to be discussed.
- The Saudi Human Genome Project has officially become a member of IRDiRC. Dr Fowzan Alkuraya is expected to become a member of the DSC in the near future.
- Elizabeth McNeil will be the TSC representative in the DSC WG on Model Systems.
- The WG on Ontologies and Rare Disease Prioritization has put forward its draft recommendations for disease ontologies and phenotype ontologies. This draft has already been circulated through the WG and will soon be circulated to the DSC. The DSC will need to approve it during its next call, and it will then be circulated to the ISC and TSC for comments, and then to the Executive Committee.

- The WG on Sequencing is also discussing a document for recommendation: the EuroGentest guidelines for diagnostic next generation sequencing. It will then be circulated to the DSC in the near future.

Deliverables

- Work on an outline of the white paper in San Diego during the ASHG meeting on October 18-22, 2014 for the present DSC members
- Write the white paper 2 to 4 weeks after the ASHG meeting
- Present the white paper to the Executive Committee at their November meeting in Shenzhen