IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 3rd Diagnostics Scientific Committee Meeting

Teleconference
10th September 2013

Organization

Organized by the Scientific Secretariat
Teleconference

Participants

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REPORT

The primary purpose of this teleconference was to review the reports of the WGs' teleconference(s) to provide feedback to them on what should be prioritized and to advise them on the next steps. All 4 WGs received instructions with capture of the Action Plan relative to their topic. Each WG has had at least one teleconference. Input on direction to the WG by the DSC is indicated with open arrows below.

WG on Ontologies and Disease Prioritization

Summary from WG - Disease prioritization

It is necessary to prepare a list of solved diseases and unsolved diseases and to define how to best keep track of progress. However, some difficulties that will need to be overcome to reach this objective include:

- How do we track what is yet unsolved as many rare diseases do not necessarily have an OMIM number.
- The definition of unsolved diseases is not clear: phenotype without a gene associated? Phenotype with more mutations to be identified? Mechanism unclear? Therapies not available?

The main purpose of IRDiRC is to promote research on rare diseases to accelerate the discovery of diagnostics and therapies. Two approaches are possible:

- Develop a fully comprehensible list of any kind of mutation that is found in any kind of phenotype that can be classified as a rare disease. This approach is useful if the purpose is to promote general genomic research but would require a lot of work.
- Focus on a restricted but solid list of diseases/phenotypes (1000-2000) limited to clear cases (monogenic, highly penetrant mutations, disease is rare, etc.). This approach would help promote research on mechanisms and collaboration with molecular researchers and model systems researchers. Moreover, Orphanet already provide a list of genes associated with diseases that is curated monthly.

Input from DSC on Disease prioritization: Although both approaches have benefits, the members of the DSC agreed that it would be best to focus on the short list first as prioritizing what is most tractable will increase experience to move forward to what is more difficult to solve.

- ⇨ Focus on assembling a list of diseases/phenotypes for rare monogenic highly penetrant rare diseases.
- ⇨ How to facilitate identification of the remaining novel RD genes should be discussed by the WG on Genome/Phenome.

Summary from WG - Ontologies

The WG aims to summarize all existing ontologies for disease, phenotype and biobanks and to recommend a forward strategy for IRDiRC for ontologies. The members of the WG will not advise

development of new ontologies but will select one or a few for IRDiRC members to recommend for use. The master ontology for rare disease phenotypes will most certainly be HPO. Most of the members of the WG are going to meet for 2 days before the ASHG to agree on 2,000 terms to map across all the ontologies.

Input from DSC on Ontologies:

- ⇨ The WG should provide a position statement on the topic of ontologies for rare diseases in the coming 6 months.
- ⇨ This standard ontology selected by the WG will be supported by IRDiRC. There will be a process in place to add terms to this standard set.
- ⇨ The 2,000 rare disease terms will be mapped to existing ontologies and adopted by IRDiRC as the minimal standard set.

WG on Sequencing

Summary from WG - Sequencing

The first priority should be adoption of sequencing standard/guidelines. There are at least 6-7 guidelines at the moment world-wide.

The WG felt strongly that sequencing should be done by health care system not by researchers. In Europe, each country has its own politics around funding for clinical sequencing. IRDiRC should point at the countries reimbursing sequencing as example.

How to classify variants. The cancer community is addressing this topic. Human Variome Project (HVP) is planning to write guidelines on this and it would be wise not to duplicate what they are doing. There is also a need for sharing of normal variant data as well.

Input from DSC on Sequencing:

- ⇨ Compile all guidelines available; provide recommendation for use in the next 6 months.
- ⇨ Identify one person in each country to evaluate the approach of the country on the implementation of clinical exome/genome sequencing.
- ⇨ Identify and collaborate with HVP and others (to be identified) on classification of variants.

WG on Model systems

Summary from WG – Model systems

The WG has a lot of ideas in term of collaboration. The members of the WG gave the impression that model systems researchers feel disconnected from the other researchers. Members of the WG wish to be informed about novel disease genes so that they can investigate the mechanisms early in the process when they have the appropriate resources and expertise. Their idea is to develop a market place to

facilitate collaboration between researchers discovering new disease genes and model system researchers.

From the discussion, it seems important to promote rare diseases research among model systems researchers through engagement of IRDiRC in scientific meetings.

Input from DSC on Models systems: It is not clear what the WG could focus on in the short term. Should they prioritize model systems research to study the mechanisms of diseases tractable for treatment such as degenerative diseases preceded by a period of normalcy?

- ⇨ How would such a prioritization work? Would there be a list of diseases that are tiered for therapeutic configuration based on a set of criteria? Could IRDiRC have a list of diseases we are interested in for therapeutic configuration for the model system community to access? This requires more discussion by the DSC at the next meeting and input from the TSC.
- ⇨ The implementation of such market place would necessitate resources and could be prioritized for a funding call, more details would need to be provided to the DSC to bring this to the Executive.
- ⇨ At the time of the first teleconference, a human geneticist was not yet member of the WG.

WG on Genome/Phenome

Summary from WG - Genome/Phenome

This WG already held 2 teleconferences.

The WG thinks that IRDiRC should take the lead for rare diseases among the initiative Global Alliance (GA). Their strategy would be to show the members of GA that IRDiRC has the coordinated resources for this purpose and would thus be a natural leader. If the Executive Committee agrees, the WG will prepare a short white paper to present to GA.

The second point discussed by the WG is the need of crosstalk between databases to advance the re-interpretation of genome/phenome data to solve some of the RD and to interpret other mutations in genes that we already know. RD-Connect may be able to support part of this project but it is still implementing. There are also local efforts in UK (Decipher) and Canada. There should be communication between these initiatives but the infrastructure necessary is currently inexistent.

Input from DSC on Genome/Phenome:

- ⇨ The chair of the DSC will gather more information on Global Alliance at the next Executive Committee meeting and provide input on next steps to the WG on this matter.
- ⇨ The DSC is very enthusiastic on the crosstalk platform and encourages the WG to move this forward as it is key to the success of part of the first objective of IRDiRC – to identify the remaining genes responsible for rare diseases.

Next DSC meeting

It was decided that the next face-to-face meeting of the DSC will be held in Prague before the end of the first week of December. The DSC meeting will be combined with a one-day workshop aiming to engage groups from Central and Eastern Europe in IRDiRC.