IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 9th Diagnostics Scientific Committee Meeting

Glasgow, UK
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Agenda

1. Roundtable and updates on DSC activities
2. Role of the Diagnostics Scientific Committee (DSC)
3. Proposals for IRDiRC Recommended projects
4. Update on Matchmaker Exchange (MME) Task Force
5. Potential Task Forces for 2016-2018
6. Renewal of DSC membership
7. Discussion and opinion paper writing on DSC roadmap and recommendations

REPORT

1. Introduction

The Chair of the Diagnostics Scientific Committee (DSC) opened the meeting and members introduced themselves.

2. Role of the Diagnostics Scientific Committee (DSC) in Task Forces (TFs)

Governance Structure

Currently 13 members constitute the DSC. Four TFs have been launched this year. The mandate of the DSC needs to be updated in terms of the new role of Sci Comms now that the TFs are launched. A main objective of the Sci Comms remains to define research priorities for the Exec Comm as IRDiRC is composed of funding agencies who wish to be advised on areas of funding for future calls. The Sci Comms should present identified gaps to the Exec Comm on a regular basis.

2015 update on mandate of the Sci Comm

- Act as scientific coordinating bodies
- Propose research priorities for consideration by Exec Comm
- Propose policies and guidelines for adoption by Exec Comm
- Identify actionable projects and contribute to the organisation of workshops
- **Contribute to the establishment of Task Forces to advance selected projects**
- **Evaluate, validate and make recommendations based on project workshop outcomes**
- **Propose reviewers to review submissions for "IRDiRC Recommended"**
- **Endorse and present the Rapporteur's report for "IRDiRC Recommended"**
- Address emerging issues of scientific nature
- Organise the scientific programme of IRDiRC conferences
- Encourage exchange of protocols and best practices, and agree on standard operating procedures, quality standards, roadmap to reach IRDiRC goals in their scientific area

During the joint meeting of the three Sci Comms, this mandate was modified. It is now the following:

- Act as scientific coordinating bodies
- Propose research priorities for consideration by Exec Comm
- Propose policies and guidelines for adoption by Exec Comm
- Identify actionable projects and contribute to the organisation of workshops
- **Contribute to the establishment of Task Forces to advance selected projects, nominate members and help populate the workshop**
- **Evaluate, validate and make recommendations based on project workshop outcomes**
- **Review submissions for "IRDiRC Recommended"**
- Address emerging issues of scientific nature
- Contribute to the preparation of annual State-of-Play Report

- Organise scientific programme of IRDiRC conferences
- Encourage exchange of protocols and best practices, and agree on standard operating procedures, quality standards, roadmap to reach IRDiRC goals in their scientific area

3. Proposals for IRDiRC Recommended projects

IRDiRC Recommended was launched to highlight resources of high interest and utility to the research community and to accelerate research and collaboration. The application process is described on the IRDiRC website (http://www.irdirc.org/activities/irdirc-recommended/). Applications are reviewed by experts. Four applications have been submitted, two of which from Spain (a registry and a platform to interpret genomic variants) that are country-specific. PhenomeCentral has applied and is under review.

Clearer instructions on criteria for applying are needed. The DSC should recommend what resources should be proposed for recommendation. Once the Scientific Secretariat (Sci Sec) receives the reviews, they will be sent to the Sci Comms who will report to the Exec Comm.

Efforts to reach out to potential IRDiRC Recommended projects

Matchmaking databases:

- GemApp
- GeneMatcher
- DECIPHER
- ClinGen
- LOVD
- Mutation nomenclature
- OMIM
- Orphanet
- ORDO
- HPO
- ICHPT

Action: develop an email with attachments so that these groups can be targeted by the identified individuals.

Variant type databases:

- ExAC Browser
- EVA (Exome Variation Analyzer)
- EVS (Exome Variant Server)

All these tools are not RD specific, but are widely used by the research community. It was suggested that IRDiRC work collaboratively with the Human Variome Project which awards a similar quality stamp, "HVP Recommended" (http://www.humanvariomeproject.org/solutions/recommended-systems.html).

Action: check appropriateness of these databases for IRDiRC Recommended.

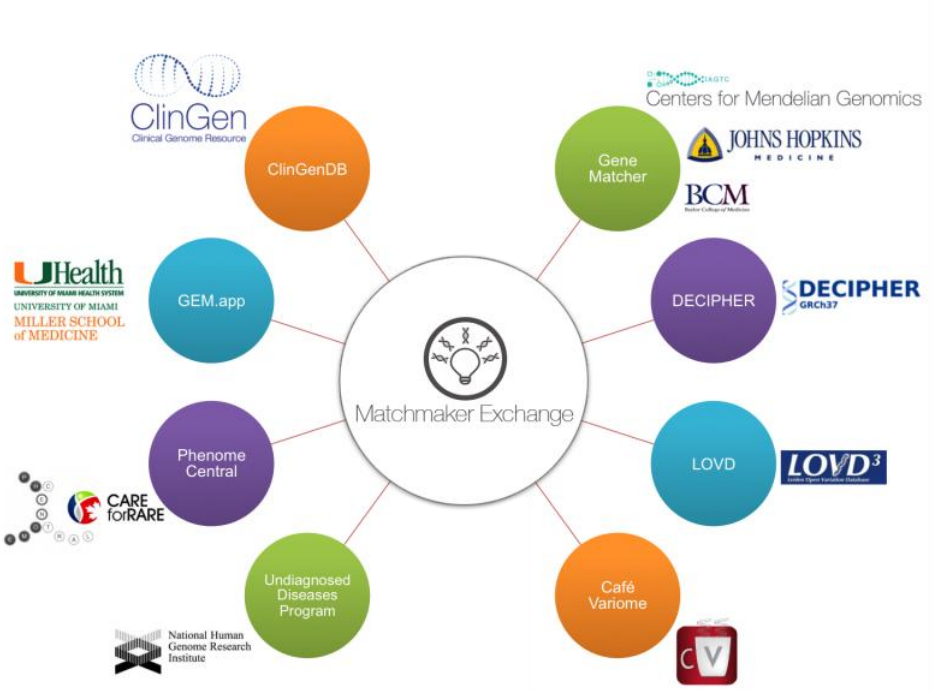
Knockout lists:

- Human homozygous gene knockout list
    - Richard Trembath, Queen Mary University of London
        - ~700 genes
        - http://webspace.qmul.ac.uk/dvanheel/EastLondonGenes&Health/
    - Kari Stefansson, Letters from Iceland, *Nature Genetics* 28 April 2015; 47:425
        - ~1100 genes
        - http://www.ncbi.nlm.nih.gov/pubmed/25807282
    - Fowzan Alkuraya King Faisal Specialist Hospital and Research Center, Saudi Arabia
        - 170 genes
        - http://www.ncbi.nlm.nih.gov/pubmed/24367280

Action: compile all these resources, examine overlap in the listed genes, compare with OMIM and Orphanet disease genes, and with the mouse knockout consortium resources.

4. Update on Matchmaker Exchange (MME) Task Force

The current pace of gene discovery is declining; an observation supported by Orphanet and OMIM data. Contributing factors include increasing rarity of disease presentations and that data is being siloed in individual clinical and research laboratories as well as databases (e.g. PhenomeCentral, GeneMatcher, DECIPHER, GemApp, etc.). The need to connect all these data to enable discovery started Matchmaker Exchange, launched in 2013 at the ASHG, and in partnership with IRDiRC and ClinGen. The contents and structure of each database are different, for example:



- GeneMatcher contains only the gene (almost 2,000) and no phenotypic description;
- DECIPHER contains gene, variant and phenotype with associated HPO terms. It contains only the top five genes for an unsolved case and no exome data;
- PhenomeCentral contains all the exome variants for each case and all the phenotypes using HPO terms; and,
- GemApp contains all the exome variants with disease name but without phenotype.

4.1 Pilot

An API was developed to enable connection of the databases within the network and is based on 'query by example' – which means that a patient must be entered into a database to instigate the search. Matching is based on the lowest common denominator in terms of information contained with the pairwise connection of two databases.

The project started by connecting PhenomeCentral and GeneMatcher and this connection is live. Matching between these databases is based on prioritized genes. A testset of 50 solved cases with a candidate gene identified were entered into PhenomeCentral and GeneMatcher databases; all 50 hits came back successfully. Another testset of 45 unsolved cases of flagged candidates from PhenomeCentral were queried in GeneMatcher. The point-to-point query returned 10 possible hits, including 6 false positives (different phenotypes), 2 unresolved cases and 2 potentially significant matches.

The API ready to connect to DECIPHER to PhenomeCentral, but has not yet gone live.

4.2 Future prospects and unsolved issues

- Several improvements to increase sensitivity and specificity of the current version of the API need to be considered. For example, phenotype, gene and inheritance pattern data could return a score reflecting the chance the match will validate; this requirement development and optimization over time.
- The next year must be dedicated to demonstrating that the tool if beneficial and that the number of false positives are minimized, in order for the community to buy into it as a useful solution, at least for the short term.
- The MME tool will serve to solve part of the n-of-1 problem for a couple of years, but will not be the complete solution to matchmaking.
- Longer-term solutions include a MME hub which would overcome point-to-point matching process that is the current approach. Database owners within MME not willing to become part of the hub can remain separate and represent a hub themselves. Funding will be necessary to build such a hub.
- Thought must be given to different models to integrate large public databases with full variant and phenotype datasets that scientists can manipulate. Members of the TF are engaging with other initiatives to explore other approaches.

4.3 Next MME TF workshop

The next workshop will be held at ASHG 2015 (6-10 October, Baltimore) around two meetings.

- Day session (Tuesday 6 October): Closed working meeting for MME on implementing API V1 & Vision for API V2, including the hub model. Morning session for API owners, users and (pilot) result reporters. Afternoon session for the broader group of interested and potential users.

- Evening session (Wednesday 7 October): Community engagement, an open 2 hour event to engage the medical genetics community in MME, provide tutorials and solicit feedback on the current model for genomic matchmaking. This event will be open to participants interested in solving cases and who are not necessarily database producers, owners or contributors.

4.4 Outputs and reporting

- Summary on the need for funding for MME current and future versions to IRDiRC funders.
- Special issue of Human Mutation, 16 papers have been submitted and are being reviewed for publication. These include the databases, matching modeling, and examples of successful matches. The deadline for acceptance of these articles is 15 July. Copies will be distributed at the ASHG in October 2015 and as part of the TF workshop sessions.

5. Potential Task Forces for 2016-2018

The Chair of the DSC will present these TF projects at the Exec Comm meeting in Montreal, 11 September 2015.

5.1 Variant data sharing for RD patient diagnosis

A TF would aim to:

- Enable and incentivise international connections and collaborations for data sharing
- Develop methods to share optimally – possibly through a 'hub'
- Identify groups interested and analyse what must be done at one centre to connect to another
- Put database leaders in touch to identify obstacles to data sharing
- Hold a workshop at the ESHG 2016 to demonstrate mechanism and show some results (possibly from Holland and Belgium)

This project could be funded by E-Rare or another support mechanism (travel for centre to centre data collection and connection). IRDiRC could support a workshop, but not the background work. Global Alliance is working on this topic, but not for patient discovery.

Action: Launch TF in 2016

5.2 Case based matching for gene discovery

A TF that will essentially be an extension of MME and hub building.

Action: Launch TF in 2016

5.3 New approaches to solve unsolved RD; beyond the exome

As 60-70% of exomes are not providing patient with diagnoses, a TF based on data sharing and best practices for interpretation will aim to:

- Identify key unsolved diseases and organise a workshop around these types of disease that are likely to be mosaic, genetically heterogeneous, noncoding mutations, methylation anomalies, etc.
- Address strategies to develop best practices on how to go about this type of research – WGS, RNASeq, methylation studies, etc.
- Highlight successful approaches
- Discuss recognition of these needs by funding agencies – a one pager background has been written on the needs and ways to reach objectives

Action: Launch TF in 2017

5.4 Model systems to support variant interpretations

A TF will aim to:

- Identify methods to evaluate variants and demonstrate if and how they cause disease
- Encourage the model organism systems community to develop high throughput assays for variant interpretation in cell based models
- Develop tools and strategies to use on moderate throughput platform-based approaches

Action: Launch TF in 2017-2018

5.5 Strategies for diagnostic translation

A TF should be set up to formulate recommendations to countries on the strategic approach to diagnosis using NGS, given that a large numbers of patients are not successfully diagnosed due to limited access to genetic testing, including sequencing approaches.

A TF will aim to:

- Identify diagnostic successes using different sequencing methods
- Map methods of reimbursement
- Map means of access
- Translate from a concept to methods available in healthcare systems
- Write a position paper on strategies and incremental approaches for diagnosis, guidelines for targeted and exome sequencing and how to provide access to these tests
- Partner with ESHG, ASHG and other societies and colleges

Action: Launch TF in 2015-2016

6. Renewal of DSC membership

Members are nominated for three years. Half the group has attended meetings on a regular basis. The Chair of the Exec Comm will speak to consortium members on identifying active member to participate in the DSC. A discussion was also held on succession plan for the Chair of the DSC.

7. Discussion and opinion paper writing on DSC roadmap and recommendations

The Chair of the DSC has put together a draft.
Title: Beyond the Exome: Enabling the Diagnosis of Most Rare Genetic Diseases by 2020

Contributors:

- Members of the DSC
- Working Group chairs
- Members of the Working Groups
- Scientific Secretariat
- Members of the ISC
- Orphanet
- OMIM
- Industry

Targeted journals: Possibility to have the same article published in two or more journals – joint publication by the American Journal of Human Genetics and the European Journal of Human Genetics would be ideal.

Target: Background literature for a joint conference "building bridges session" – at either ASHG or ESHG.

Content:

- Molecular etiology of RD
- Pace of RD gene discovery since 2010 and highlighting the decline in discovery in 2014 and discussion of possible reasons why this was observed (2012-2013: 290 to 310 genes discovered a year; 2014: 190 genes identified)
- Role of IRDiRC
- Focused task and strategic actions to diagnose most RD by 2020