Coordinating Office Position Paper

AP02-2012: Assigning Pathogenicity to a Genetic Variant ICO Comments

PP-ICO-2012-07

27 September, 2012

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Authorisation:
This Position Paper has been prepared by Timothy D. Smith and represents the official position of the Human Variome Project Coordinating Office only. It does not represent an official position of the Human Variome Project, its Consortium, Advisory Councils or International Scientific Advisory Committee.

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Heather Howard

I Context

The International Coordinating Office (ICO) received the attached Activity Proposal (AP) on the 31st of August, 2012. Pursuant to the Project's Standards Development Process (PD06-2011) we are forwarding it to the International Scientific Advisory Committee (ISAC) for referral to a Sponsoring Council (SC). Further pursuant to the Standards Development Process we have prepared the following comments on the AP for the ISAC and SC.

II Comments

Background

The accurate interpretation of genetic variants is fundamental to the ability to provide appropriate health care and a key part of the mission of the Human Variome Project. The development, adoption and continued use of standardised processes, based on qualitative, quantitative, or a mixture of both, methods is necessary to ensure that interpretations are consistent with current knowledge, able to be defended as required and can be repeatedly generated.

Proposals exist for the classification categories that variants should be assigned to (e.g. Plon *et al.*, 2008), but to date no guidance on how to assign variants to particular categories has yet been published that is applicable across the genome.

Scope of Work

We recommend that an HVP Working Group (WG) be convened to develop guidance on processes that should be undertaken when classifying variants with regards to their pathogenicity. As this activity is relevant across both channels of Project activity (gene/disease specific collection and country specific collection), our recommendation would be for the International Scientific Advisory Committee to act as the SC for this activity.

The convened WG should be chartered to:

1. review existing guidance on pathogenicity classification;
2. prepare a list of *guiding principles* for classification processes that are broadly applicable across the entire genome; and
3. develop a defined qualitative/quantitative (as applicable) process for the classification of genetic variants that can be freely adapted for specific use cases.

It is difficult to ascertain at this early stage whether the result of this activity should be an HVP Standard or Guideline. Such a determination can only be made when more information about the process to be developed are known. Our position would be to lean toward publication as a standard, but care will need to be taken in making such a decision that it does not place an unreasonable burden on the Project's infrastructure members to comply.

We support the intention of the AP submitter to see the result of the WG's efforts published in a high-profile academic journal, but must caution the SC to ensure that such publication does not limit the Project's ability to publish, disseminate and create derivatives of the work during the course of its normal activities.

Possible Working Group Members

We recommend that the SC ensure broad representation of skills in the WG, as well as a broad representation of the different categories of diseases with a genetic basis or component, including, but not limited to: cancer, metabolic disorders, and dysmorphology.

Available Assistance from the ICO

The ICO is able to provide the following assistance to the WG:

- secretarial assistance;
- face-to-face meeting organisation;
- phone and video conferencing facilities;
- collaborative authoring tools.

The ICO is not in a position to assist the WG financially.

III Summary of Recommendations

We recommend:

- The ISAC act as Sponsoring Council for this activity
- The ISAC charter a WG to carry out the scope of work recommended in this paper
- The resultant work be published as an HVP Standard if such publication does not unnecessarily burden Project infrastructure members
- The resultant work be jointly published in a high-profile academic journal

IV References

Plon, S. E., Eccles, D. M., Easton, D., Foulkes, W. D., Genuardi, M., Greenblatt, M. S., Hogervorst, F. B., Hoogerbrugge, N., Spurdle, A. B., and Tavtigian, S. V. (2008). Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Human Mutation*, **29**(11), 1282–1291.

HVP Activity Proposal

Standard for Assigning Pathogenicity to a Genetic Variant

Marc S. Greenblatt

August 16, 2012

1) The need that the proposal addresses

The functional effects and pathogenicity of many genetic variants cannot be assessed with enough confidence to use them to make clinical decisions. No standard criteria for pathogenicity are in use, and different testing laboratories may offer differing interpretation sof the same variant. As sequencing technologies increase in power and use, many more variants of uncertain significance will be identified in genes associated with susceptibility to disease and will need to be interpreted.

2) Scope of the proposal,

A group of scientists with expertise in genetic variation and its relationship to genetic diseases of various types will reach a consensus on a process to be used to classify the pathogenicity of genetic variants associated with a variety of diseases (including, e.g., cancer susceptibility, congenital structural defects, and metabolic diseases).

3) Plan of action (including possible members of the Working Group),

Researchers who have published high quality papers related to assessing pathogenicity will be recruited to the Working Group and surveyed to refine the proposal that is outlined below. Some suggested Pathogenicity Working Group members: Sean Tavtigian, Steven Brenner, Heidi Rehm

4) Resources needed:

No major resources identified.

5) Deliverables

The outcome should be a manuscript, to be submitted to a high profile journal, that will establish a guideline or standard to be used by laboratories that perform genetic testing.

6) Recommendations regarding whether the final document should be published

Yes, the final document should be published

Proposal for classifying a genetic variant as pathogenic or neutral:

The classification process for all variants for all forms of genetic disease should follow the following principles:

1) Classification should be finalized only if more than one line of evidence is used

2) Classification should involve teams of experts, not one person, group, or entity

3) One line of evidence must associate the variant to the genetic condition, and another line of evidence must associate the variant with abnormal protein function/structure

4) Each line of evidence should have clearly defined criteria, approved by appropriate experts

5) A standardized system should be used to classify variants.