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Coordinating Office Position Paper

AP04: Sequence Variant Description Committee ICO Comments

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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 7th of November, 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 HGVS nomenclature system for sequence variant descriptions has existed for well over a decade and has achieved a reasonable level of adoption. Certain specialised sub-fields within the human genetics community still use legacy systems, but increasingly less so, and often only alongside the more widely understood HGVS system. This level of adoption has led to the HGVS systems being referred to as a *de-facto* standard.

However, as the AP submitter points out, a more robust method of maintaining and extending the system is required. This AP proposed the creation of a "Sequence Variant Description Committee" that would exist perpetually to both extend the current system and to answer questions about the system and provide training materials.

Such a committee does not quite fit into the current work practices of the Human Variome Project Consortium. The proposed activity goes beyond the development of a single Standard or Guideline, and as such, is beyond the scope of a Working Group. At the same time, the proposed committee would be empowered to generate Standards and/or Guidelines under the SDP, which is not a function that an Interest Group is empowered to do.

To work around this, the ICO would recommend that a Working Group be chartered to review the current nomenclature system, extend it as they see fit and publish this as an HVP Standard. The publication mentioned in the AP that describes the current recommendations would be the first part of the Working Group's activities. Once the Working Group has published their Standard, the group should be maintained as an HVP Interest Group to provide advice, training etc. as specified in the AP. The Interest Group could also actively discuss and debate extensions to the HVP Standard published by the Working Group, and submit new APs as required to extend the Standard.

Scope of Work

We recommend that an HVP Working Group be chartered, with the International Scientific Advisory Committee acting as SC, to:

- publish a review of current sequence variant description recommendations; and
- develop an HVP Standard on sequence variant description that:
 - provides a method for the unambiguous description of all sequence variant at the DNA, RNA and protein level; and
 - is usable by both humans and computers.

The resultant standard should be published in a peer-reviewed journal, however, care must be taken 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.

Once the Working Group has finished its task of developing the Standard, the members should be asked to form an Interest Group to:

- maintain a web-site that contains the Standard as well as explanatory examples, further clarifications and other resources;
- answer questions and clarify issues regarding the implementation of the Standard;
- discuss and debate proposals to extend the Standard;
- submit further APs to extend the Standard; and
- promote the use of the Standards through the development of a web-based educational package.

Possible Working Group Members

The AP Submitter has proposed a number of possible Working Group Members. The SC should consider if there is a need to broaden the geographic representation of the Working Group. We also note that they have specified that the WG be limited to 5-7 individuals. The SC will need to balance the benefits of a small number of WG members (easier communication, etc.) with the drawbacks associated with limiting membership.

Available Assistance from the ICO

The ICO is able to provide the following assistance to the WG and the ensuing Interest Group:

- secretarial assistance;
- face-to-face meeting organisation and venues;
- phone and video conferencing facilities;
- an email list.

The AP submitter has indicated that resources are required to engage the services of a consultant to develop a web-based educational package. We recommend that before external parties are engaged, the Education and Training Interest Group be contacted to see if one of their members would be willing to volunteer their services to assist in the development of such a package. If a suitable person is not able to be found, the International Coordinating Office can assist with a fund-raising initiative for this activity.

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
- The resultant work be jointly published in a high-profile academic journal

- Upon completion of the HVP Standard, the WG continue on as an Interest Group to perform the functions described in this paper.
- The WG consult with the Education and Training Interest Group to collaborate on a web-based educational package.

Activity Proposal

Sequence variant description committee

Need

Stimulated by the HGVS, standards have been developed regarding the description of sequence variants, the so called *HGVS recommendations for the description of sequence variants* ("Mutation nomenclature"). Over time, these recommendations have developed into a standard that is used world-wide, esp. in the field of human genetics.

Questions regarding the current recommendations and requests for modifications and extensions directed at the HGVS are currently collected, answered and discussed by Johan den Dunnen, using the HGVS website (www.HGVS.org/mutnomen). Final decisions on specific topics are made a bit ad-hoc, based on community opinions, gathered through the website and discussed at meetings of the HGVS and HVP. What is highly desired is a committee of experts that meets regularly to discuss the topics raised and together make a more official decision.

Scope

The "*Sequence variant description committee*" should cover at least;

- the description of sequence variant(s) on DNA, RNA and protein level
- the curation of the HGVS website covering the *HGVS recommendations for the description of sequence variants* (www.HGVS.org/mutnomen)
- answer questions and clarify issues regarding the existing standards
- make proposals, ensure community discussion and finally decide on requests to extend the current recommendations where necessary/desired
- promote the use of the standards, a.o. by developing a web-based educational package

Plan of action

Assign a group of experts (5-7), covering all areas where sequence variant detection and description are used (genetics, biology). Include at least 1 (bio)informatics expert to ensure that the standards developed can be implemented in software.

Resources required

Time. Administrative support from HVP. A room to meet & discuss regularly, preferably connected to HGVS/HVP and/or ASHG/eSHG meetings. I consider development of a web-based educational package as essential to further promote the use of the existing standards. Hiring somebody to achieve this within a reasonable time-frame seems appropriate (estimated cost USD 5-10,000).

Expected deliverables

A document describing the current recommendations to be published in a peer-reviewed scientific journal. This paper should replace the last publication from 2000 in Human Mutation). A draft is ready for a final check by the committee, the paper will be published, on behalf of the members of HGVS.

Recommendation

People that are knowledgeable on the subject and responsive when asked, so obvious candidates for the Committee, include;

- Raymond Dalglish (Leicester, UK) - gene variant database expert, active LSDB curator
 - Peter Taschner (Leiden, NL) - gene variant database expert, (bio)informatics (Mutalyzer)
 - Jean McGown-Jordan (Ottawa, Canada) - member ISN committee, asked to participate like JdD is member of the ISCN
- Representatives from other stakeholders;
- representative from US commercial labs (Heidi Rehm?)
 - representative from central repositories (NCBI/EBI - Donna Maglott or Fiona Cunningham)
 - Johannes Zschocke, on a regular basis positively criticizing current recommendations