Association for Clinical Genetic Science
Part of the British Society for Genetic Medicine

ACGS Quality Survey: Intragenic dosage variants and exon numbering

This survey was conducted in summer 2015. The main aim was to seek a consensus on how intragenic deletions and duplications are described and presented in clinical reports. This summary presents the main findings. A full analysis of the findings, and a list of all comments submitted, is presented on the accompanying Excel workbook.

The ACGS Quality Subcommittee proposes to form a small team to develop a consensus on this subject (to include molecular genetic, cytogenetic and bioinformatics input) and put forward a proposal for consultation.

Our survey coincided with a review by HGVS on its own nomenclature, and we were pleased to be able to submit the survey findings to HGVS for information. We are also very pleased to be able to share below a reply from Prof. Dr. Johan T. den Dunnen, representing the HGVS/HVP/HUGO sequence variant description working group, including replies to many of the individual comments submitted to our survey.

Key points from survey

- A consensus approach is needed.
- For all descriptions, a reference is needed for the nomenclature/numbering used.
- >50% of respondents rate “established HGVS nomenclature” for describing intragenic CNVs as “poor” or “unacceptable”.
- “Proposed HGVS nomenclature” favoured a little better, but respondents were still very much split between rating this as “good” or “poor”.
- Respondents supported (88.9%) use of LRG “final approved” status genes for exon numbering when these are available, and some respondents pointed out that any differences to legacy exon numbering should be made clear.
- Views were very split over the proposed nomenclature/description policies suggested, although the highest scoring option was to use LRG “final approved” status exon numbering when available and otherwise use an alternative referenced exon numbering (legacy or LRG “pending” status).

Other points

- Genomic co-ordinates, e.g. hg19, should be considered as there is a general move towards use of these alongside cDNA/gene nomenclature.
- Ideally a consensus nomenclature/description should be compatible with output data from modern/emerging analyses such as WES and WGS bioinformatics pipelines.
- Even once a consensus nomenclature/description is agreed, additional descriptions beyond this will be appropriate in some cases, particularly since for clinical reports the results need to be clear to the clinician/user.
- This is relevant to molecular genetic and cytogenetic services, although the majority of respondents were from molecular genetics.

Reply from Johan den Dunnen (representing the HGVS/HVP/HUGO sequence variant description working group)

Thanks for the copy, interesting reading, very helpful. Below I have some specific remarks on comments I encountered several times. Might be good to share this with the people that completed the survey.

I frequently read comments which more or less indicate people use HGVS while they do not "know/understand" HGVS. This should not happen of course but when there is no course/training available it is difficult to learn the rules. I/HGVS would be happy to assist getting this organised

Replies to specific comments:

- HGVS - Time-consuming, confusing to clinician, and subject to constant revision
    - *Any correct description will be time-consuming yet it is absolutely essential to prevent mistakes. It should be noted that HGVS is not "subject to constant revision". Since 2000 only errors in the original publication have been clarified, additions have been made once and a second set of additions is discussed at the moment.*

- HGVS - May be more accurate but nomenclature is getting more and more complicated and hence open to misinterpretation by those that do not follow the latest updates to the system.
    - *Overall this is not really true. The increasing complexity derives from recommendations to describe complex changes not covered in the original publication. Recommendations for simple changes have not changed.*

- HGVS can be very confusing to non-experts.
    - *1) non-experts should not use HGVS*
    - *2) HGVS is to describe variants, not for clinical reporting. To me it is obvious that "confusing" descriptions like c.(123+1_234-1)_(345+1_456-1)del are followed by an explanation in words like "a deletion of exons 3-6 in the ABC1 gene". Still, although simpler in description, "exons 3-6" are meaningless as well.*

- HGVS - It can be quite tricky to get it right but working with ClinVar helps to sort out the problems
    - *Please note that tools to help with HGVS exist (e.g. Mutalyzer incl. the Name Checker and Description Extractor). In addition, when variants are submitted to a gene variant database (like LOVD) these tools are build in to assist getting the right description. In databases like ClinVar and LOVD also in general the correct description can be found as an example.*

- HGVS - If the test detects a deletion of exon 5, but there are no probes in exon 4 or 6, then the proposed HGVS nomenclature would be misleading.
    - *This is a good example why the recommendation to use a description like c.234-?_345+?del is currently questioned. The suggested description format c.(123+1_234-1)_(345+1_456-1)del showing that flanking exons were not tested.*

- LRG - Not all genes have an LRG
    - *This is because nobody took the effort to request that an LRG is made.*

- LRG - If the LRG entry is still subject to change, then this should not be used as this could lead to discrepancies and errors in the future.
    - *By definition an LRG is stable and will not change! [editors' note: this comment and reply probably relate to the distinction between 'pending' and 'approved' LRGs]*

- HGVS - The suggestion to arbitrarily choose the centre of the probe for nomeclature purposes when an exon is large is a little daft if the point of this proposal is to develop a system which names dels and dups in an unequivocal and accurate manner!
    - *Agreed, ...but what is the alternative? Using MLPA or PCR and getting a product of an exon does not mean the entire probe sequence was present in the sample for hybridisation. Furthermore nobody can say how much of the probe must be present minimally to get a product. Therefore the suggestion is made to arbitrarily take the middle of the probe.*

- MLPA - In the case of deletions and duplications detected by MLPA, I think it's sufficient to indicate the exons deleted / duplicated if the MRC-Holland kit and version is indicated.
    - *Where in 10 or 20 years will I be able to find a detailed description of the kit used?*