Describing variants

"mutation nomenclature"

recommendations for the description of DNA changes

tinyurl.com/ VEPTC-4

Johan den Dunnen

chair SVD-WG

http://varnomen.HGVS.org

DirectPoll

Q & A

scan QR code

or go to http://etc.ch/VEPa

Subjects

Reporting sequence variants

- who decides

- where do I find the rules

varnomen.HGVS.org

- describing variants

brief, basics only org

- HGVS in practice

Q&A sessions

exercises

your problem

Affiliations

THE HUMAN VARIOME PROJECT

get all variants/consequences shared

HGVS
HUMAN GENOME VARIATION SOCIETY

standards for variant description and databases

ISCN

standards for cytogenetic variant descriptions

LOVD
Leiden Open Variation Database

software for web-based gene databases

HGVS standard

The format

The format of a complete variant description is **reference:description**, e.g.;

```
*       NM_004006.2:c.4375C>T
```

NC_000011.9 : g.111548892del

NOTE: spaces added for clarity only

Standards

- **essential**
  to understand each other
  to exchange information

- **preferably ONE standard**
  used world-wide
  agreed by everybody

- **..but difficult**
  everybody agrees
  ...when their standard is used
  how to agree on changes ?
  which authority to decide ?

Celsius / Fahrenheit
kilometers / miles
liter / gallon

Still a problem?

Genetics inMedicine Official Journal of the American College of Medical Genetics

Home | Current Issue | Archive | Podcasts | For Authors & Referees | About the journal

Archive > Volume 17 > Issue 5 > Article

GENETICS IN MEDICINE | ACMG STANDARDS AND GUIDELINES

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards PhD, Nazneen Aziz PhD, Sherri Bale PhD, David Bick MD, Soma Das PhD, ... Gastier-Foster PhD, Wayne W. Grody MD, PhD, Madhuri Hegde PhD, Elaine Lyon PhD, El... Spector PhD, Karl Voelkerding MD & Heidi L. Rehm PhD ; on behalf of the ACMG Laborat... Quality Assurance Committee

ACMG: follow the HGVS recommendations ...

but...

In addition, this ACMG recommendation supports three specific exceptions to the HGVS nomenclature rules: 1) "X" is still considered acceptable for use in reporting nonsense variants in addition to the current HGVS recommendation of "*" and "Ter"; 2) it is recommended

X to *

- **protein changes**

historically the X used for "stop codon"

> IUPAC amino acid codes
X = any amino acid

> NCBI amino acid codes
X = any amino acid, * = translation stop

>>> change X to * / Ter

p.Arg321*
p.Arg321Glufs*13
p.*535Glnext*17

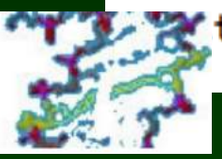
The problem

alternative descriptions

- **share & retrieve**
  - ***when alternative descriptions are accepted it becomes problematic to find previous reports***

```
.          .          .          .                    g.73678
ttttgatgtgtgtgtgtgtgtgtgtgtttttttaacag                c.1210-1
```

NCBI **dbSNP** Short Genetic Variations



HGVS Names
NC_000007.13:g.117188660_117188661insTG
NC_000007.13:g.117188660_117188661insTGTG
NC_000007.14:g.117548606_117548607insTG
NC_000007.14:g.117548606_117548607insTGTG
NG_016465.4:g.87823_87824insTG
NG_016465.4:g.87823_87824insTGTG
NM_000492.3:c.1210-35_1210-34insTG
NM_000492.3:c.1210-35_1210-34insTGTG

HGVS Names
NC_000007.13:g.117188661_117188662TG[11][12
NC_000007.14:g.117548607_117548608TG[11][12
NG_016465.4:g.87824_87825TG[11][12]
NM_000492.3:c.1210-34_1210-33TG[11][12]

HGVS Names
NC_000007.13:g.117188661_117188664delTGTG
NC_000007.14:g.117548607_117548610delTGTG
NG_016465.4:g.87824_87827delTGTG
NM_000492.3:c.1210-34_1210-31delTGTG

HGVS Names
NC_000007.13:g.117188661_117188666delTGTG
NC_000007.14:g.117548607_117548612delTGTG
NG_016465.4:g.87824_87829delTGTGTG
NM_000492.3:c.1210-34_1210-29delTGTGTG

HGVS Names
NC_000007.13:g.117188661_117188662delTG
NC_000007.14:g.117548607_117548608delTG
NG_016465.4:g.87824_87825delTG
NM_000492.3:c.1210-34_1210-33del
NM_000492.3:c.1210-34_1210-33delTG

HGVS Names
NC_000007.13:g.117188682delG
NC_000007.14:g.117548628delG
NG_016465.4:g.87845delG
NM_000492.3:c.1210-13delG

HGVS Names
NC_000007.13:g.117188682G>T
NC_000007.14:g.117548628G>T
NG_016465.4:g.87845G>T
NM_000492.3:c.1210-13G>T

HGVS Names
NC_000007.13:g.117188681_117188684delTGTT
NC_000007.14:g.117548627_117548630delTGTT
NG_016465.4:g.87844_87847delTGTT
NM_000492.3:c.1210-14_1210-11delTGTT

HGVS Names
NC_000007.13:g.117188662_117188663insTG
NC_000007.13:g.117188662_117188663insTGTG
NC_000007.14:g.117548608_117548609insTG
NC_000007.14:g.117548608_117548609insTGTG
NG_016465.4:g.87825_87826insTG
NG_016465.4:g.87825_87826insTGTG
NM_000492.3:c.1210-33_1210-32insTG
NM_000492.3:c.1210-33_1210-32insTGTG

HGVS Names
NC_000007.13:g.117188682_117188683insT
NC_000007.13:g.117188682_117188683insTGTT
NC_000007.13:g.117188682_117188683insTT

HGVS Names
NC_000007.13:g.117188683delT
NC_000007.14:g.117548629delT
NG_016465.4:g.87846delT
NM_000492.3:c.1210-12delT

HGVS Names
NC_000007.13:g.117188683_117188684delTT
NC_000007.14:g.117548629_117548630delTT
NG_016465.4:g.87846_87847delTT
NM_000492.3:c.1210-12_1210-11delTT

HGVS Names
NC_000007.13:g.117188684T>G
NC_000007.14:g.117548630T>G
NG_016465.4:g.87847T>G
NM_000492.3:c.1210-11T>G

HGVS Names
NC_000007.13:g.117188684_117188685insG
NC_000007.14:g.117548630_117548631insG
NG_016465.4:g.87847_87848insG
NM_000492.3:c.1210-11_1210-10insG

HGVS Names
NC_000007.13:g.117188688T[5][7][9]
NC_000007.14:g.117548634T[5][7][9]
NG_016465.4:g.87851T[5][7][9]

HGVS Names
NC_000007.13:g.117188689_117188690insTT
NC_000007.14:g.117548635_117548636insTT
NG_016465.4:g.87852_87853insTT
NM_000492.3:c.1210-6_1210-5insTT

Variant description

the basis ***http:// varnomen.HGVS.org***

SPECIAL ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

HGVS Recommendations for the Description of Sequence Variants: 2016 Update

Hum Mutat (2016) 37:564-569

Johan T. den Dunnen,[1]* Raymond Dalgleish,[2] Donna R. Maglott,[3] Reece K. Hart,[4] Marc S. Greenblatt,[5] Jean McGowan-Jordan,[6] Anne-Francoise Roux,[7] Timothy Smith,[8] Stylianos E. Antonarakis,[9] and Peter E.M. Taschner[10] on behalf of the Human Genome Variation Society (HGVS), the Human Variome Project (HVP), and the Human Genome Organisation (HUGO)

HUMAN MUTATION 15:7–12 (2000)

MDI SPECIAL ARTICLE

Mutation Nomenclature Extensions and Suggestions to Describe Complex Mutations: A Discussion

Johan T. den Dunnen[1]* and Stylianos E. Antonarakis[2]*
[1]*MGC-Department of Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands*
[2]*Division of Medical Genetics, University of Geneva Medical School, Geneva, Switzerland*

Consistent gene mutation nomenclature is essential for efficient and accurate reporting, testing, and curation of the growing number of disease mutations and useful polymorphisms being discovered in the human genome. While a codified mutation nomenclature system for simple DNA lesions has now been adopted broadly by the medical genetics community, it is inherently difficult to represent complex mutations in a unified manner. In this article, suggestions are presented for reporting just such complex mutations. Hum Mutat 15:7–12, 2000.

KEY WORDS: complex mutation; mutation detection; mutation database; nomenclature; MDI

THE HUMAN VARIOME PROJECT

HUGO

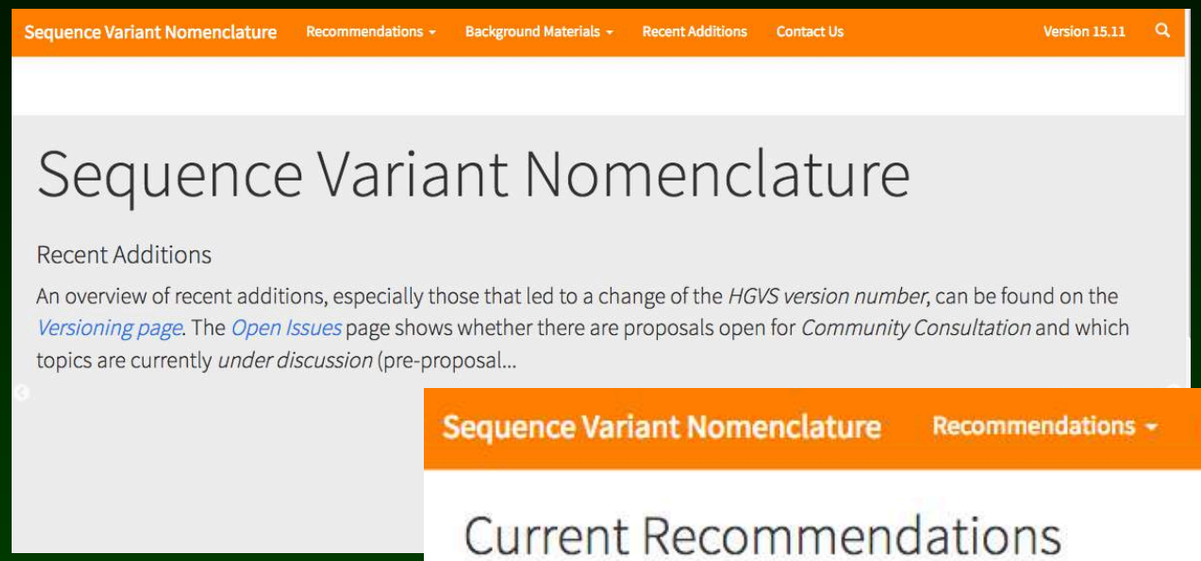
HGVS HUMAN GENOME VARIATION SOCIETY

HGVS / HVP / HUGO Sequence Variant Description working group

Working Group Members:

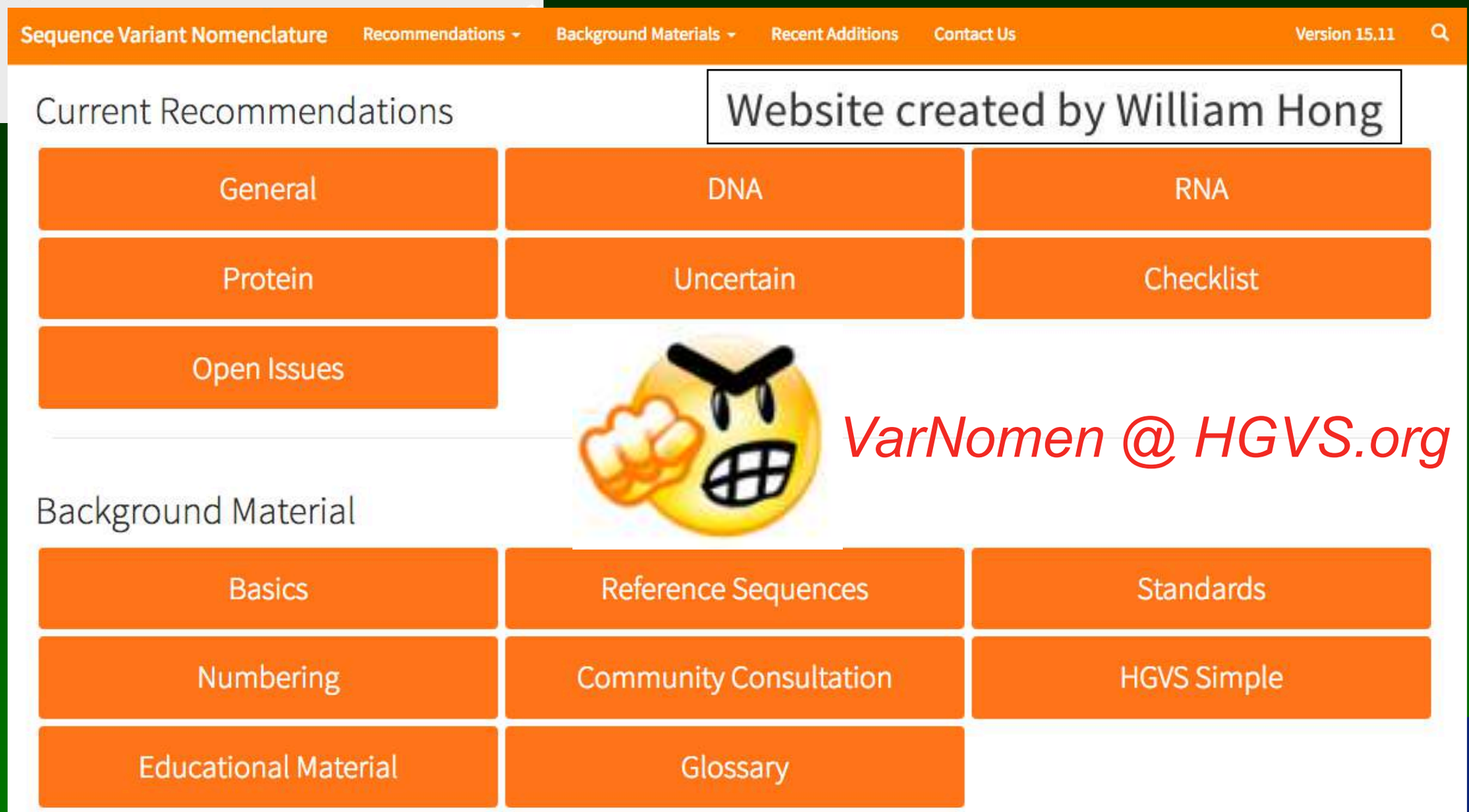
- Anne-Francoise Roux (EGT)
- Donna Maglott (NCBI/EBI)
- Jean McGowan-Jordan (ISCN)
- Peter Taschner (LSDBs)
- Raymond Dalgleish (LSDBs)
- Reece Hart (industry)
- Johan den Dunnen (chair)
- HGVS - Marc Greenblatt
- HUGO - Stylianos Antonarakis

varnomen.HGVS.org

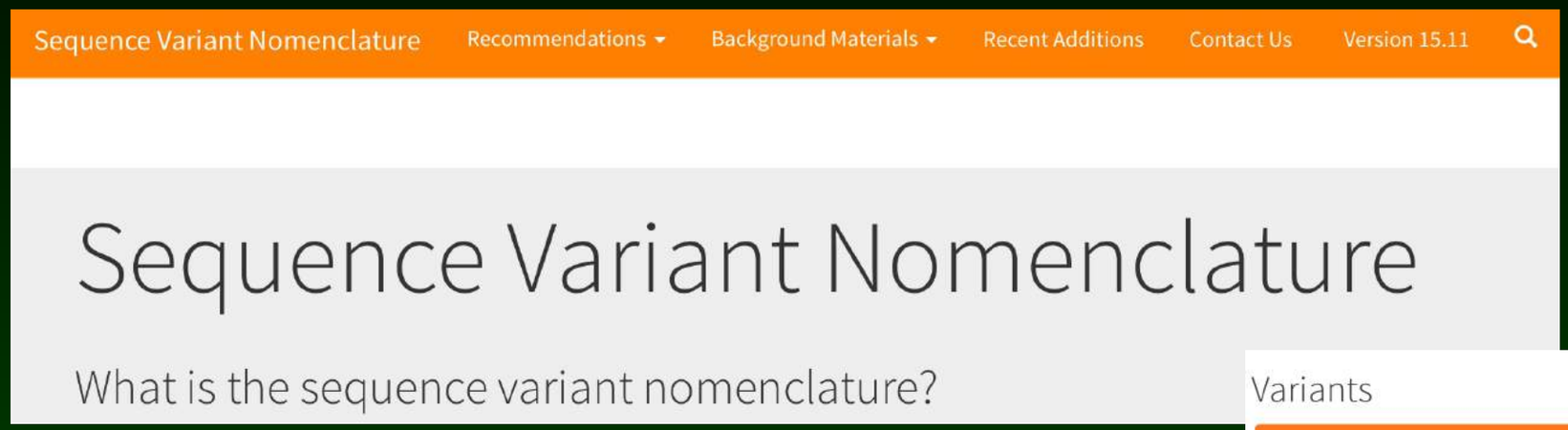


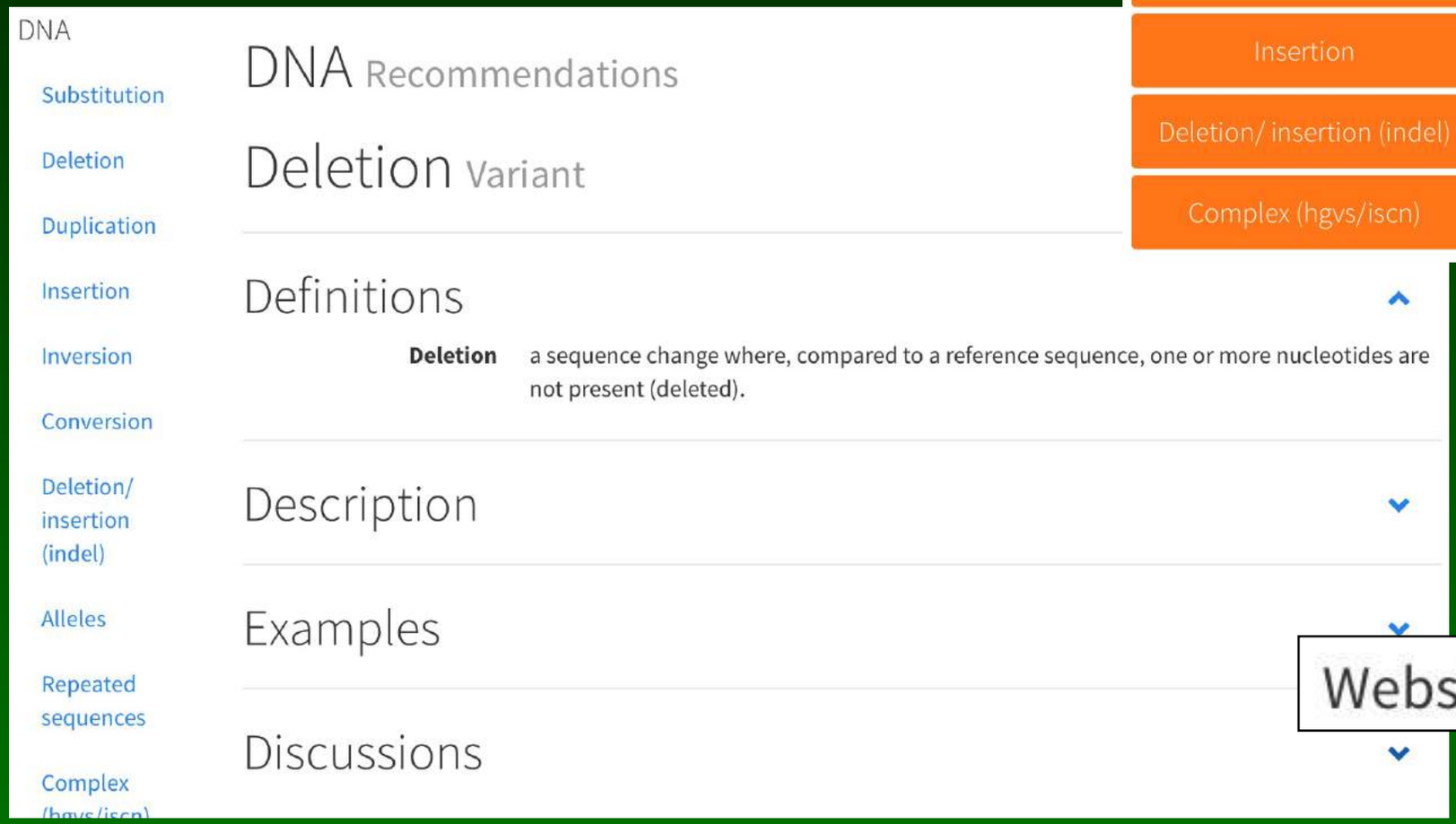
Follow the recommendations
when you disagree, ***start a debate***

do *not use private rules,*
this only causes confusion



Per variant type

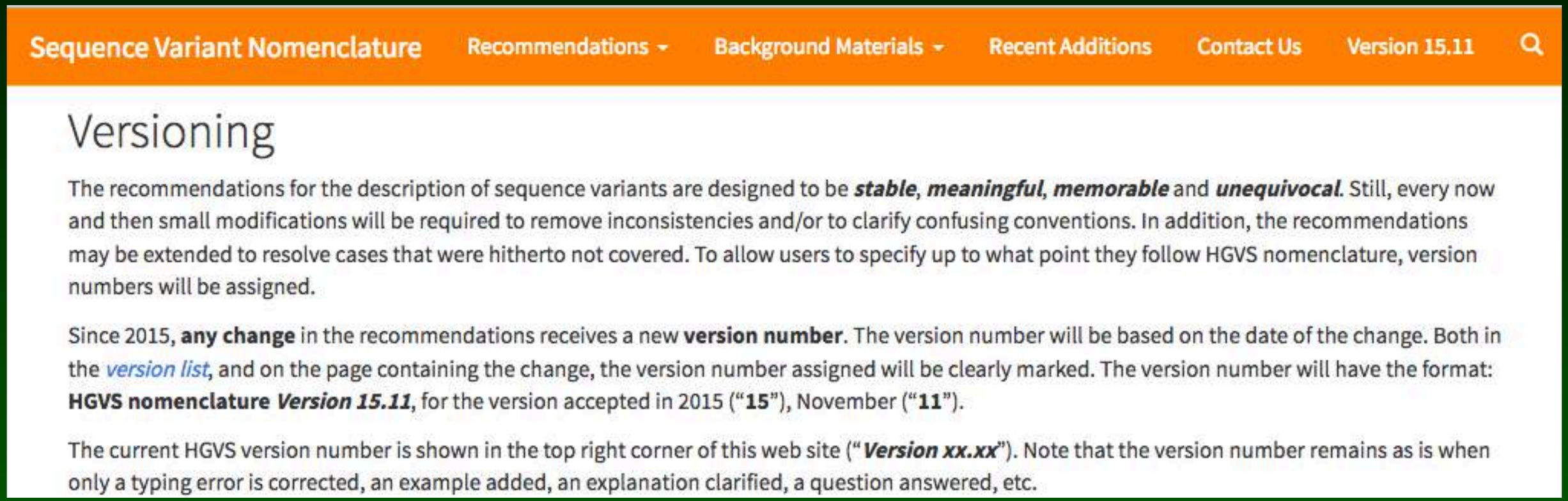




Website created by William Hong

Versioning

current version is 15.11 (Nov.2015)

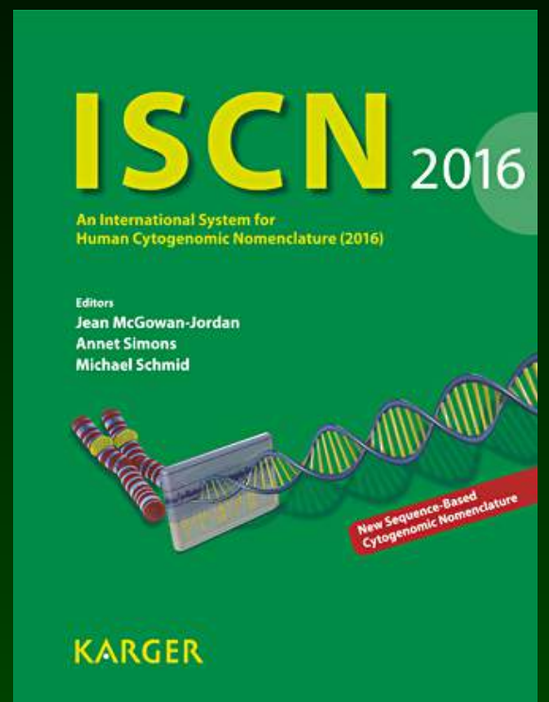


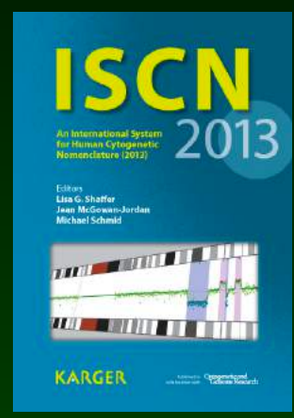
and "named extension": ISCN

Community Consultation

Community Consultation

HGVS nomenclature falls under the responsibility of the SVD-WG (*Sequence Va*
change or extend HGVS nomenclature operating according to a charter definin
Consultation step. Any proposal made by the SVD-WG will be **published on th**
2-month period (*register for email notification*). Everybody interested is asked
SVD-WG. Comments to proposals should be addressed to "Varnomen @ varion





- **SVD-WG004 (ISCN<>HGVS)**
  suggested to extend the recommendations to cover the description of structural variants, esp. translocations and chromothripsis.
  Status: under review. Closed Jan.15 (2016). Opened Nov.10 (2015).

accepted as "named extension": ISCN

Community Consultation

open NOW

Community Consultation

Proposal SVD-WG006 (circular DNA)

- **Status: open**
  proposal SVD-WG006 opens for **Community Consultation** on August 1 (2018), closing on Oct.30 (2018).

The proposal suggests to extend the HGVS recommendations to improve the description of variants affecting circular

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HGVS
HUMAN GENOME VARIATION SOCIETY

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PEOPLE

217 likes

ABOUT

These HGVS pages will be used to discuss any subject we encounter regarding the "Recommendations for the description of sequence variants".

http://www.HGVS.org/mutnomen

PHOTOS

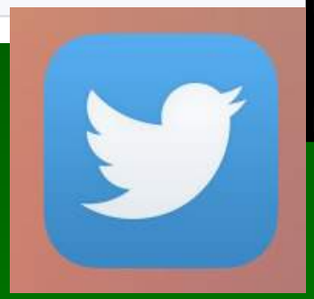
HGVS shared a link.
October 19

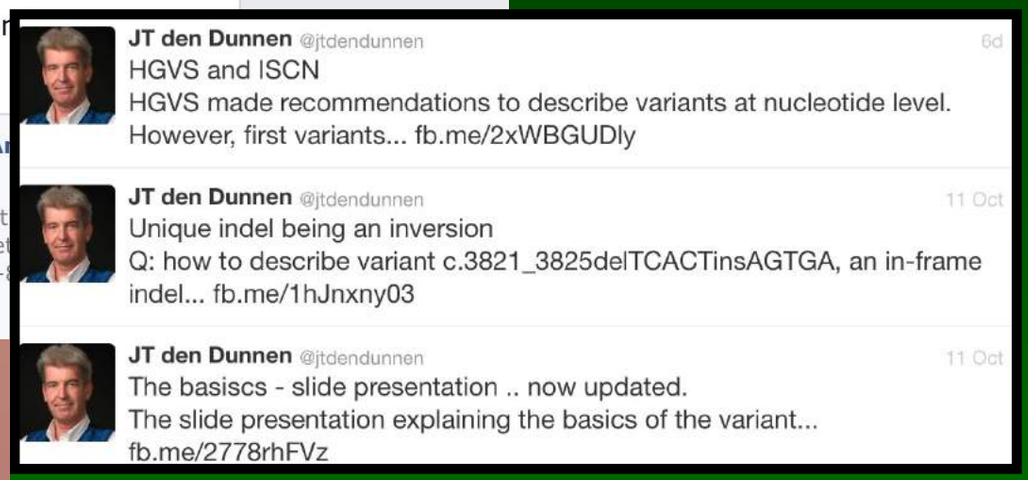
Tue. Oct. 21, 12:30-14:00, HVP Sequence Variant Description workshop ASHG, room 28A, San Diego Convention Center. What are we going to do? Discuss variant nomenclature!
After a short introduction on the basics, the recommer
open... See More

Schedule of Events | ASHG 2014 Ar
www.ashg.org
The American Society of Human Genet
Incorporated | 9650 Rockville Pike, Bet
Maryland 20814society@ashg.org • 1-8
• (301) 634-7300Privacy Policy

HGVS
October 17

Intron after stop codon
Q: how do I number a variant which is at position 13 in an intron immediately following the last nucleotide (c.876) of the stop codon? c.*0+13C>T can not be since HGVS does not use position "0".
A: since the variant is in an intron at position 13 after nucleotide c.876 the correct description is c.876+13C>T.
Interesting to note is that in this peculiar example nucleotides in the intron are numbered like c.876+1, c.876+2, c.876+3, … c.*1-3, c.*1-2, c.*1-1.



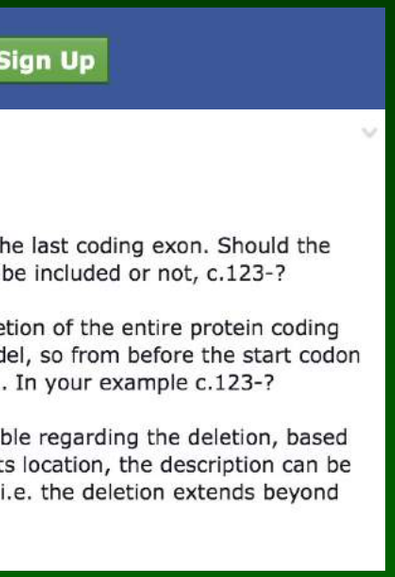


Activities

close link to gene variant databases

- **daily**
  - ***website***
  - ***answer questions***
    - ***now 1-2 daily***
    - ***started facebook/twitter***

- **promote**
  - ***lectures, posters, courses, write journals/authors/agencies, ...***
  - ***Socrative***
    - ***Questions/Answers***



HGVS
HUMAN GENOME VARIATION SOCIETY

Emotions














Nomenclature

(describing DNA variants)

Stable

Meaningful ***Memorable***

Unequivocal

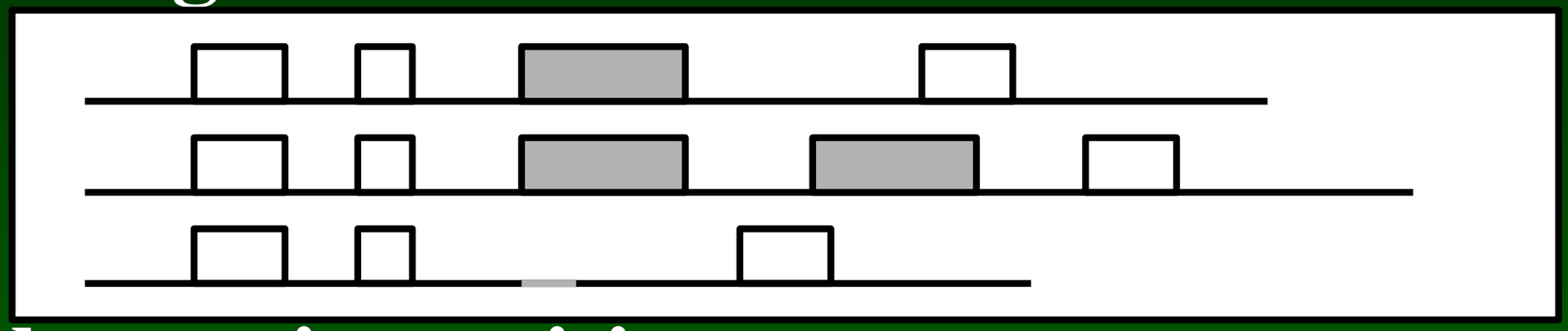
computer

Variant types

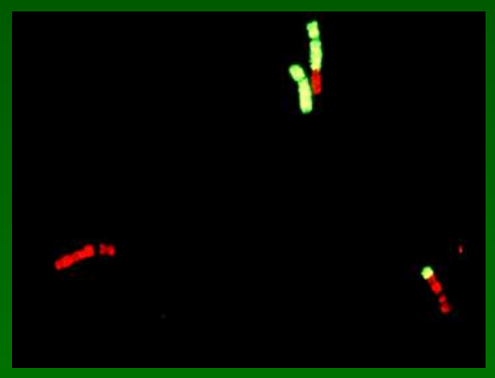
- **change in sequence**

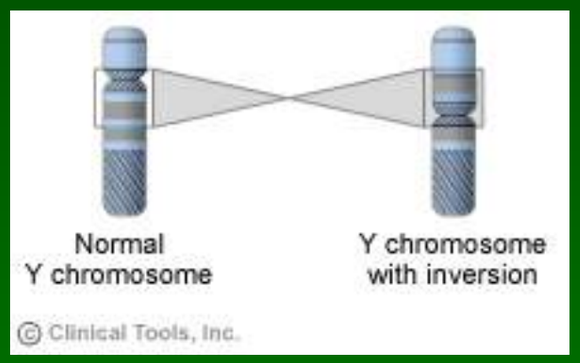
```
ACATCAGGAGAAGATGTTC GAGACTTTGCCA
ACATCAGGAGAAGATGTTT GAGACTTTGCCA
ACATCAGGAGAAGATGTT  GAGACTTTGCCA
ACATCAGGAGAAGATGTTCCGAGACTTTGCCA
```

- **change in amount** *(Copy Number Variation)*



- **change in position**





ISCN

Structural Variation (SV)

DNA, RNA, protein

- **unique descriptions**
  prevent confusion

- **DNA**
  A, G, C, T
  g.957A>T, c.63-3T>C

- **RNA**
  a, g, c, u
  r.957a>u, r.(?), r.spl?

- **protein** *(mostly deduced)*
  three / one letter amino acid code
  ** = stop codon*
  p.(His78Gln)

Basic rules

- **report what is detected**
  NOT what is predicted
  NOT p.Gly202Trp, but c.604G>T
  or c.604G>T (r.(?), p.(Gly202Trp))

- **give a reference sequence**
  accession.version number
  genomic (chromosomal) or LRG

- **use the 3' rule**
  shift change as far 3' as possible

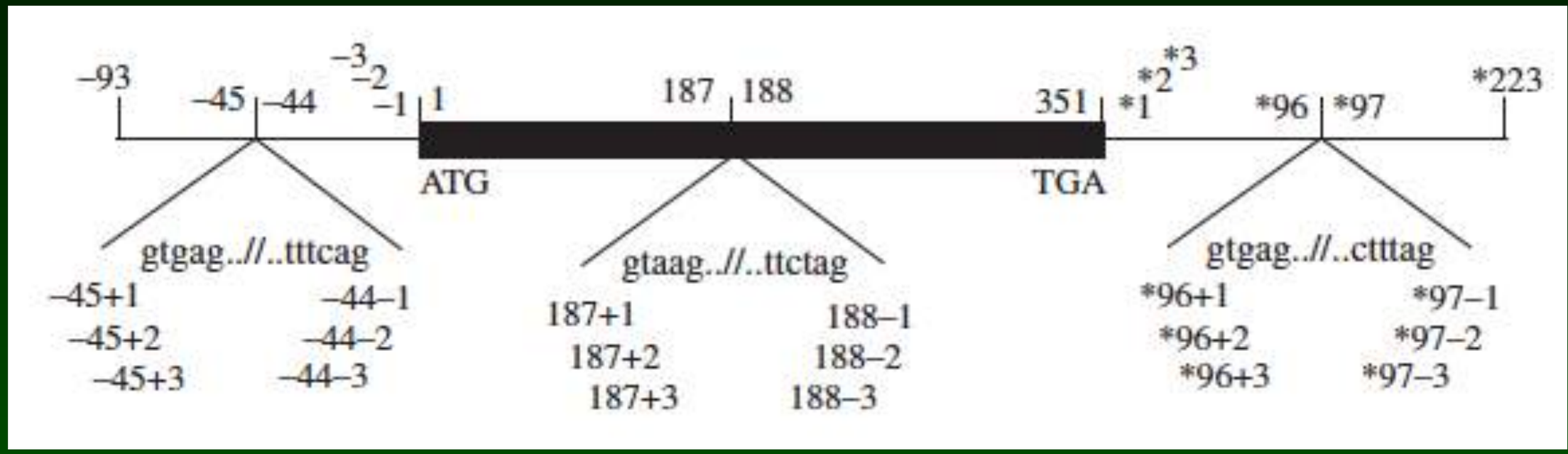
Numbering residues

- **start with 1**
  - *genomic* *1 is first nucleotide of file*
    - *no +, - or other signs*
  - *coding DNA* *1 is A of ATG*
    - *for introns refer to genomic Reference Sequence*

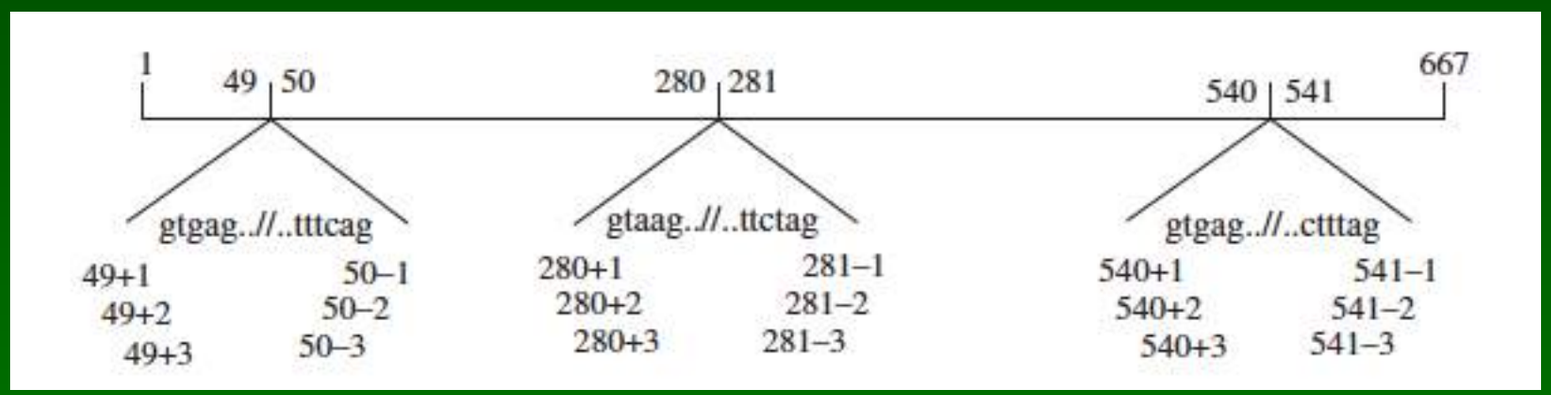
- **exception:** **coding DNA**
  - *5' of ATG* *…, -3, -2, -1, A, T, G, …*
    - *no nucleotide 0*
  - *3' of stop* **1, *2, *3, …*
    - *no nucleotide 0*
  - *intron*
    - *position between nt's 654 and 655*
    - *c.654+1, +2, +3, ……., -3, -2, c.655-1*
    - *change + to - in middle*

Reference Sequence

coding DNA reference sequence (c.)



non-coding DNA reference sequence (n.)



RefSeq files

*e.g. www.LOVD.nl/**CAV3***

exon	c.startExon	c.endExon	g.startExon	g.endExon	lengthExon	lengthIntron
1	-197	75	5001	5272	272	3360
2	76	224	8633	8781	149	1852
3	225	438	10634	10847	214	6124
4	439	542	16972	17075	104	1763
5	543	670	18839	18966	128	14963
6	671	789	33930	34048	119	912
7	790	970	34961	35141	181	8363
8	971	1065	43505	43599	95	360
9	1066	1261	43960	44155	196	2204
10	1262	1337	46360	46435	76	1460
11	1338	*2768	47896	50886	2991	

Caveolin-3 (CAV3) - coding DNA reference sequence

(used for mutation description)

(last modified January 5, 2011)

This file was created to facilitate the description of sequence variants in the CAV3 gene based on a coding DNA reference sequence following the HGVS recommendations. The sequence was taken from NG_008797.1, covering CAV3 transcript variant-1 (NM_033337.2). An alternatively spliced transcript has been reported, removing part of exon 2 (after the stop codon, NM_001234.3).

Please note that introns are available by clicking on the exon numbers above the sequence.

```
(upstream sequence)
                                                  g.5007
                                        caagtat   c.-61

.         .         .         .         .         .       g.5067
tttcagccccagccggccacacagctcggatctcctcctgtggatccccccagctctgcg   c.-1

          .         .         .         .         .       g.5127
ATGATGGCAGAAGAGCACACAGATCTCGAGGCCCAGATCGTCAAGGATATCCACTGCAAG   c.60
M  M  A  E  E  H  T  D  L  E  A  Q  I  V  K  D  I  H  C  K     p.20

          .         .         .         .         .  | 02  .   g.16722
GAGATTGACCTGGTGAACCGAGACCCCAAGAACATTAACGAGGACATAGTCAAG | GTGGAT   c.120
E  I  D  L  V  N  R  D  P  K  N  I  N  E  D  I  V  K  | V  D     p.40

          .         .         .         .         .       g.16782
TTTGAAGACGTGATCGCAGAGCCTGTGGGCACCTACAGCTTTGACGGCGTGTGGAAGGTG   c.180
F  E  D  V                                               c.180

                    .         .         .         .  | 22  .   g.67798
          ACCATCAACAGCTACGAGATGCGAAATGCAGTCAACGACGCAG | GATTCCACCTCAACAAC   c.2280
          T  I  N  S  Y  E  M  R  N  A  V  N  D  A  G |  F  H  L  N  N   p.760
AGCTACACCA
S  Y  T  T
                    .         .         .         .         .       g.67858
          CAGCTCTATGACATCATTACCATGCGGTACGCAGACAAACACATGAACATCGACTTTGAC   c.2340
          Q  L  Y  D  I  I  T  M  R  Y  A  D  K  H  M  N  I  D  F  D   p.780

                    .         .         .         .  | 23  .   g.68204
          AGTTTCATCTGCTGCTTCGTTAGGCTGGAGGGCATGTTCA | GAGCTTTTCATGCATTTGAC   c.2400
          S  F  I  C  C  F  V  R  L  E  G  M  F  R |  A  F  H  A  F  D   p.800

                    .         .         .         .  | 24  .   g.68665
          AAGGATGGAGATGGTATCATCAAGCTCAACGTTCTGGAG | TGGCTGCAGCTCACCATGTAT   c.2460
          K  D  G  D  G  I  I  K  L  N  V  L  E   | W  L  Q  L  T  M  Y   p.820

                                                            g.68671
          GCCTGA                                            c.2466
          A  X                                              p.821

                    .         .         .         .         .       g.68731
          accaggctggcctcatccaaagccatgcaggatcactcaggatttcagtttcaccctcta   c.*60

                    .         .         .         .         .       g.68791
          tttccaaagccatttacctcaaaggacccagcagctacacccctacaggcttccaggcac   c.*120
```

Calpain-3 (CAPN3) - 313 nt intron 11

(intronic numbering for coding DNA Reference

```
                    .         .         .         .         .       g.58768
gtgtgcagtcctgattggctccagcccaggaaacatactttcccagggaggacgcttcca   c.1524+60

                    .         .         .         .         .       g.58828
ggggcttctagaggggccctctggcttcctcaatacccagtgacccacagagctcctggt   c.1524+120

                    .         .         .       g.58865
atcaggaccacttgtgtttgtaacaagcaaaaaatac   c.1524+157

---------------------- middle of intron ----------------------
                  g.58866           .         .         .       g.58901
                  c.1525-156  cagggggggcattagagaggcagtggagcgggcctg   c.1525-121

.         .         .         .         .         .       g.58961
gcagaacaggtgcctgggggtcaggcttccgcatgcgggctgcagttgctggcattgcct   c.1525-61

.         .         .         .         .         .       g.59021
tccgcaggctcctcatcctcattcacatctgaagcatcttcctttctgtttcttctcaag   c.1525-1
```

Computer prefered

- **g.12158663A>G**

hint chr.11 (hg19)

Computer prefered

- g.12158663A>G
- g.23669859>C
- g.89112396G>A

no relation to RNA & protein

- g.112775623C>G
- g.56569443A>T
- g.12741333T>G
- g.188153979G>C

Numbering - coding DNA

- **c.2396-6G>A**

in the 3' half of an intron,
6 nucleotides 5' of the splice acceptor site

splitting amino acid 799

Human prefered

- **c.1637A>G**
  protein coding region
- **c.859+12T>C**
  in intron (5' half)
- **c.2396-6G>A**
  in intron (3' half)

relation to RNA & protein

- **c.-23C>G**
  5' of protein coding region (5' of ATG)
- **c.*143A>T**
  3' of protein coding region (3' of stop)
- **c.-89-12T>G**
  intron in 5' UTR (5' of ATG)
- **c.*649+79G>C**
  intron in 3' UTR (3' of stop)

HGVS
HUMAN GENOME VARIATION SOCIETY

Types of variation

- **simple**
  - *substitution* — *c.123A>G*
  - *deletion* — *c.123del*
  - *duplication* — *c.123dup*
  - *insertion* — *c.123_124insC*
  - *other*
    conversion, inversion, translocation, transposition

- **complex**
  - *delins* — *c.123delinsGTAT*

- **combination of variants**
  - *two alleles* — *c.[123A>G];[456C>T]*
  - *>1 per allele* — *c.[123A>G;456C>T]*

Substitution

- **substitution designated by ">"**
  - ***> not used on protein level***

- **examples**

genomic	***g.54786A>T***
cDNA	***c.545A>T***
	(NM_012654.3 : c.546A>T)
RNA	***r.545a>u***
protein	***p.(Gln182Leu)***

Deletion

- **deletion**

  designated by "del"
  range indicated by "_"

- **examples**

  c.586_591del

  *c.586_591del**TGGTCA** (not c.586_591del**6**)*

  c.546del

  *c.546del**T***

3' rule

```
Reference    ATAGCTTTCAGGA
Sample       ATAGCT TCAGGA
```

Describe as g.6del
g.7del
g.8del

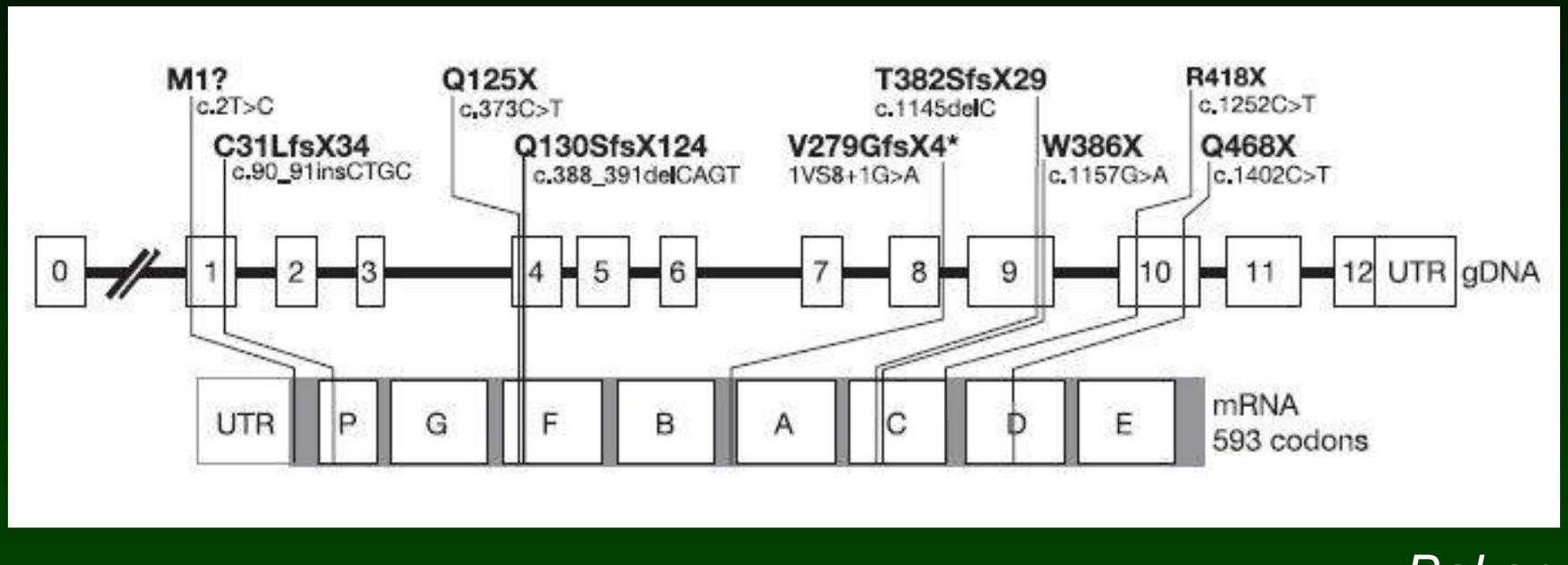
?

By definition this is described as **g.8del**

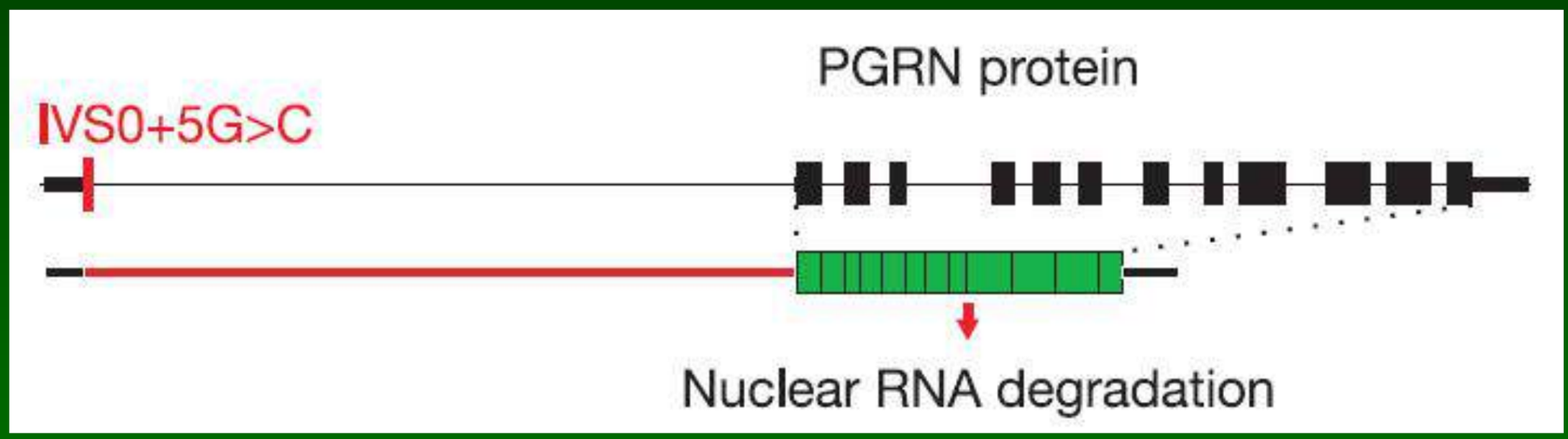
HGVS 3’ rule

Exon 0

Progranulin
Aug.2006



Baker, Nature 442: 916



Cruts, Nature 442: 920

HGVS applied correctly?

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www.hgvs.org

HGVS Nomenclature in Practice: An Example from the United Kingdom National External Quality Assessment Scheme

Zandra C. Deans,[1]* Jennifer A. Fairley,[1] Johan T den Dunnen,[2] and Caroline Clark[3]

[1]UK NEQAS for Molecular Genetics, NHS Lothian, Royal Infirmary of Edinburgh, Little France Crescent, Edinburgh, UK; [2]Clinical Genetics and Human Genetics, Leiden University Medical Center, Leiden, Nederland; [3]Department of Molecular Genetics, Medical Genetics, Polwarth Building, Aberdeen, UK

```
...ggccagcgtggaca          acCccc...
...ggccagcgtggacaGCGTGGACAacGccc...
```

(both variants on same chromosome)

c.[2303_2311dup;2314C>G] / c.2312_2314delinsGCGTGGACAACG

or c.[2303_2311dup(;)2314C>G]

HGVS applied correctly?

**HGVS Nomenclature in Practice:
An Example from the United Kingdom National External Quality Assessment Scheme**

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

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- **26 participating labs**
- **21 different descriptions**
  (DNA & protein combined)
  5 shared + unique 21x

  6 correct HGVS,
  12 DNA variant "correct",
  8 not correct

c.2303_2311dup
c.2312_2314delinsGCGTGGACAACG
c.2312_2314delACCinsGCGTGGACAACG
c.2311_2312insTGTCCACGC
c.2300_2301insCAGCGTGGA
c.2300_2301insCAGCGTGGA
c.2302_2310dup
c.2303_2311dup
c.2312_2320dupGCGTGGACA
c.2311ins/dupGCGTGGACA
c.2303_2311dup
c.2300_2301insCAGCGTGGA
c.2300_2301insCAGCGTGGA
c.2303_2311dup
c.2303_2311dupGCGTGGACA
c.2300_2301insCAGCGTGGA
c.2301_2302insCAGCGTGGA
c.2310_2311dupAGCGTGGAC
c.2301_2302ins9
c.2311_2312insGCGTGGACA

c.2311_2312ins9 and c.2314C>G

Applied correctly?

Lab	*Mutalyzer*	
c.2303_2311dup	c.[2303_2311dup;2314C>G]	
c.2312_2314delinsGCGTGGACAACG	c.2312_2314delinsGCGTGGACAACG	
c.2312_2314delACCinsGCGTGGACAACG	c.2312_2314delinsGCGTGGACAACG	
c.2311_2312insTGTCCACGC	*c.2311_2312insTGTCCACGC*	*not corrected*
c.2300_2301insCAGCGTGGA	c.2303_2311dup	
c.2300_2301insCAGCGTGGA	c.2303_2311dup	
c.2302_2310dup	c.2303_2311dup	
c.2303_2311dup	c.2303_2311dup c.2314C>G	
c.2312_2320dupGCGTGGACA	c.2312_2320dup	*error Mutalyzer*
c.2311ins/dupGCGTGGACA	reports error	
c.2303_2311dup	c.2303_2311dup	
c.2300_2301insCAGCGTGGA	c.2303_2311dup	
c.2300_2301insCAGCGTGGA	c.2303_2311dup c.2314C>G	
c.2303_2311dup	c.2303_2311dup	
c.2303_2311dupGCGTGGACA	c.2303_2311dup c.2314C>G	
c.2300_2301insCAGCGTGGA	c.2303_2311dup	
c.2301_2302insCAGCGTGGA	*c.2301_2302insCAGCGTGGA*	*not corrected*
c.2310_2311dupAGCGTGGAC	c.2310_2311dup	*error Mutalyzer*
c.2301_2302ins9	Reports error c.2314C>G	
c.2311_2312insGCGTGGACA	*c.[2303_2311dup;2316C>G]*	*not corrected*
c.2311_2312ins9 and c.2314C>G	Reports error Reports error c.2314C>G	

Support tools

LUMC Mutalyzer DNA tools Batch Jobs Web Services External links Help About

http:// www.mutalyzer.nl

Welcome to the Mutalyzer website

The aim of this program suite is to support checks of sequence variant nomenclature according to the guidelines of the Human Genome Variation Society.

Name Checker

The Name Checker takes the complete sequence variant description as input and checks whether it is correct.

Examples: AB026906.1:c.274G>T, NG_012337.1(SDHD_v001):c.274G>T

Variant description using HGVS format

Syntax Checker

Takes the complete sequence variant description as input and checks whether the syntax is correct.

Position Converter

Converts chromosomal positions to transcript orientated positions and vice versa.

SNP Converter

Allows you to convert a dbSNP rsId to HGVS notation.

Description Extractor

Allows you to generate the HGVS variant description from a reference sequence and an observed sequence.

Reference File Loader

Allows you to load and use your own reference sequence.

Batch Checkers

Interfaces accepting a list of inputs that can be used for large quantities of checks.

Web Services

Provides instructions for the web services.

VariantValidator.org

Welcome to VariantValidator.org

A range of tools to meet your needs

Validation of single variant descriptions

- VariantValidator

Batch tools with options to select the gene(s) and transcript(s) you are interested in

- **VCF files** - VCF to HGVS
- **Batch jobs** - Batch Validator

Support tools

ClinGen
Clinical Genome Resource

ClinGen Allele Registry

Allele Registry | Pathogenicity Calculator | Login | Forgot Password?

Search Variants in ClinGen Allele Registry

Type of search

Select One

Query

For example: Select type of search to l

Do not have transcript/HGVS expression?

For a substitution with gene symbol, position, reference and alternate alleles known, please use this servic

Gene and variation based query

Alternatively, please use this service to identify allele interactively if HGVS expression or transcript is not a

Interactively generate variation

NM_004006.2

```
-244    TCCTGGCATC AGTTACTGTG TTGACTCACT CAGTGTTGGG ATCACTCACT TTCCCCCTAC
-184    AGGACTCAGA TCTGGGAGGC AATTACCTTC GGAGAAAAAC GAATAGGAAA AACTGAAGTG
-124    TTACTTTTTT TAAAGCTGCT GAAGTTTGTT GGTTTCTCAT TGTTTTTAAG CCTACTGGAG
-64     CAATAAAGTT TGAAGAACTT TTACCAGGTT TTTTTTATCG CTGCCTTGAT ATACACTTTT
-4      CAAAATGCTT TGGTGGGAAG AAGTAGAGGA CTGTTATGAA AGAGAAGATG TTCAAAAGAA
57     AACATTCACA AAATGGGTAA ATGCACAATT TTCTAAGTTT GGGAAGCAGC ATATTGAGAA
117    CCTCTTCAGT GACCTACAGG ATGGGAGGCG CCTCCTAGAC CTCCTCGAAG GCCTGACAGG
177    GCAAAAACTG CCAAAAGAAA AAGGATCCAC AAGAGTTCAT GCCCTGAACA ATGTCAACAA
237    GGCACTGCGG GTTTTGCAGA ACAATAATGT TGATTTAGTG AATATTGGAA GTACTGACAT
297    CGTAGATGGA AATCATAAAC TGACTCTTGG TTTGATTTGG AATATAATCC TCCACTGGCA
357    GGTCAAAAAT GTAATGAAAA ATATCATGGC TGGATTGCAA CAAACCAACA GTGAAAAGAT
417    TCTCCTGAGC TGGGTCCGAC AATCAACTCG TAATTATCCA CAGGTTAATG TAATCAACTT
477    CACCACCAGC TGGTCTGATG GCCTGGCTTT GAATGCTCTC ATCCATAGTC ATAGGCCAGA
537    CCTATTTGAC TGGAATAGTG TGGTTTGCCA GCAGTCAGCC ACACAACGAC TGGAACATGC
597    ATTCAACATC GCCAGATATC AATTAGGCAT AGAGAAACTA CTCGATCCTG AAGATGTTGA
657    TACCACCTAT CCAGATAAGA AGTCCATCTT AATGTACATC ACATCACTCT TCCAAGTTTT
717    GCCTCAACAA GTGAGCATTG AAGCCATCCA GGAAGTGGAA ATGTTGCCAA GGCCACCTAA
777    AGTGACTAAA GAAGAACATT TTCAGTTACA TCATCAAATG CACTATTCTC AACAGATCAC
837    GGTCAGTCTA GCACAGGGAT ATGAGAGAAC TTCTTCCCCT AAGCCTCGAT TCAAGAGCTA
897    TGCCTACACA CAGGCTGCTT ATGTCACCAC CTCTGACCCT ACACGGAGCC CATTTCCTTC
957    ACAGCATTTG GAAGCTCCTG AAGACAAGTC ATTTGGCAGT TCATTGATGG AGAGTGAAGT
1017   AAACCTGGAC CGTTATCAAA CAGCTTTAGA AGAAGTATTA TCGTGGCTTC TTTCTGCTGA
```

DirectPoll

Q & A

scan QR code

or go to http://etc.ch/VEPa

Exercises

for exercise to try applying HGVS and using some support tools:

tinyurl.com/ VEPTC-4e

Correct?

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

- **NM_01234.3 : c.65+2T>A**

Not correct

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

- **NM_01234.3 : c.65+2T>A**
  variant nucleotide not in reference
  correct NG_022335.1(NM_01234.3):c.65+2T>A
  NC_000005.10(NM_01234.3):c.65+2T>A

- **LRG_123:c.957G>T**
  reference transcript missing (LRG_123t1)

- **NG_01234.3:c.1A>G**
  reference transcript missing (NM_01234.3)

Correct?

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

- **c.123-?_456+?del**

MLPA detected deletion

Correct?

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

- **c.123-?_456+?del**

MLPA detected deletion

NO, fails to describe the extent of the deletion

correct is something like

c.(122+1_123-1)_(456+1_457-1)del

or c.(?_123-1)_(456+1_?)del

LUMC

Suggestions made

- **SVD-WG003 (exon del/dup)**
  suggested to describe exon deletions/duplications using the format c.(233+1_234-1)_(1234+1_1235-1)del.
  Status: Oct.6 (2015) new proposal to be made. Closed Jul.16 (2015). Opened May 14 (2015).

c.(122+1_123-1)_(456+1_457-1)del

c.(122+?_123-?)_(456+?_457-?)del

c.(122_?_123)_(456_?_457)del

c.(122_123)_(456_457)del

c.(122|123)_(456|457)del

c.(122^123)_(456^457)del

Correct?

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

- **c.(122+1_123-1)_(456+1_457-1)dup**

MLPA detected

Duplication

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

- **c.(122+1_123-1)_(456+1_457-1)dup**

MLPA detected

- **...is it a duplication?**

you detected only an extra copy

c.?ins(122+1_123-1)_(456+1_457-1)

or ISCN c.(122+1_123-1)_(345+1_346-1)x3

Correct?

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

…ATG TCT AGT TCT TGG… > …ATG TCT TCT TGG…
…Met Ser Ser Ser Trp… > …Met Ser Ser Trp…

a. p.(Ser2del)
b. p.(Ser3del)
c. p.(Ser4del)

p.(Ser4del)

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

- **report change at level described**

on protein level, forget DNA position

```
…ATG TCT AGT TCT TGG…   >   …ATG TCT TCT TGG…
…Met Ser Ser Ser Trp…   >   …Met Ser Ser Trp…
```

most 3' position possible is arbitrarily assigned

so p.(Ser4del) with c.7_9del

not p.(Ser2del)

request to change

not consistent with overall recommendations

Correct?

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

g.1234567_1239870 I gom

Recent addition

g.1234567_1239870 l gom

NOTE: reference sequences can be assumed to be known, spaces in descriptions used for clarity only.

Community Consultation

- **SVD-WG005 (gom/lom)**
  suggests to extend the HGVS recommendations to allow description of changes in general methylation status
  Status: Open. Oct.20 (2016). Closes Dec.31 (2016).

gom = gain of methylation
lom = loss of methylation
l ('pipe') = change of state (not of sequence)

Q & A

"variant nomenclature"

socrative by MasteryConnect

www.socrative.com

student

Johan den Dunnen

VarNomen @ HGVS.org

www.socrative.com