Describing translocations by extending HGVS sequence variation nomenclature

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Reciprocal translocations

- Standing Committee on Human Cytogenetic Nomenclature
- ISCN 2013 guidelines:
  \[ t(9;22)(p24;q11) \]
  \[ t(9;22)(p24;q11)(9qter\rightarrow9p24::22q11\rightarrow22qter; \]
  \[ 22pter\rightarrow22q11::9p24\rightarrow9pter) \]

Derivative chromosomes:
- Structurally rearranged with intact centromeres
  \[ \text{der}(9)\ t(9;22)(p24;q11) \]
  \[ \text{der}(22)\ t(9;22)(p24;q11) \]

www.cydas.org
Reciprocal translocations

- HGVS recommendations for disrupted gene:
  - Indicate breakpoint flanking positions:
    \[t(9;22)(p24;q11)(NM_123456.1:c.2684_2685)\]
  - Submit breakpoint sequence to GenBank
    - Provide accession and version numbers
  - No recommendations for detailed description

www.cydas.org
Proposed description components and format

• ISCN translocation description (bands optional)
  \( t(9;22)(p24;q11) \)

• Chromosomal RefSeq accession and version numbers
  Build hg19: chr9: NC_000009.11, chr22: NC_000022.10

• Breakpoint flanking positions on derivative chromosomes
  chr9: between g.5069031 and g.5069032
  chr22: between g.23631784 and g.23631785

• ISCN break and reunion indicator :: (double colon)

Format translocation description:
  \(<\text{ISCN}>)(<\text{der(1) breakpoint junction}>;<\text{der(2) breakpoint junction}>\)

Format der(1) breakpoint junction:
  chr1:<flanking position>::chr2:<flanking position>
Proposed translocation rules I

1) Order of breakpoint descriptions follows ISCN rules

2) Reference sequence order depends on breakpoint location relative to centromere

3) Chromosome N sequence always in forward orientation in derivative chromosome der(N) description

4) Follow aim HGVS general position rule: Maintain longest unchanged sequence
Proposed translocation rules I

1) Order of breakpoint descriptions follows ISCN rules
   • Sex chromosome(s) first, X before Y
   • Autosomes: low to high number
   • der(X) > der(Y) > der(1) > …> der(22)
   • der number depends on chromosomal origin intact centromere

Format translocation description:

\[(<\text{ISCN}>)((<\text{der(1) breakpoint junction}>;<\text{der(2) breakpoint junction}>)\]
Proposed translocation rules II

2) Reference sequence order depends on breakpoint location relative to centromere

3) Sequence of der(N) chromosome always in forward orientation

Chr 1 long arm (breakpoint position > centromere position)
<der(1) breakpoint junction> =
    chr1:<flanking position>::chr2:<flanking position>

Chr 1 short arm (breakpoint position < centromere position)
<der(1) breakpoint junction> =
    chr2:<flanking position>::chr1:<flanking position>
Proposed translocation rules III

4) Follow aim HGVS general position rule:
   maintain longest unchanged sequence

General rule: Change occurs at most 3’ position in RefSeq

Adapted to translocations:
   a) First RefSeq flanking position: most 3’ position
      Exception: RefSeq in opposite orientation: most 5’
   b) Second RefSeq flanking position: most 5’ position
      Exception: RefSeq in opposite orientation: most 3’
Reciprocal translocation - long arms

t(1;2)(q;q)

Note: Examples use fictitious g. positions!
Reciprocal translocation long - short

t(1;2)(q;p)

Note: Examples use fictitious g. positions!
Reciprocal translocation - short arms

t(1;2)(p;p)

chr1
NC_1

p q

234 235

123 235

der(1)t(1;2)

chr2:g.123::chr1:g.235

chr1
NC_1

p q

123 124

234 124

der(2)t(1;2)

chr1:g.234::chr2:g.124

Note: Examples use fictitious g. positions!
Reciprocal translocation short - long

t(1;2)(p;q)

Note: Examples use fictitious g. positions!
Reciprocal translocation format

\((<\text{ISCN}>)(<\text{der}(9) \text{ breakpoint junction}>;<\text{der}(22) \text{ breakpoint junction}>))\)

\[\begin{align*}
\text{der}(9) & \rightarrow 22 \rightarrow 9 \\
\text{chr}22: g. 23631785_51304566 & \rightarrow \text{chr}9: g. 5069032_141213431 \\
\text{ISCN} & \downarrow \\
t(9;22)(p24;q11)(\text{ochr}22: g. 23631785::\text{chr}9: g. 5069032; \\
\text{chr}22: g. 23631784::\text{ochr}9: g. 5069031) & \uparrow \\
\text{der}(22) & \rightarrow 22 \rightarrow 9 \\
\text{chr}22: g. 1_23631784 & \rightarrow \text{chr}9: g. 1_5069031
\end{align*}\]

Note: Use Chromosomal RefSeq Acc. Nos.: chr 9: NC_000009.11  chr 22: NC_000022.10
Flanking positions used in the description are indicated in yellow
Conclusions

• New HGVS translocation guidelines complement ISCN
  • ISCN + detailed HGVS breakpoint description

• Use of familiar notations:
  • Double colons (::): break and reunion
  • o: opposite orientation

• HGVS translocation descriptions
  • more efficient
  • single line per breakpoint in gene variant databases
Further extensions

- Applicable to dicentric chromosomes, isochromosomes
  - Use ISCN rules regarding chromosome order
  - Replace t by dic or idic or i
    - dic(13;13)(q14;q32)(chr13:g.345::ochr13:578)
    - idic(13)(q22)(chr13:g.432::ochr13:g.432)
    - i(17)(q10)(chr17:g.186::ochr17:g.186)

- Insertions between breakpoint flanking positions
  - chr1:<flanking position>::ATGC::chr2:<flanking position>
  - chr1:<flanking position>::oAB_123456.7:g.120_4567::chr2:<flanking position>

- Note: Examples use fictitious g. positions!
The simplest alternative

- Allele descriptions based on sequence concatenation
  - Chromosomal RefSeq accession and version numbers
  - Position ranges (<position a>_<position b>)
  
g.[NC_1:a_b;NC_2:c_d;….;NC_x:y_z]

- Very simple, but all information about type of change lost

- Useful alternative for very complex changes
  - chromothripsis

- NGS of complex cases insufficient: cytogenetics required
Acknowledgments

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https://mutalyzer.nl/

www.lovd.nl
www.lovd.nl/DMD
www.lovd.nl/mendelian_genes

Queries for gene variant databases:
Gene_symbol.lovd.nl
Reciprocal translocations in VCF4.1

- VCF4.1: file describing variants identified by NGS
  - 1 line per position
  - 2 lines per breakpoint
  - New ALT field description:

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http://www.1000genomes.org/wiki/Analysis/Variant%20Call%20Format/vcf-variant-call-format-version-41

ALT    Meaning

- [p[    piece extending to the right of p is joined after t
- [p[    reverse comp piece extending left of p is joined after t
- ]p]t   piece extending to the left of p is joined before t
- ]p]t   reverse comp piece extending right of p is joined before t

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HGVS meeting, Paris adapted for HGVS website

June 8, 2013