LEIDEN UNIVERSITY MEDICAL CENTER

Describing translocations by extending HGVS sequence variation nomenclature

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THE HUMAN VARIOME PROJECT

HGVS HUMAN GENOME VARIATION SOCIETY

GEN2PHEN

Reciprocal translocations

- Standing Committee on Human Cytogenetic Nomenclature
- ISCN 2013 guidelines:

  t(9;22)(p24;q11)

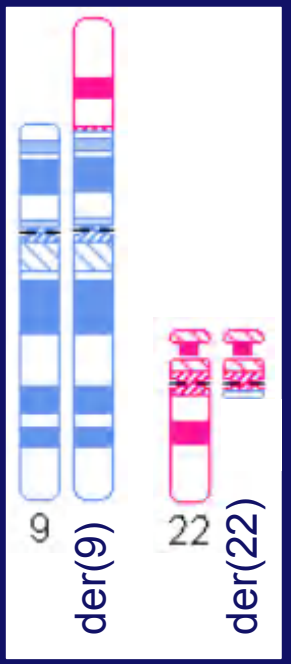
  t(9;22)(p24;q11)(9qter→9p24::22q11→22qter;
  22pter→22q11::9p24→9pter)

  Derivative chromosomes:

  - Structurally rearranged with intact centromeres

  der(9) t(9;22)(p24;q11)

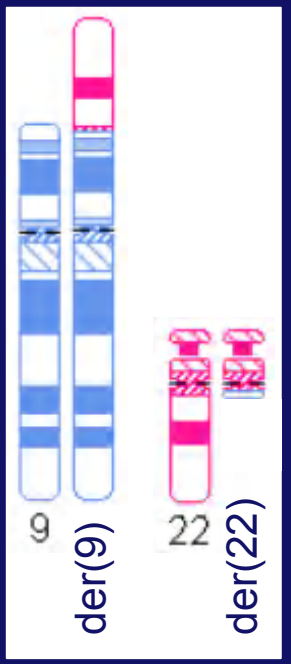
  der(22) t(9;22)(p24;q11)



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:

(<ISCN>)(<der(1) breakpoint junction>;<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

der(9) 22  9

der(22) 22  9

Format translocation description:

(<ISCN>)(<der(1) breakpoint junction>;<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:

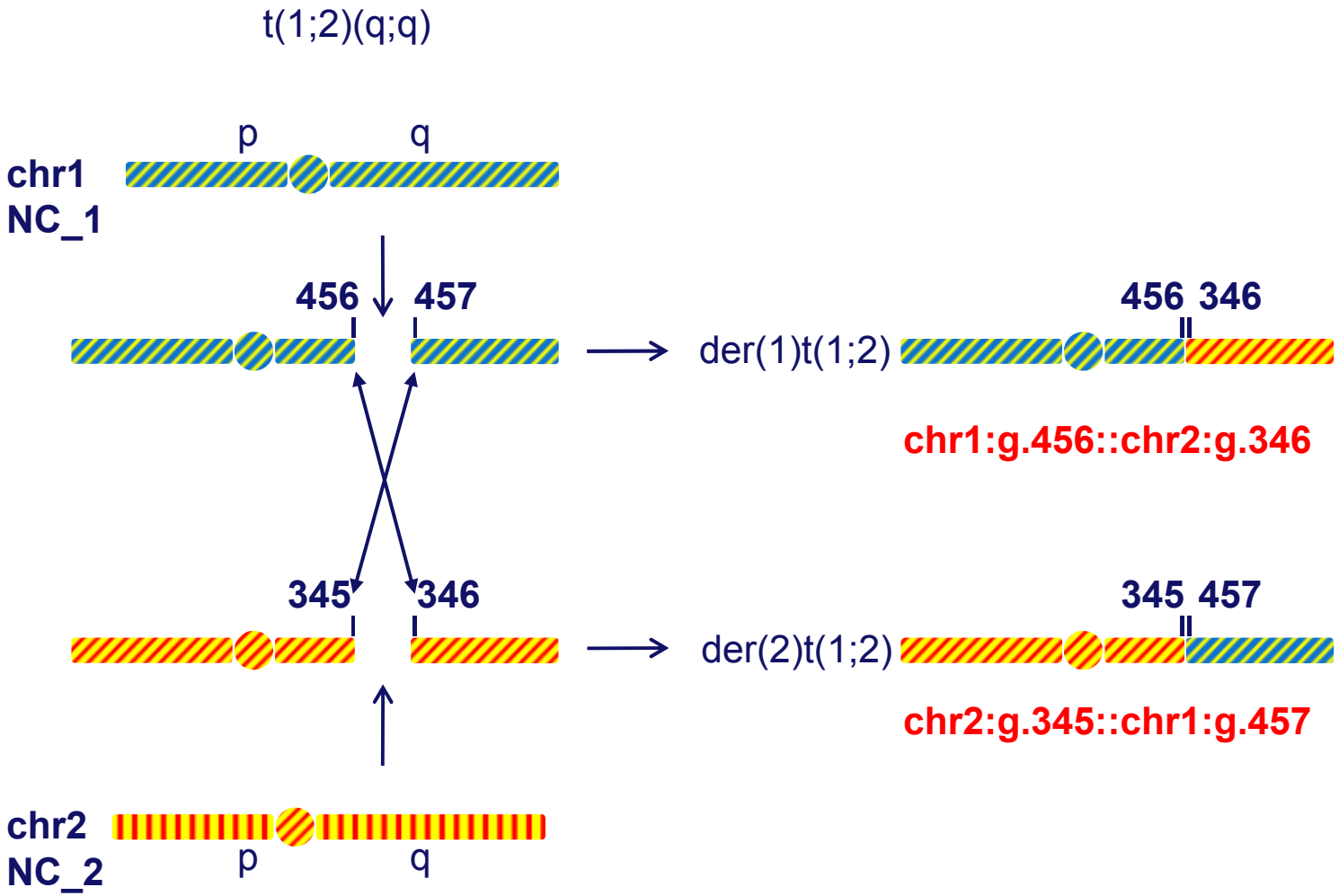
a) First RefSeq flanking position: most 3' position

Exception: RefSeq in opposite orientation: most 5'

b) Second RefSeq flanking position: most 5' position

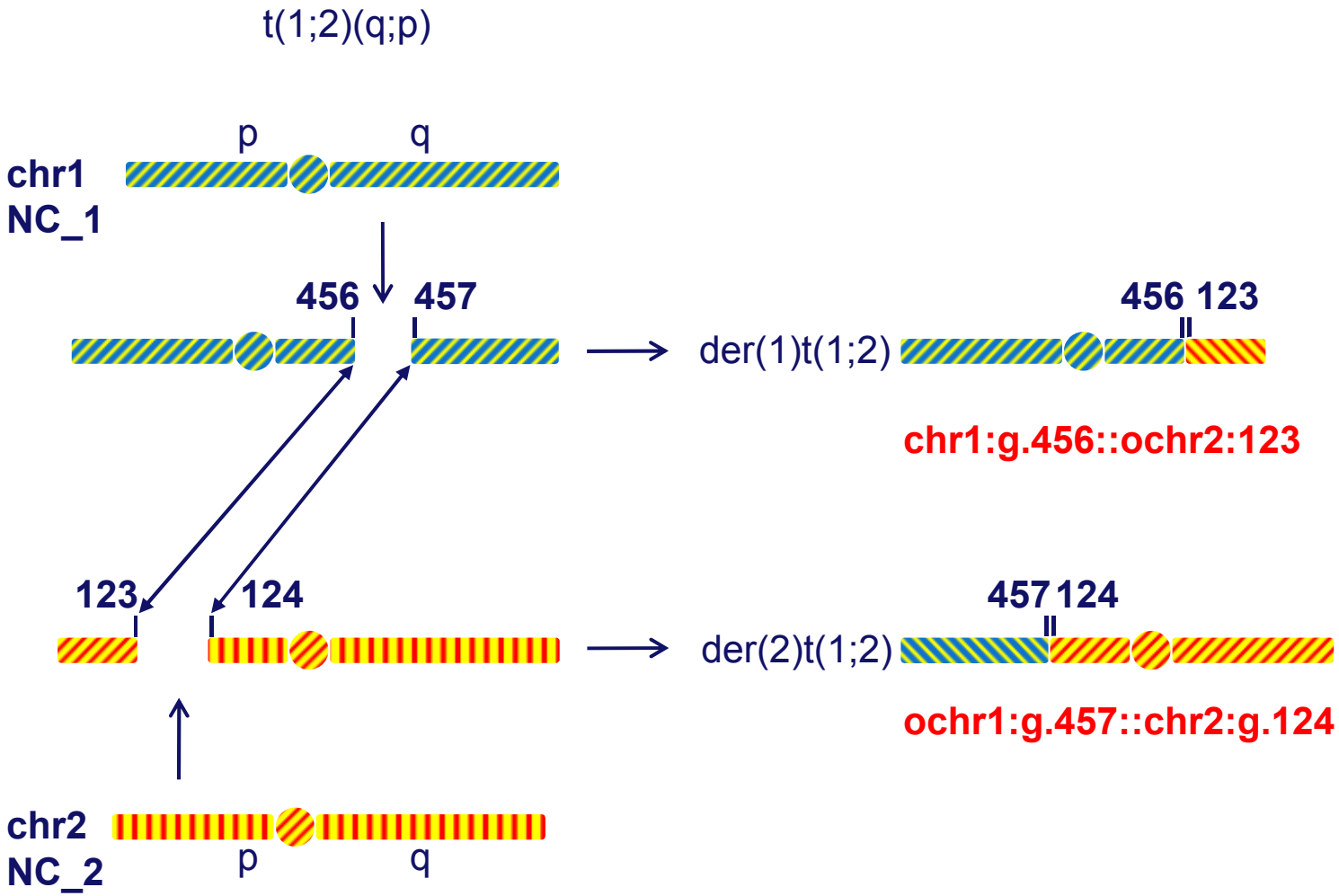
Exception: RefSeq in opposite orientation: most 3'

Reciprocal translocation - long arms



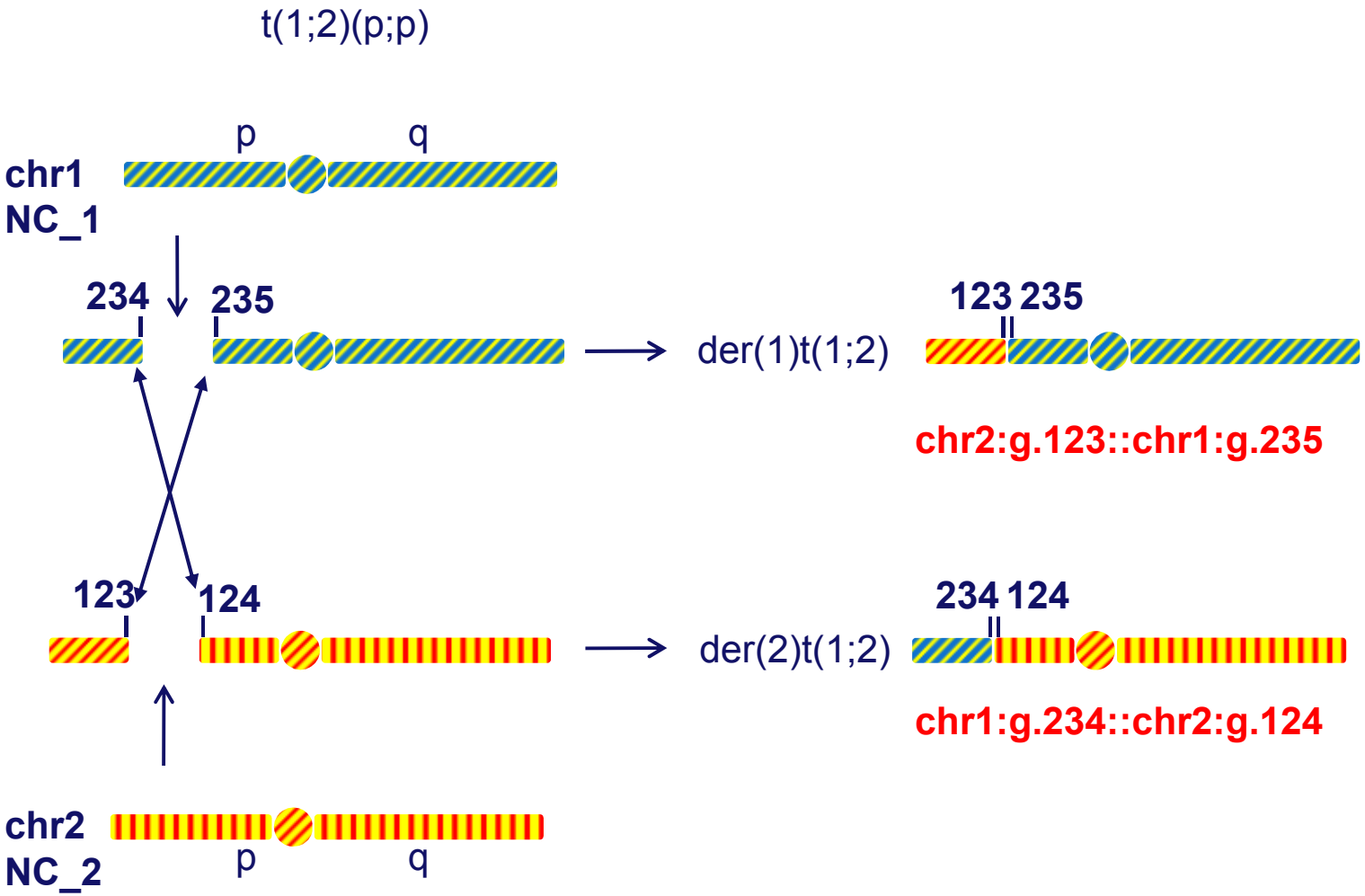
Note: Examples use fictitious g. positions!

Reciprocal translocation long - short



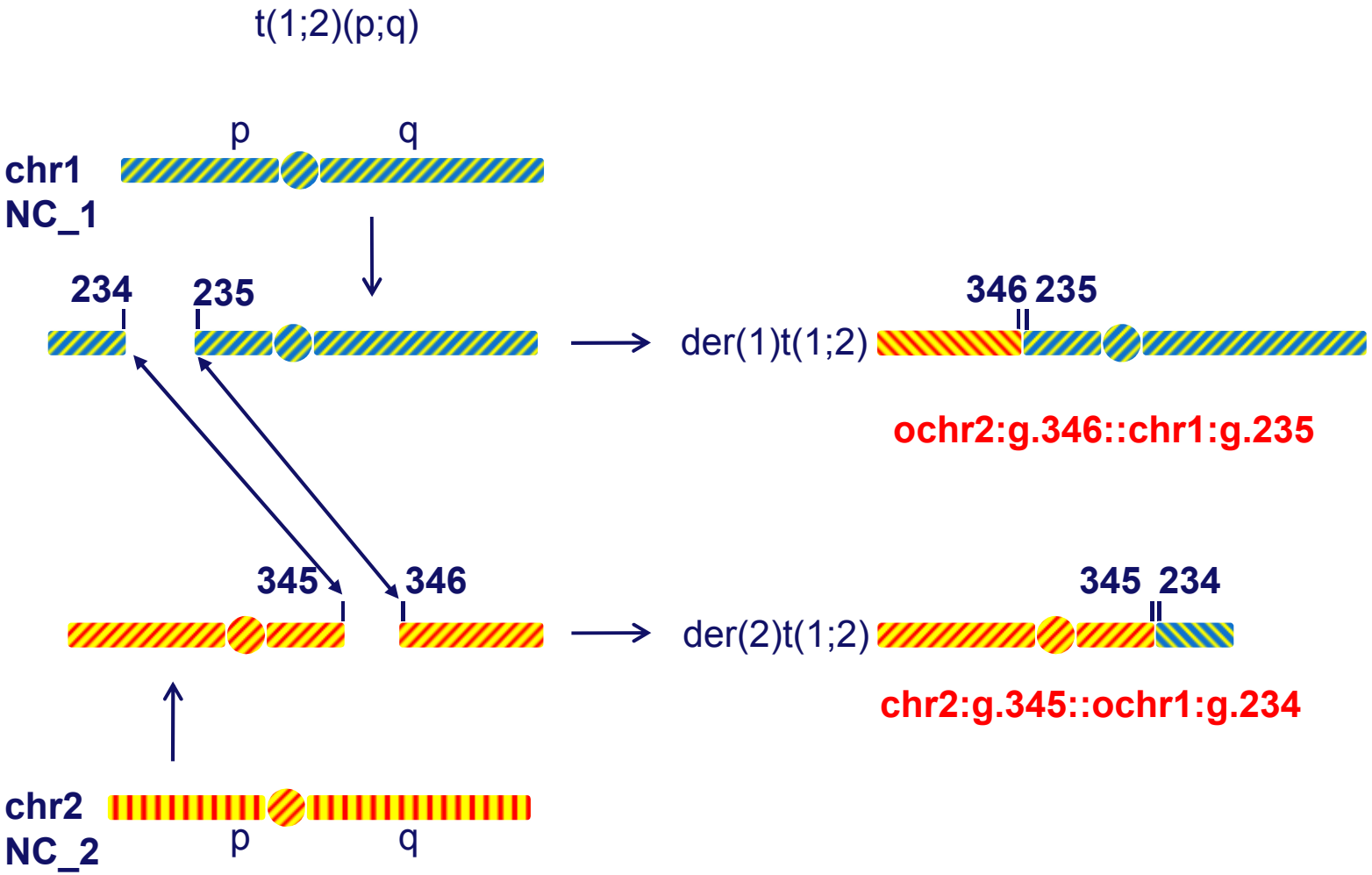
Note: Examples use fictitious g. positions!

Reciprocal translocation - short arms



Note: Examples use fictitious g. positions!

Reciprocal translocation short - long



Note: Examples use fictitious g. positions!

Reciprocal translocation format

(<ISCN>)(<der(9) breakpoint junction>;<der(22) breakpoint junction >)

chr22:g. 23631785_51304566 chr9:g.5069032_141213431

ISCN

t(9;22)(p24;q11)(ochr22:g.23631785::chr9:g.5069032;
chr22:g.23631784::ochr9:g.5069031)

chr22:g.1_23631784 chr9:g.1_5069031

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]

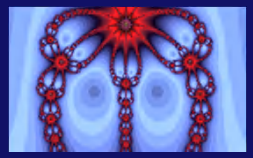
- Very simple, but all information about type of change lost
- Useful alternative for very complex changes
  - chromothripsis
- NGS of complex cases insufficient: cytogenetics required

Acknowledgments

LUMC, Human Genetics

Jeroen Laros

Johan den Dunnen



https://mutalyzer.nl/

LUMC, Clinical Genetics

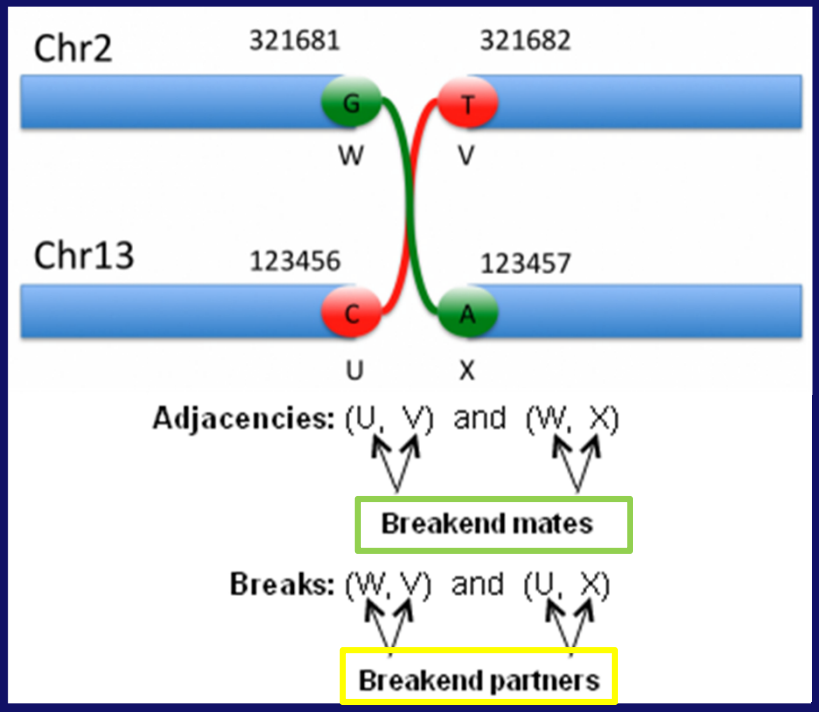
Mariette Hoffer

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:

ALT	Meaning
t[p[	piece extending to the right of p is joined after t
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

CHROM	POS	ID	REF	ALT	QUAL	FILT	INFO
2	321681	bnd_W	G	G[13:123457[	6	PASS	SVTYPE=BND;MATEID=bnd_X;EVENT=RR0
2	321682	bnd_V	T	]13:123456]T	6	PASS	SVTYPE=BND;MATEID=bnd_U;EVENT=RR0
13	123456	bnd_U	C	C[2:321682[	6	PASS	SVTYPE=BND;MATEID=bnd_V;EVENT=RR0
13	123457	bnd_X	A	]2:321681]A	6	PASS	SVTYPE=BND;MATEID=bnd_W;EVENT=RR0

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