



LEIDEN UNIVERSITY MEDICAL CENTER

Describing translocations by extending HGVS sequence variation nomenclature

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

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

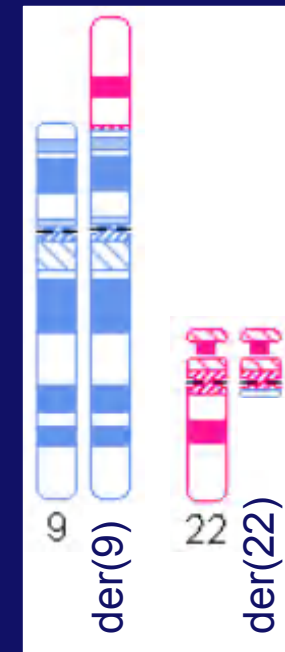
$t(9;22)(p24;q11)(9qter \rightarrow 9p24::22q11 \rightarrow 22qter;$
 $22pter \rightarrow 22q11::9p24 \rightarrow 9pter)$

Derivative chromosomes:

- Structurally rearranged with intact centromeres

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

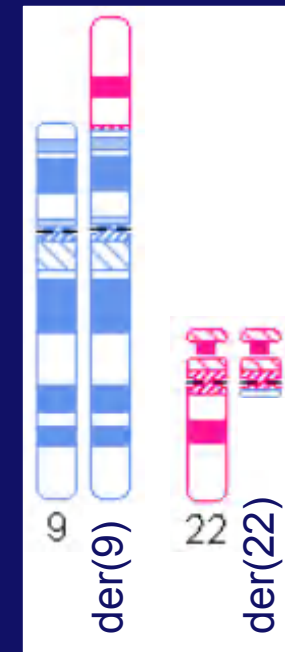
$der(22) t(9;22)(p24;q11)$



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



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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>`

- 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

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>)

- 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>

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

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

Adapted to translocations:

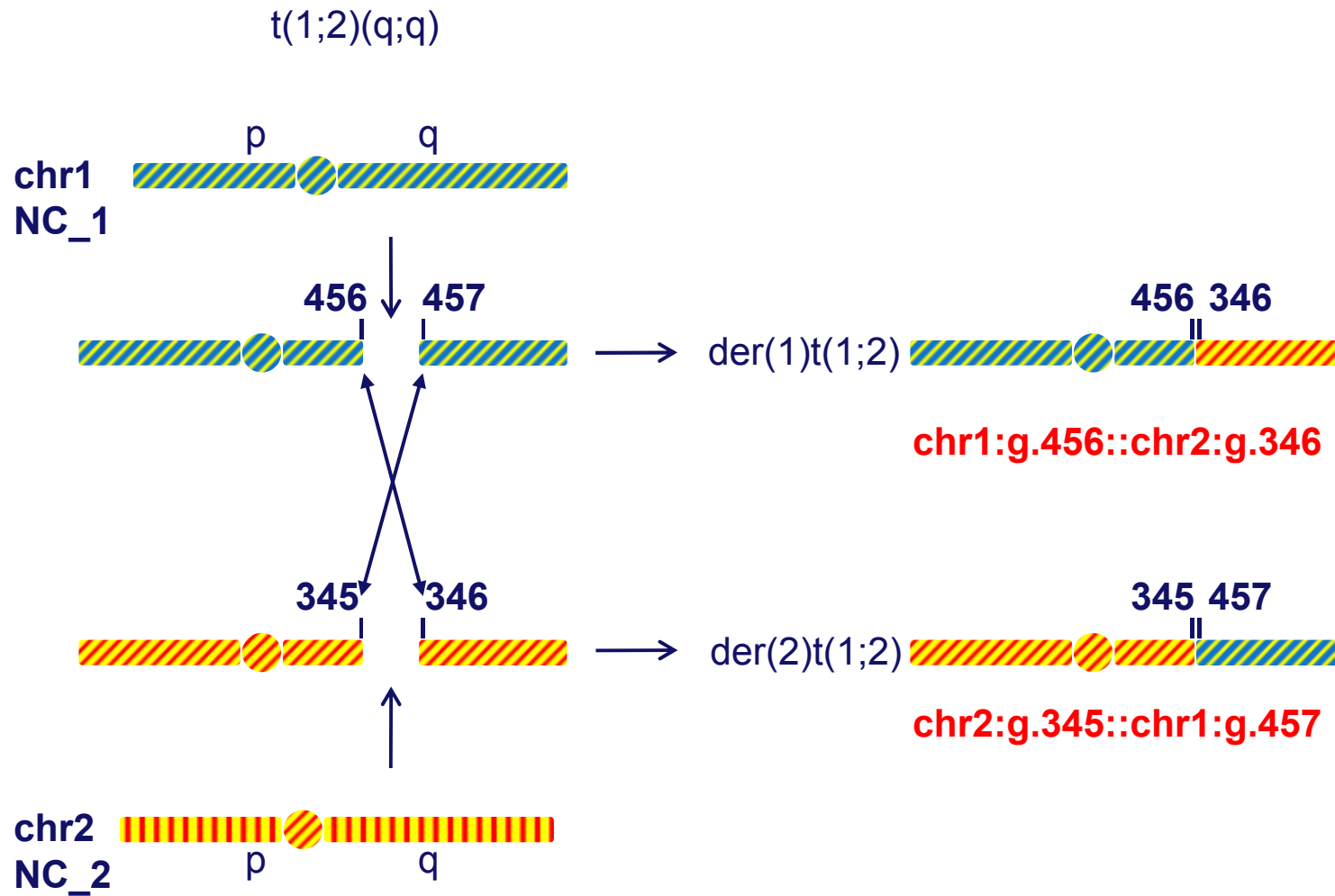
a) First RefSeq flanking position: most 3' position

Exception: RefSeq in opposite orientation: most 5'

b) Second RefSeq flanking position: most 5' position

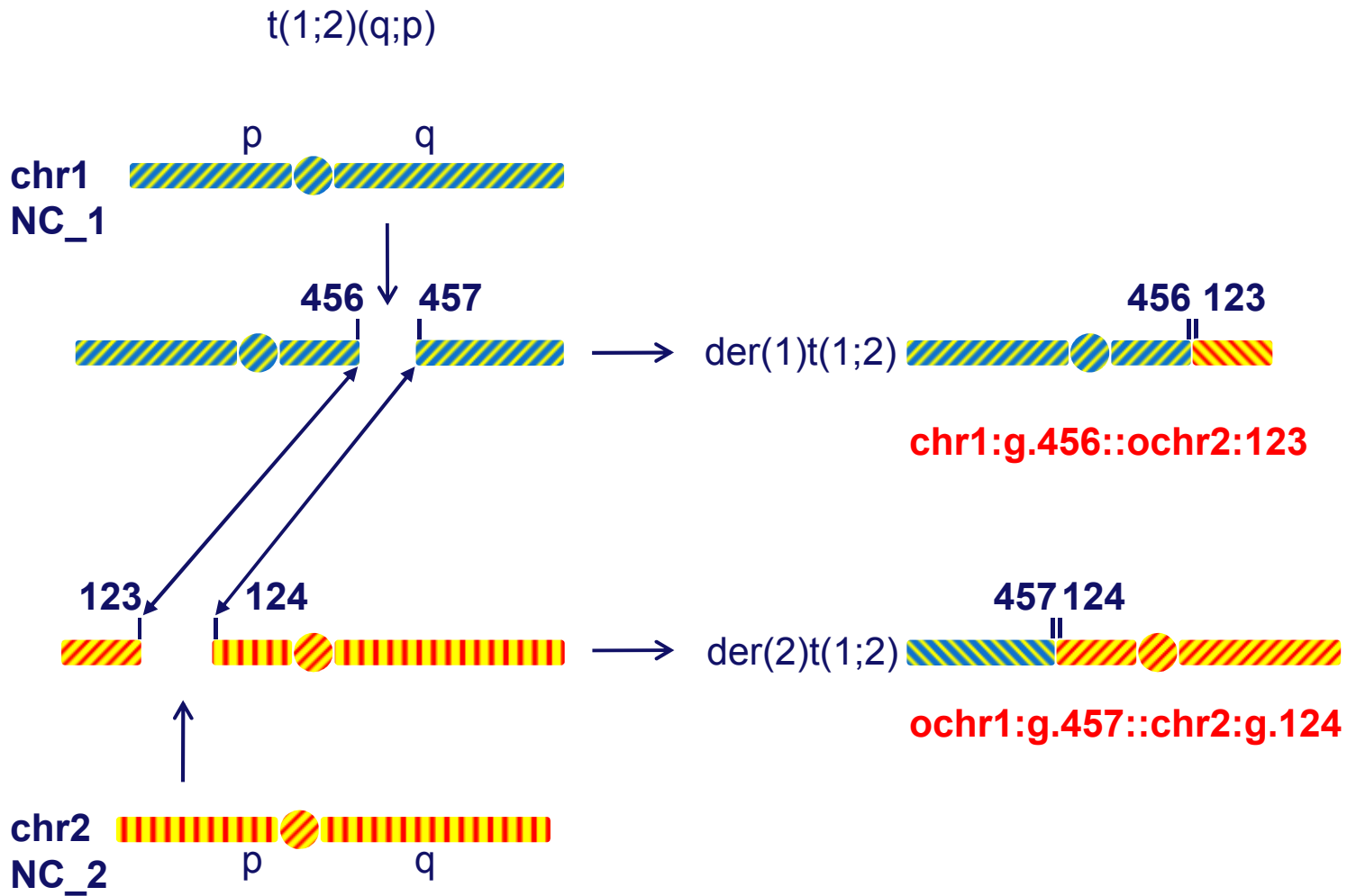
Exception: RefSeq in opposite orientation: most 3'

Reciprocal translocation - long arms



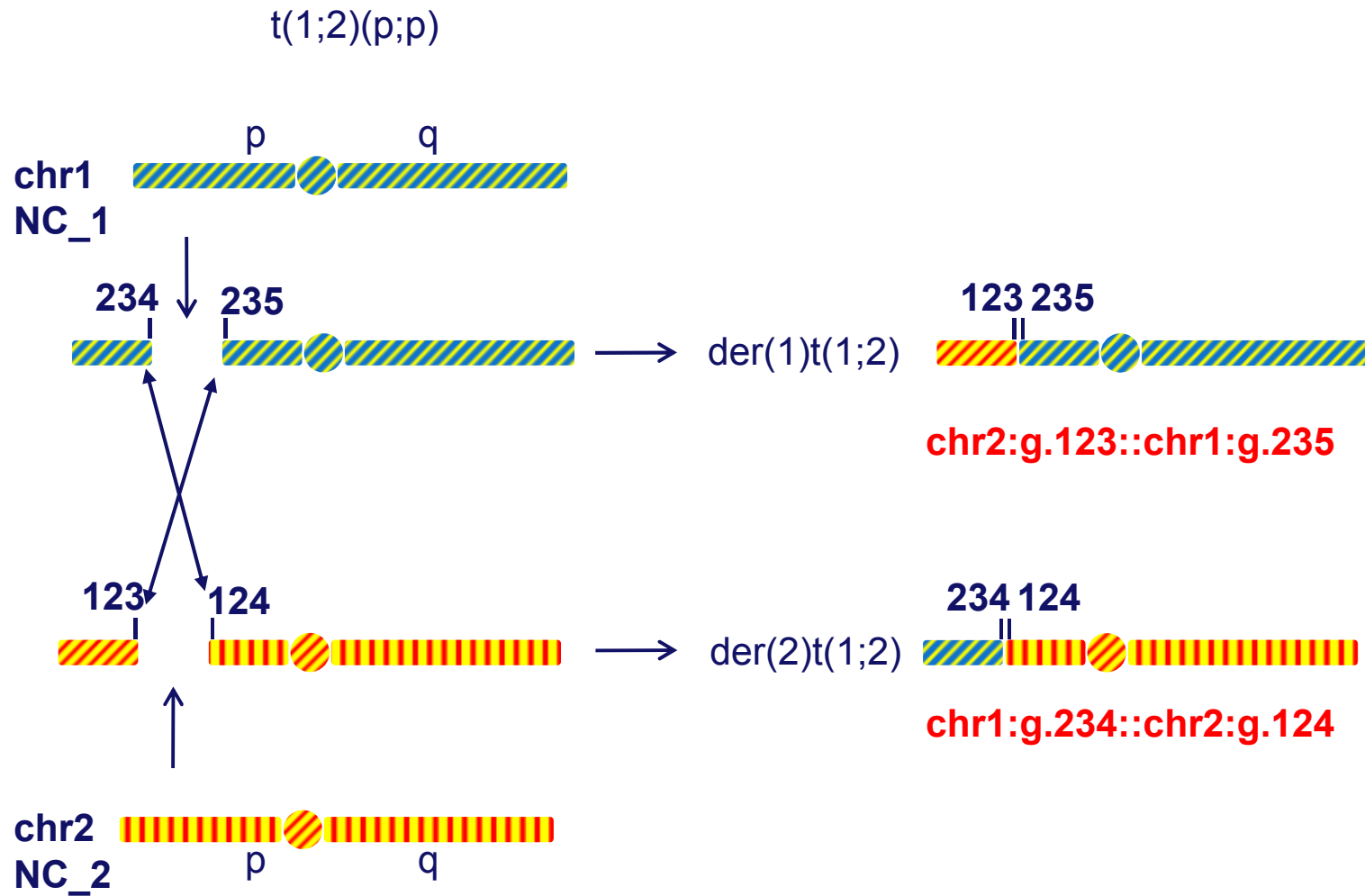
Note: Examples use fictitious g. positions!

Reciprocal translocation long - short



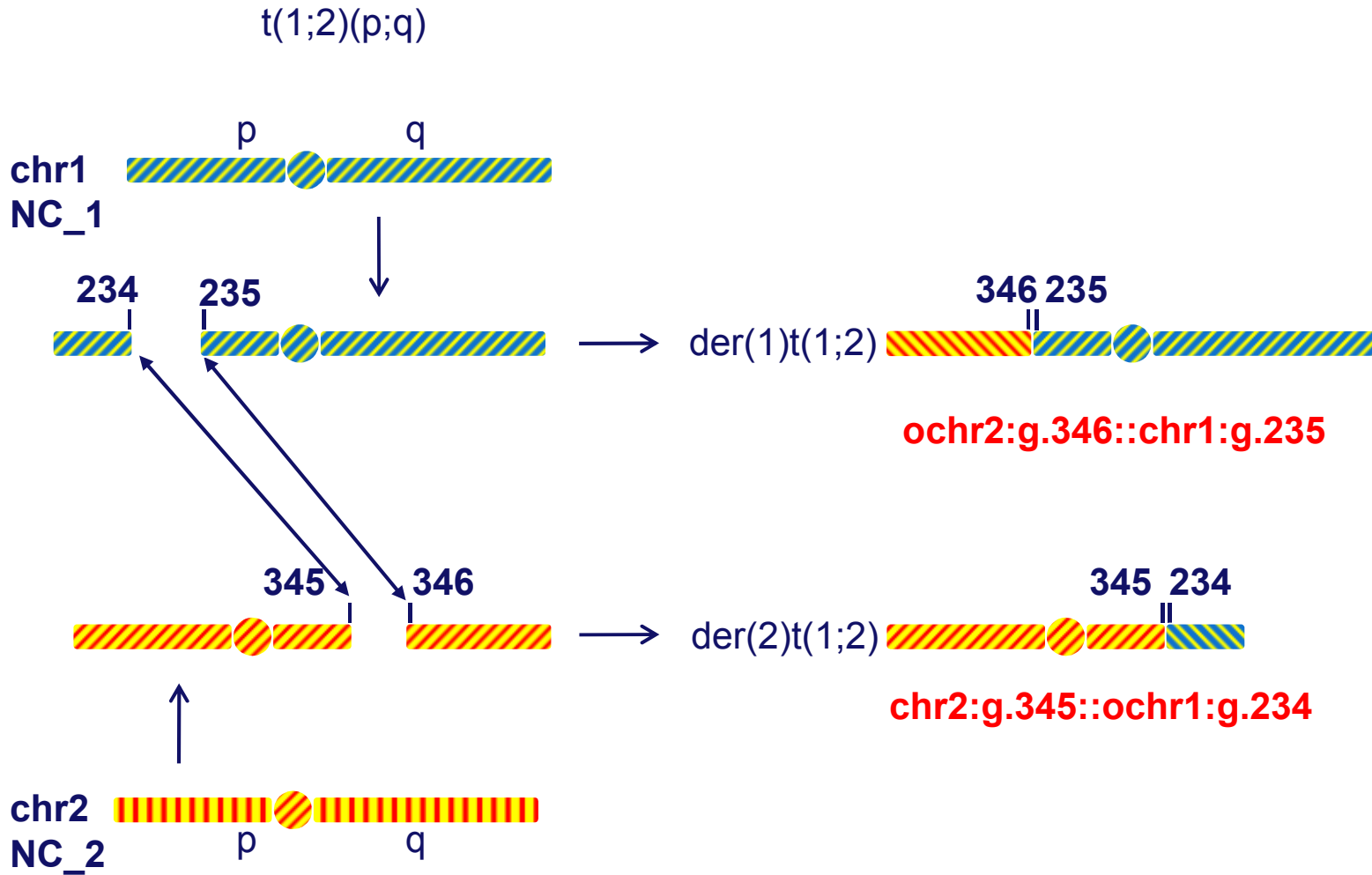
Note: Examples use fictitious g. positions!

Reciprocal translocation - short arms



Note: Examples use fictitious g. positions!

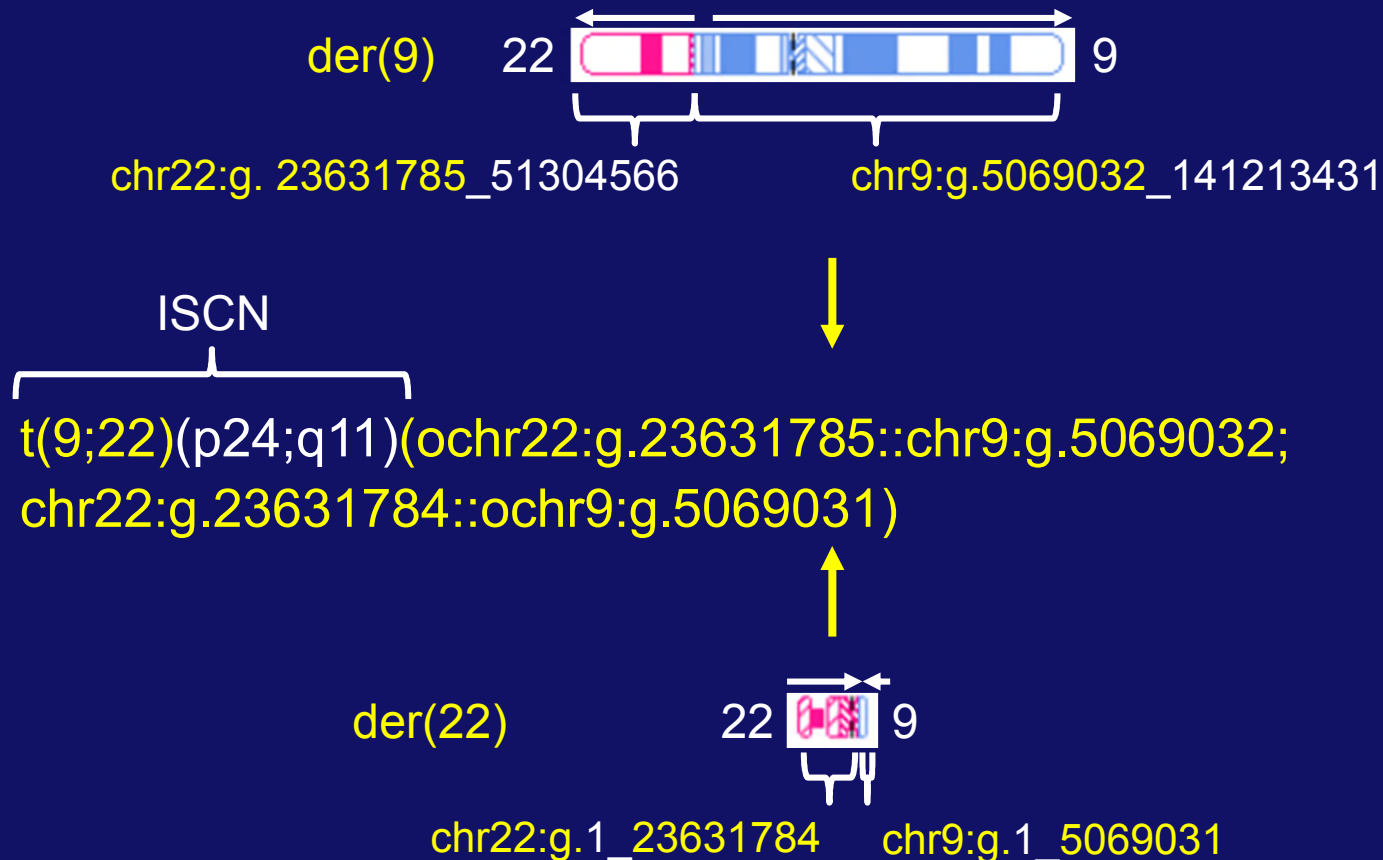
Reciprocal translocation short - long



Note: Examples use fictitious g. positions!

Reciprocal translocation format

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



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

- 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

- 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!**

- Allele descriptions based on sequence concatenation
 - Chromosomal RefSeq accession and version numbers
 - Position ranges (<position a>_<position b>)

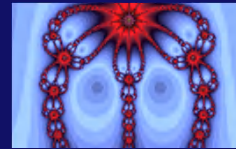
g.[NC_1:a_b;NC_2:c_d;.....;NC_x:y_z]

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

LUMC, Human Genetics

Jeroen Laros

Johan den Dunnen



<https://mutalyzer.nl/>

LUMC, Clinical Genetics

Mariette Hoffer



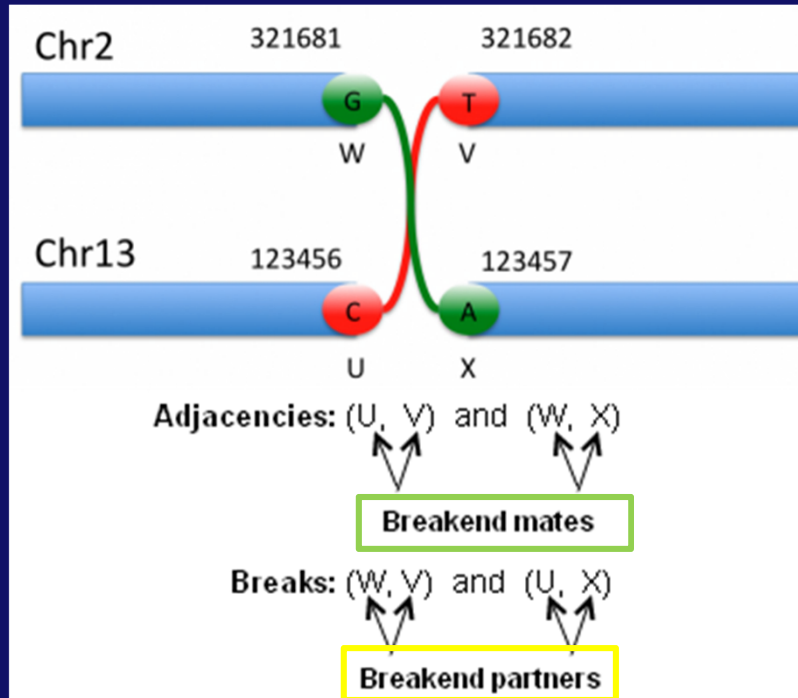
www.lovd.nl

www.lovd.nl/DMD

www.lovd.nl/mendelian_genes

Queries for gene variant databases:
Gene_symbol.lovd.nl

- 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