Genome Mapping nomenclature and ISCN 2024

***R. Hastings*[1,2], Sarah Moore[3], Jean McGowan-Jordan[4]**

1. GenQA, NHS Lothian, Royal Infirmary of Edinburgh, Edinburgh, EH16 4UX, United Kingdom.
2. GenQA, Oxford University Hospitals NHS Foundation Trust, Oxford, OX3 9DU, United Kingdom.
3. Genetics and Molecular Pathology, SA Pathology, Adelaide, Australia.
4. CHEO Dept. of Genetics, and Pathology and Laboratory Medicine, University of Ottawa, Ottawa, Canada.

Introduction

The International System for Cytogenomic Nomenclature (ISCN) is used by geneticists globally to describe structural and numerical changes at a genome level. The ISCN Standing Committee recently asked the genetics community to submit proposals for required changes or addendums to ISCN 2020[b]. This poster discusses some of the changes to the new ISCN 2024, including new chapters.

This nomenclature will enable scientists and diagnostic laboratories to communicate structural variation, haplotypes and repeat expansion results effectively and without ambiguity to clinicians, public databases and in publications. The new cytogenomic genome mapping nomenclature will be described and compared to array and sequence ISCN nomenclature in different settings through worked examples.

Understanding ISCN and describing the abnormal results accurately can be challenging and this poster will also present the tools, webinars and External Quality Assessments (EQAs) available that laboratories can use to train staff and check their competence.

OGM

The new Genomic Mapping nomenclature for cytogenomics incorporates elements of karyotyping, microarray and region-specific ISCN. It will be published in a peer reviewed journal and as a book. Results obtained by Genome mapping will be suffixed with the abbreviation ogm. The abnormalities covered include:

Normal

ogm (X,1–22)×2 **or** ogm (X,Y)×1,(1–22)×2 **or where sex not disclosed** ogm (X,?)×1,(1-22)×2

Aneuploidy

ogm (X)×1,(Y)×2,(8)×3,(21)×3

Deletion

ogm[GRCh38] 17q11.2(29069481_30273120)×1 **or**
ogm[GRCh38] del(17)(q11.2)(29069481_30273120)

Duplication

ogm[GRCh38] 6q21q25.1(113900000_149100000)×3 **or**
ogm[GRCh38] dup(6)(q21q25.1)(113900000_149100000)

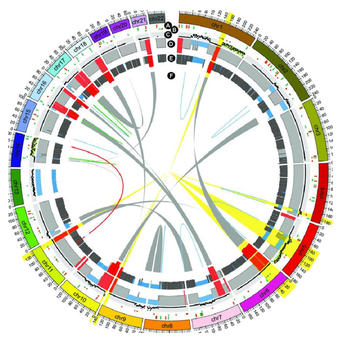


Fig 1. Circos plot from a MM with t(11;14) plus other gains/losses

Insertion

ogm[GRCh38] ins(2)(p24.3p12.2p11.2)(19,781,841~19,799,854;80,780,708_87,576,955) **or**
ogm[GRCh38] der(2)(pter→p24.3::p12.2→p11.2::p24.3→p12.2::p11.2→qter)
(pter→19,781,841~19,799,854::80,780,708_87,576,955::19,781,841~19,799,854_
80,780,708::87,576,955→qter)

Translocation

ogm[GRCh38] t(6;7)(q21;q32.1)(108,976,886~108,982,237;128,310,022~128,316,239)
The tilde (~) is used to demonstrate the region of uncertainty

ogm[GRCh38] t(3;12)(q26.2;p13.2)(169,465,166;11,802,643)(MECOM::ETV6)
Translocation resulting in a fusion of the *MECOM* gene cluster and *ETV6*

Methods

ISCN is an effective means to communicate accurately genomic results globally to clinicians. It is also needed for clear communication in publications for the advancement of knowledge as well as for consistency in genomic databases. Describing cytogenomic abnormalities accurately can be challenging, requiring an understanding of both the nomenclature and aetiology of chromosomal structural variation.

With the advent of new molecular cytogenomic technologies the need for a nomenclature to describe the findings is required. Genome mapping technologies are relatively new cytogenomic techniques that use labelled DNA to assemble genome maps for high-resolution structural variation detection. In addition to the detection of both balanced and unbalanced structural variation, genome mapping can detect copy number changes analogous to chromosomal microarray analysis. In time, genome mapping may replace traditional cytogenomic assays (karyotyping, FISH, and SNP-arrays) in constitutional studies and the evaluation of neoplasia as both balanced and unbalanced structural variants (SVs) can be detected.

The ISCN Standing Committee (ISCN SC) sent out a request to the genomics community for suggestions in November 2022. The ISCN SC received 146 suggestions and also reviewed the current nomenclature (ISCN 2020[b]) to reduce ambiguity and inconsistencies within and across the different chapters.

ISCN 2024

General

- ❖ Restructure of book so Generic rules are summarised at the beginning of the book
- ❖ Specific technique rules at the beginning of relevant chapter
- ❖ Use of GRCh38 throughout for band designation and nucleotides in arr, rsa, seq and ogm
- ❖ Improved consistency between the different technologies
- ❖ ISCN examples for hydatidiform moles and complete moles to be added for different techniques
- ❖ Consistency in the use of spaces across the different techniques
- ❖ Removal of Meiotic chromosomes chapter (Access via website)

Constitutional ISCN

- ❖ ISCN structural chromosome examples will be merged into one chapter

FISH

- ❖ Clarification of FISH rules and removal of detailed FISH ISCN for breakapart and fusion probes

Neoplasia ISCN

- ❖ Clarification that the chromosome band resolution represents the resolution seen using the specific technique and isn't adjusted to the gene location

Array, seq and rsa ISCN

- ❖ rsa fusion genes changed: normal: rsa (BCR,ABL1)x2 abnormal: rsa (BCR::ABL1)x1
- ❖ Clarification of terminology *e.g.,* when to use sup vs dup in sequence ISCN
- ❖ More complex examples in array and seq chapters added
- ❖ New acronym for uniparental disomy detected molecularly umat and upat
- ❖ Aneuploidy examples for seq
- ❖ Example of a tabulated array result
- ❖ New chapter on Genome mapping (ogm prefix)

Educational Tools available to laboratories

There are several educational tools available online and a selection of them are detailed below:

Although GenQA is an EQA provider offering >120 EQAs, including an ISCN EQA, it also offers many different educational resources including webinars, workshops and **GENie**

Webinars

GenQA offers FOCUS ON webinars on various genomic topics, the recordings of which are available on the GenQA YouTube channel:

- ❖ EQA for ISCN
- ❖ Constitutional ISCN for beginners
- ❖ Acquired ISCN nomenclature for beginners
- ❖ ISCN for beginners
- ❖ ISCN 2020

Workshops

- ❖ ISCN workshops on Constitutional and/or Neoplasia ISCN in 2022 & 2023.
- ❖ A further ISCN workshop is planned for September 2023 in Amsterdam.

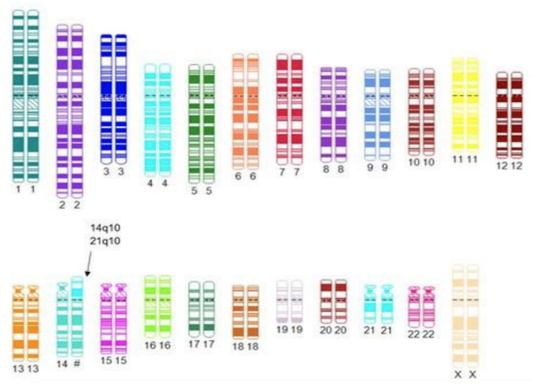
GENie

This is an online training and competency tool in genomics for individuals. GENie is modular and allows individuals to select which area of genomics they need to evidence their competence. A new module on ISCN competency will be available in late Autumn 2023.

CyDAS

Some ISCN errors occur because the rearrangement is incorrectly described. Although CyDAS is based on ISCN 1995, it is still a useful tool to check whether the nomenclature used describes the rearrangement seen on G-banding. By entering the chromosome breakpoints, a karyogram is produced (see below) that should reflect what was seen (www.cydas.org). The ISCN can then be updated to reflect the rules within ISCN 2020[b].

Fig 2. 46,XX,der(14;21)(q10;q10) ideogram created via CyDAS



EQA

Several EQA providers include ISCN in their assessments and/or have a specific ISCN EQA

Acknowledgements: The authors would like to thank the ISCN SC, OGM working group, Genomics community for providing valuable suggestions for inclusion in ISCN 2024.

Conflicts of interest: Dr Ros Hastings is both a consultant for GenQA and the ISCN SC Chair.

References

a. McGowan-Jordan, J., Hastings, R.J., Moore, S. (2020). ISCN 2020: An International System for Human Cytogenomic Nomenclature. DOI: 10.1159/isbn.978-3-318-06867-2. S. Karger, Basel. Also https://iscn.karger.com/Reporting guidelines

b. Deans, Z.C., Ahn, J.W., Carreira, I.M., Dequeker,E., Henderson, M., Lovrecic, L., Õunap, K., Tabiner, M., Treachy, R., van Asperen, C.J.(2022). Recommendations for reporting results of diagnostic genomic testing. Eur. J. Hum. Genet. 30:1011-1016. doi: 10.1038/s41431-022-01091-0

Conclusion

ISCN 2024 will include a full revision of the nomenclature for consistency and incorporate the new ogm nomenclature. It is advised that the text of the report refers to ISCN 2024. If a follow up samples was reported using an earlier version of ISCN it is helpful to inform the clinician if the ISCN string for the same structural abnormality has changed[b] *e.g.,* 46,XX,inv(9)(p23p22) when previously it had been 46,XX,inv(9)(p22p23) in ISCN 2016.

Presenting author:
Rosalind Hastings
Ros.hastings@genqa.org