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***E.C.A. Newsletter**

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Editor of the E.C.A. Newsletter:

Konstantin MILLER
Institute of Human Genetics
Hannover Medical School, Hannover, D
E-mail: miller.konstantin@mh-hannover.de

Editorial committee:

J.S. (Pat) HESLOP-HARRISON
Genetics and Genome Biology
University of Leicester, UK
E-mail: phh4@le.ac.uk

Kamlesh MADAN
Dept. of Clinical Genetics
Leiden Univ. Medical Center, Leiden, NL
E-mail: k.madan@lumc.nl

Mariano ROCCHI
President of the E.C.A.
Dip. di Biologia, Campus Universitario
Bari, I
E-mail: mariano.rocchi@uniba.it

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E.C.A. on Facebook

As mentioned in earlier Newsletters, E.C.A. is on Facebook.
You will find announcements of interesting articles, related to cytogenomics or to biology in general, and also pictures and stories from social events related to E.C.A. and its members. Also our E.C.A. conferences will be covered on Social Media.
You can see the weekly posts and announcements via the direct link

https://www.facebook.com/Cytogeneticists/ or on the updated E.C.A. website **http://www.e-c-a.eu/**

You will find a selection of interesting Facebook posts in this Newsletter starting at page 10.
Please contact us (mariano.rocchi@uniba.it) if you wish to share an interesting news item or a pertinent article.

President's Address

Dear Members of the ECA Community, Colleagues, and Friends

The 2025 European Cytogenomics Conference which will take place at KU Leuven, 29 June to 1 July 2025. This is the most important event of the ECA, when we get together every two years. As President of the ECA, it is both my honor and privilege to invite you to join us in Leuven.

The conference aims to bridge the fundamental knowledge of classical cytogenetics with the most recent technical innovations, such as the massive, high-fidelity sequencing.

There are diverse sessions during the conference on the latest research, such as, on the relationship between disease and structural variation and disease and nuclear organisation. These are, of course, in addition to the regular features on the up-to-date developments in Clinical Cytogenomics, Cancer Genomics, Prenatal Diagnosis, Animal and Plant Cytogenomics etc. The details of the program and names of the invited speakers will soon appear on the website.

The conference aims to promote exchange of ideas and experiences; we invite all participants to submit abstracts of their research as posters. Some of these will be selected for oral presentations in the various conference sessions or as short presentations in the Permanent Working Groups. It will be an opportunity to strengthen our community and establish new collaborations.

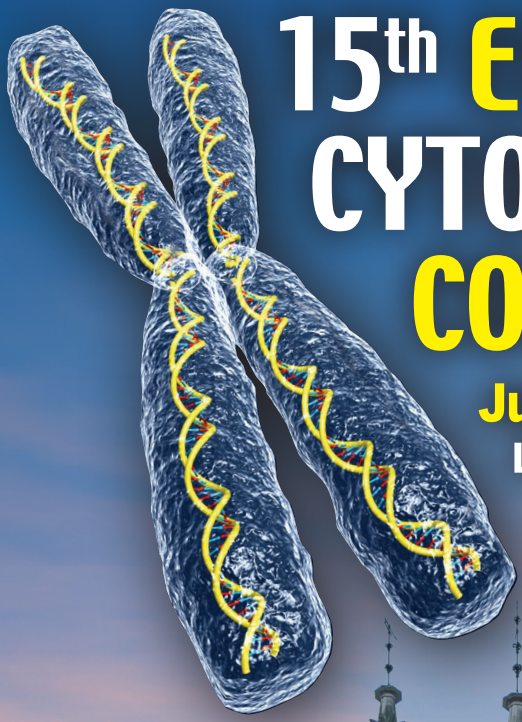
We are very pleased to host the congress at KU Leuven, an institution that has stood at the forefront of European academia for six centuries. Incidentally, KU Leuven will be celebrating its 600th anniversary in 2025; the celebrations will be taking place in various forms throughout the year. A good time to visit Leuven!

I look forward to welcoming you in Leuven,

Kind regards,

Mariano Rocchi
E.C.A. President

European Cytogeneticists Association



15th EUROPEAN CYTOGENOMICS CONFERENCE

June 29-July 1, 2025

LEUVEN, BELGIUM

www.eca2025.org

European Cytogeneticists Association

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ECA 2025 - The 15th European Cytogenomics Conference will take place in **Leuven, Belgium** on **June 29 - July 1, 2025.** Please save the date!

Innovative Format

We are evolving the conference format to include a series of pre-conference workshops designed to provide hands-on experience and in-depth knowledge on specialized topics.

Program Highlights

Several eminent scientists have agreed to contribute their expertise in various fields of cytogenomics, complemented by presentations in developing areas.

The meeting covers all aspects of chromosome and genome biology as well as clinical cytogenomics. The scientific sessions cover **technological advances** in long and short read sequencing, in situ sequencing, methylation analysis, multi-omics, single cell omics, cfDNA analyses; **fundamental aspects of genome biology** including centromere organization and evolution; **telomeres and genome aging,** animal and plant cytogenomics, structural variation, chromatin structure, the origins and evolution of aneuploidy in cancers and chromosomal disease mechanisms; **microplastic genome toxicity; clinical progress** including constitutional and acquired cytogenetics; preimplantation and prenatal diagnosis; **AI in cytogenomics and medicine.**

Permanent Working Group workshops will include presentations on topical issues, large project outcomes, and introductions to cytogenomic websites and databases.

Participants are invited to present their findings as posters some of which will be selected for presentation during the conference sessions and workshops. There will be many opportunities for early-career scientists to make presentations and be involved in discussions.

Registration

Registration details and early bird discounts are available on our conference website. Be sure to secure your spot early to take advantage of these offers.

We look forward to welcoming you to the **15th European Cytogenomics Conference** in Leuven!

For more information, visit our conference website **www.eca2025.org**

For any inquiries, please contact the conference organizing secretariat at **eca2025@eca2025.org**

ISCN 2024: A review of some of the changes and improvements

Ros Hastings and Nicole Chia
ISCN Chair and Vice-Chair
Oxford, UK and Brisbane, Australia

Summary
The ISCN 2024 edition represents one of the most significant reviews of the nomenclature to provide a more user-friendly nomenclature with improved consistency across the different cytogenomic techniques. Consequently, new chapters on generic ISCN rules (Chapter 4) and genome mapping (Chapter 9) are introduced.
To assist laboratories in the transition and implementation of ISCN 2024 to describe cytogenomic findings, this report highlights some of the major changes. Due to the major restructuring of ISCN 2024, it was not possible to highlight the changes in the margins of the book. The changes and improvements are provided in detail in Chia *et al*., 2025 (manuscript submitted). ISCN 2024 is available (https://iscn.karger.com) either as book plus online or as online only.

Introduction
ISCN was first published in 1971 and further versions have been introduced subsequently every 4-5 years. The ISCN Standing Committee (ISCN SC) considered feedback and inconsistencies or ambiguity in nomenclature that were identified through the ISCN forum (www.ISCN.karger.com), diagnostic and research laboratories and Quality Assurance programs globally (College of American Pathologists, CAP, Genomic Quality Assessment, GenQA, Royal College of Pathologists of Australasia Quality Assurance Program, RCPAQAP and Australian Society of Diagnostic Genomics Quality Assurance Program, ASDGQAP). The ISCN SC is aware that it is essential that ISCN maintains its clinical relevance and is representative of current trends, changes in technologies as well as the increased complexity of results detected by cytogenomic techniques. Consequently, a major review was agreed involving the restructuring of the ISCN 2020 chapters and the text, so the nomenclature is more user-friendly, the rules are more evident, and any outdated text removed or updated.

It is a requirement designated by the International Standing Committee, External Quality Assessment (EQA) providers (referred to as Proficiency Testing [PT] in the USA), national accreditation governing bodies and professional examination boards that the current version of the ISCN is used. The transition period for the adoption of ISCN 2024 will vary between the different bodies and it is advisable to check the deadline beforehand.

Overview of changes in ISCN 2024
ISCN 2024 consists of 16 chapters and each chapter has a list of contents of the main sections and subsections, vastly improving the search capability within the online and hardcopy versions of ISCN 2024. This ISCN edition has been reformatted with consolidation and re-positioning of sections. The ISCN SC has removed the chapter on meiotic chromosomes in ISCN 2024 due to the lack of applicability diagnostically. The changes specific to individual chapters are detailed below.

- **Chapter 1 Historical Introduction** has been summarised and includes the significant events in the field of cytogenomic nomenclature.
- **Chapter 2 Normal Chromosomes** merges the previously separate chapters in ISCN 2020 on 'Normal Chromosomes' and 'Normal Variable Chromosome Features'. A new section on euchromatic variants and subsection on copy number variants and structural variants has been included. The subsection on the 'molecular Basis of Banding' and the idiograms are relocated to the Appendix (Chapter 15).
- **Chapter 3 Symbols and Abbreviated Terms** has been updated and includes some new abbreviations.
- **Chapter 4 General Rules** incorporates all the generic rules including uncertainty in chromosome band or band designation, order of cytogenetic abnormalities, plus improved rules for mosaics, chimeras and clones. The general principles table has been extended to

include additional principles. To improve communication and discussion of the rules and relevant examples within the nomenclature, the ISCN SC introduced alphabetical annotation of rules and principles and Roman numerals numbering of all examples within each chapter.

In order to standardise and improve consistency of cytogenomic nomenclature reporting from different technologies, the following changes have also been implemented:

(a) No spaces given in ISCN except
  - Between the technique/genome build and the result *e.g.,* rsa (X,Y)×1, (13,18,21)×2 and arr (13)×3
  - Between symbols or abbreviations *e.g.,* psu dic
  - Before and after the abbreviations, con, sep, or, mos and chi

(b) Use of the rsa nomenclature for targeted analysis where only a specific chromosome or chromosome region is analysed

(c) When the size of unrelated clones/cell lines is the same and the complexity of related clones is equivalent, four simple rules can now be applied sequentially to ascertain the cell line/clone order in the ISCN.

Although the Karyotype and Microarray formats were described in ISCN 2020, the different systems were not entirely transparent. This has been rectified in Chapter 4, Section 4.7 where examples for the different technologies are given for each system within the Karyotype and Microarray formats:

(a) Karyotype format includes the Abbreviated, Short and Detailed Systems
  - Abbreviated system *e.g.,* ish 7(D7Z1)×1[15]/7(D7Z1)×2[20]
  - Short system *e.g.,* 46,XX,del(5)(q13)
  - Detailed system *e.g.,* 46,XX,del(5)(pter→q13:)

(b) Microarray format includes the Abbreviated, Short and Extended Systems
  - Abbreviated system *e.g.,* arr (18)x3
  - Short system e.g., arr[GRCh38] 18p11.32q23(102,328_79,093,443)×3
  - Extended system *e.g.,* arr[GRCh38] 22q11.2(18889117×2,18929329_21113 70×1,21116218×2)

Where clarity of the sex complement is required, the normal sex chromosome may be listed in arr and ogm nomenclature.

- **Chapter 5 Karyotype** incorporates part of chapter 8 'Numerical Chromosome Abnormalities' and Chapter 9 from ISCN 2020. This chapter includes the description of normal results, numerical abnormalities, structural abnormalities and specification of structural rearrangement for conventional cytogenomic findings. To reduce the risk of misinterpretation and improve clarity, some of the previous ISCN example descriptions have been reworded. One significant change to the nomenclature is for normal results where the gender is not to be disclosed: the new abbreviation '**U**' may be applied, *e.g.*, 46,U,+21. A new section to describe complex insertions (Section 5.5.9.3) is provided. Finally in order to provide clarity on the appropriate application of the abbreviations '**der**' and '**rec**' in the ISCN, a new Recombinant Chromosomes section has been added (Section 5.5.15).
- **Chapter 6 Neoplasia** has been restructured to provide more clarity in the application of rules and to reduce ambiguity *e.g.*, the order of chromosome abnormalities (Section 6.3.2) and order of clones (Section 6.3.3). Other changes include:
  (a) New figures to illustrate divergent clonal evolution and clonal evolution in cytogenetically unrelated stem lines with associated karyotype ISCN (Section 6.3.4)
  (b) Provision of more composite examples
  (c) Clarification that the band location of a rearrangement given in the ISCN represents the resolution seen *i.e.,* the rearrangement band location is not adjusted to the reflect the gene location
  (d) Clarification of previously conflicting rules: chromosome **gain** is reported before **loss** for the same chromosome in different clones/cell lines (Section 4.2, Table 3; Section 6.3.3)
  e.g., 45~48,XY,+15,–15,del(17)(p11.2)[cp8]

(e) An additional table (Table 8) with different karyotype abnormalities and their associated abnormality count has been included in Section 6.5 to demonstrate the application of counting clonal chromosome abnormalities (Table 7).

- **Chapter 7 *In situ* Hybridization**
  An improvement to this chapter is the addition of a section on the general principles and rules that are applicable to both metaphase and interphase *in situ* hybridization (see Section 7.1.1) plus separate sections for the specific rules that apply either to metaphase FISH (**ish**) or interphase FISH (**nuc ish**). The *in situ* hybridization sections on extended chromatin, reverse ish and chromosome analysis of microdissected chromosomes present in ISCN 2020 have been removed in the latest version of ISCN (2024).
  Some of the rules detailed in the general principle section include:
  (a) The listing of probes in the ISCN description of *in situ* hybridization has been simplified to include only the identifiers and lists them in order of preference as STS marker name (D-number or BAC Clone), gene symbol, or probe manufacturer's name for region or loci/locus
  (b) The normal control probe may be included when additional information is gained from its inclusion *e.g.,* for sex determination or for the differentiation of an interstitial or terminal deletion
  (c) Non-tandem duplications in metaphase *in situ* hybridization are given as two separate **single plus** (+) signs separated by a comma whereas tandem duplications are indicated by a **double plus** (++) sign following the probe
  (d) The rule for the order of probes when a multi-probe assay is undertaken is: telomere probe is designated as most terminal, then whole chromosome paints, followed by the subtelomere probe (Section 7.2.1)
  (e) The subtelomeric metaphase *in situ* hybridization section has been expanded with subsections for normal and abnormal signal patterns (see Section 7.2.6)
  (f) The multicolor chromosome paint and partial chromosome paint nomenclature sections have been integrated into the metaphase FISH section (Sections 7.2.7 and 7.2.8)

  There are new sections for mosaic and chimeric signal patterns (Section 7.4) and multiple copies in the same gene in neoplasia (Section 7.6) which include both metaphase (**ish**) and interphase (**nuc ish**) examples.
  The ISCN description for interphase *in situ* hybridization has been simplified and standardized with new examples and figures:
  (a) Only a short system nomenclature is provided as the detailed system has been removed (Section 7.3.2)
  (b) The nomenclature for multiple probe kits has been standardised so the probes are listed according to the separate hybridisations whether or not there is a normal or abnormal signal patterns (Section 7.3.2 viii)
  (c) The use of the **multiplication** (×) sign in ISCN has been made consistent with metaphase FISH and other technologies *e.g.,* rsa.
    - The **multiplication** (×) sign is given outside the parenthesis if the signal patterns are the same for all the probes within a hybridization *e.g.,* nuc ish (ABL1,BCR)×2(ABL1 con BCR)×1 [100] and nuc ish (3'IGH×2,5'IGH×3) (3'IGH con 5'IGH)×1[210/237]
    - If the signal patterns for each probe are different then the **multiplication** (×) sign is given inside the parenthesis for each probe (no change to ISCN 2020)
  (d) Clarification of the interphase FISH rules for the order of cell lines and clones are given in Section 7.3.3.1
  (e) The Relative Position of Signals section (Section 7.3.4) has been reorganised into subsections for Adjacent, Dual Fusion, Breakapart and Tricolor probes with examples of normal and abnormal signal patterns.
- **Chapter 8 Microarray** has more nomenclature examples for reporting chimeras, complete moles and partial moles (Section 8.2.6) and complex results (section 8.2.7). The Nomenclature Specific to SNP Microarrays Section (Section 8.2.6) introduces new

abbreviations **umat** and **upat** to describe whole/segmental uniparental disomy where the parent of origin has been determined. Section 8.2.7 includes an example for reporting a complex result in a tabular format and under the chromoanagenesis subsection (Section 8.2.7.1), plus a diagram depicting the underlying mechanism of chromoplexy, chromothripsis and chromoanasynthesis (Figure 10) (Zepeda-Mendoza and Morton, 2019). Finally, when the copy number cannot be determined or is too large to enumerate then a **question mark** in **square brackets** (**[?]**) can be used instead of a range.

e.g., arr[GRCh38] 2p24.3(15,911,477_ 15, 976,076)amp[?],(8)×2~3[0.8],(22)×4[0.8]

- **Chapter 9 Genome Mapping** is a new chapter detailing the nomenclature used to describe findings from genome mapping technologies and is platform agnostic so it can be used for either optical genome mapping or electronic genome mapping (ISCN 2024, Moore et al., 2023). The results can either be given using the karyotype or microarray format (see Section 9.3) depending on whether the nature of the rearrangement is apparent.
  (a) The karyotype format can be used where the nature of the structural rearrangement has been defined. The karyotype format describes the structural abnormality *e.g.,* **del**, **dup**, **inv**, the chromosome breakpoints and nucleotides but does not include the copy number
  (b) The microarray format is applied to describe the chromosome breakpoints and nucleotides and includes the copy number.
  (c) Depending on the abnormalities present, a combination of karyotype and microarray format can be used in an ISCN description, however only one format can be used to describe different aberrations of a single chromosome.
- **Chapter 10 Region-Specific Assays (RSA)** has been expanded to include more targeted investigations as requested by diagnostic centres. This is a practical addition to the ISCN and is used to describe the findings of targeted analysis performed for a specific aneuploidy, known rearrangement, copy number change or methylation pattern and can be found in the following sections:
  - Chromosome analysis (Sections 10.2.1 and 10.3),
  - Microarray (Sections 10.3 and 10.4),
  - Partial gain or loss (Section 10.4),
  - Balanced translocations and fusion genes (Sections 10.2.2 and 10.5),
  - Expansion repeats (Section 10.6)
  - Methylation specific MLPA (ms-MLPA) for imprinting investigation (Sections 10.2.3 and 10.7).

  In addition, examples for complete and partial moles have been added to Section 10.3.2 plus targeted microarray analysis for known copy number variation *e.g.,* family studies, have been included in Section 10.4.2.

  The nomenclature for describing the findings from the targeted analysis of fusion genes has also changed so it is harmonized with the ISCN description for other technologies (Section 10.5).
  (a) The use of the **double colon** (**::**) applies where there is evidence of fusion or juxtaposition of genes (Section 10.2.2). This replaces the use of the abbreviations 'neg' and 'pos' in ISCN 2020.
  (b) For normal findings, no evidence of fusion or juxtaposition, the gene loci are listed in numerical order separated by a **comma** (**,**) (Section 10.5.1) *e.g.,* rsa (ABL1,BCR)×2
  (c) For abnormal results the active oncogene fusion is listed (Section 10.5.2) *e.g.,* rsa (BCR::ABL1)×1

  The nomenclature for targeted investigation of methylation disorders using methylation-specific ms-MLPA technology includes a new acronym, '**rsa-ms**', at the beginning of the ISCN description plus new abbreviations to describe the patterns of methylation: normal methylation pattern (**met**), absence of methylation (**lom**) and gain of methylation (**gom**).
- **Chapter 11 Sequencing** has been expanded to include more examples and specific principles to provide more constructive information on the use of ISCN and HGVS (Section 10.2.1). The ISCN examples are applicable to different platforms and bioinformatic algorithms, aneuploidy, level of complexity and mosaicism and the text states whether either the ISCN and HGVS nomenclature should be used together, either

can be used or where ISCN alone is more informative to describe the structural aberrations and copy number variants.

- **Chapters 12 Breakage and Instability; 13 References** and **14 Members of the Standing Committee** have been updated**.** In Chapter 12, a new abbreviation for multiradial, (**mr**) is included.
- **Chapter 15 Appendix** now includes three sections from Chapter 2 (ISCN 2020): Molecular Basis of Banding, Chromosome Banding and the idiograms. The idiograms, G-banded and R-banded karyograms are hopefully easier now to find and compare.

Educational Platforms

The online version of the current and previous versions of ISCN are available on https://iscn.karger.com Once logged in, the genomics community can access the forum where ISCN queries or feedback suggestions for changes to ISCN can be submitted. The forum is for ISCN related queries only.

Several webinars and education platforms are also available to help centres learn the differences between ISCN 2020 and ISCN 2024 and assist in the adoption of ISCN 2024 into the diagnostic service. Many Global and National External Quality Assessment (EQA) providers assess ISCN within their EQAs and give feedback on common misconceptions/errors. One EQA provider (GenQA) has a specific ISCN EQA for the different cytogenomic technologies. In addition, there are webinars on ISCN 2024 available on the ASHG and GenQA websites (https://www.ashg.org/?s=ISCN and www.youtube.com/channel/UCVOthv312-ZFkPK9M4pu7mQ respectively), as well as presentations from the ISCN SC at the Cancer Genomics Consortium (CGC) and other National conferences including an ISCN workshop at the next ECA meeting delivered by Prof Jean-Michel Dupont. Finally, there is a modular online competency tool, GENie (htpps://www.genqa.org/genie) available for ISCN 2024. A module for basic level constitutional karyotyping is currently available and other modules for the different chapters of ISCN 2024 are currently under development (personal communication Prof Sandi Deans). Each ISCN module will have three levels, basic, advanced and complex.

Conclusion

The ISCN SC has undertaken a most significant review of the nomenclature resulting in the publication of ISCN 2024. It is hoped that the genomics community will encompass the changes to the formatting and content of the chapters and find the search capabilities enhanced with increased transparency of the nomenclature principles and rules. A fundamental change within the current version is the standardization of the ISCN across the different genomic applications and technologies. The aim to provide consistency of the ISCN description and minimise ambiguity and misinterpretation. It is highly recommended that users carefully review the ISCN 2024 to familiarize themselves with all the nomenclature changes across the different chapters.

Acknowledgments

All ISCN examples are given with permission from Karger who own the copyright.

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Paris Conference (1971): Standardization in Human Cytogenetics. Birth Defects: Original Article Series, Vol 8, No 7 (The National Foundation, New York 1972); also in Cytogenetics 11:313–362 (1972).

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Literature on Social Media

E.C.A. is now also present on Social Media. Here are announcements of interesting articles that we have posted on Facebook. The articles and news items are related to cytogenomics or to biology in general. If you have relevant articles that you would like to share, please contact mariano.rocchi@uniba.it.

ICE AGE CYTOGENOMICS: UNVEILING ANCIENT CHROMOSOME MYSTERIES

An innovative technique has recovered intact DNA from a 52,000-year-old woolly mammoth preserved in Siberian permafrost, marking a significant milestone in paleogenomics. Researchers discovered fossilized chromosomes from ear tissue and reconstructed them, revealing the genome's organization with unprecedented resolution. Using the Hi-C technique adapted for degraded DNA, they assembled 28 chromosome-length scaffolds, uncovering preserved chromosome territories, compartments, loops, Barr bodies, and inactive X chromosome (Xi) superdomains.

Published in Cell (1), the study showed that the genome compartments in mammoth skin resemble those in Asian elephant skin, providing insights into gene activity and repression at the mammoth's death. They identified about 1,000 sites with differential activity, including genes related to growth, immune adaptation, and cold tolerance.

Notably, the authors speculate that the DNA was preserved over millennia in a glass-like substance called chromoglass. This raises questions about the long-term durability of genetic material under specific conditions. The discovery points to promising future applications for PaleoHi-C in examining a wide range of biological materials.

[1] https://www.cell.com/cell/fulltext/S0092-8674(24)00642-1

BDELLOID ROTIFERS, AN EVOLUTIONARY PUZZLE

Bdelloid rotifers are a class of rotifers that reproduce exclusively through parthenogenesis, meaning females produce offspring without fertilization by males. Typically, mutations and sexual reproduction generate variability essential for surviving in an ever-changing environment. In this regard, bdelloid rotifers are considered an "evolutionary scandal." Recently, some answers to this puzzle have emerged. These microscopic animals gain diversity by stealing genes from other organisms through horizontal gene transfer, including genes from bacteria. In a paper titled “Bdelloid rotifers deploy horizontally acquired biosynthetic genes against a fungal pathogen” in Nature Communications, Nowell et al. report a paradigmatic example.

The paper has an intriguing tale. The reported results suggest that bdelloid rotifers may be a promising source of new antimicrobial compounds. Traditionally, the search for antimicrobials has focused on bacteria and fungi, but many potential compounds are often toxic to animal cells. Bdelloid rotifers, however, appear to have spent millions of years (~40) acquiring antimicrobial synthesis capabilities from various life forms and adapting them for use in animal cells to defend against bacteria and fungi. Therefore, studying the secondary metabolome of bdelloid rotifers could be highly valuable in discovering new antimicrobial agents for treating animal infections.

[1] https://www.nature.com/articles/s41467-024-49919-1

WHY CHILDBIRTH IS PROBLEMATIC IN HUMANS

In humans, during birth, the large head of the fetus must pass and rotate through a relatively small, rigid, and twisted birth canal, making childbirth a lengthy and risky process. This is not the case for other mammals, some of which have neonates that are proportionally larger than human babies relative to the size of the maternal birth canal. The unique situation in humans arose, during evolution, as a trade-off between the need

for an efficient delivery, and the strong constraints imposed by an upright posture. An upright posture requires a rigid pelvis to support the fetus and to enable efficient bipedalism.
These concepts are well explored in an article which appeared in Am J Obstet Gynecol (1).
As Dobzhansky famously stated: Nothing in biology makes sense except in the light of evolution!

[1] https://www.ajog.org/article/S0002-9378(22)00733-5/fulltext

CELL BIOLOGY TRACING MEIOTIC ERRORS IN LIVE OOCYTES

Chromosome segregation errors in oocytes lead to aneuploidy in eggs, a major cause of miscarriage and congenital disease. Errors are more likely to occur with age, especially with smaller chromosomes, but the reasons for this pattern are poorly understood. Takenouchi et al. (1) estab lished a method to identify and track targeted chromosomes throughout meiosis in live mouse oocytes. This method revealed that smaller chromosomes actively move toward the inner region of the spindle equator, creating a chromosome size–based spatial arrangement on the metaphase plate. Inner positioning of smaller chromosomes increases the risk of their premature separation, a hallmark of aging-associated errors in oocytes.

[1]https://www.science.org/doi/10.1126/science.adn5529

TANDEM REPEATS AND PHENOTYPIC VARIATION

Microsatellites and minisatellites naturally bring to mind forensic genetics or diseases caused by their expansion. Their variability stems from their inherent propensity for changes, far more frequent than point mutations. In a review article in TIG, D.G. King (1) examines them from a different perspective, as indicated by the title of the first paragraph: “Tandem repeat polymorphisms influence phenotypic variation”. We are in the realm of evolvability. The impact of tandem repeat variations may be subtle on their own. However, when acting together, their significance can become substantial. The authors draw a comparison: "Just as tuning knobs offer musical instruments fine, reversible adjustments, tandem repeats similarly provide a rich foundation for reversible, incremental mutation effects."
A similar article has been published by Lamkin and Gymrek in Nature Review Genetics (2).
These two papers highlight a crucial point regarding "missing heritability" in Genome-wide association studies (GWAS), specifically noting the absence of tandem repeat variation. They stress that this variability must be considered, especially given its direct role in phenotypic variation.

[1] https://www.cell.com/trends/genetics/abstract/S0168-9525(24)00175-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952524001756%3Fshowall%3Dtrue
[2] https://www.nature.com/articles/s41576-024-00736-8

GENES THAT INFLUENCE MENOPAUSE AGE

Genome-wide association studies (GWAS) are based on common SNP variants. However, recent papers have highlighted some limitations, for example, the exclusion of tandem repeat variants, which are a significant source of phenotypic variation, from arrays (1, 2). Another inherent bias in GWAS is the absence of rare variants on the genotyping arrays.
GWAS have identified genes involved in age at menopause, but these have explained only a small portion of the large variation observed in the general population of women. In contrast, two recent studies (3, 4) have focused on rare variants and genes that account for much larger variations. For example, women homozygous for a stop-gain variant in CCDC201 experience menopause 9 years earlier than other women (4). Another key gene is ZNF518A, which is involved in DNA repair. Unsurprisingly children of mothers with

these variants have a higher mutation load, and the gene is also implicated in tumorigenesis. Summaries or News & Views commentaries on the two papers are available. (5).

[1] https://www.cell.com/trends/genetics/abstract/S0168-9525(24)00175-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952524001756%3Fshowall%3Dtrue
[2] https://www.nature.com/articles/s41576-024-00736-8
[3] https://www.nature.com/articles/s41586-024-07931-x
[4] https://www.nature.com/articles/s41588-024-01885-6
[5] Nature | Vol 633 | 19 September 2024

MANAGEMENT OF SECONDARY FINDINGS IN DNA SEQUENCING

Secondary findings in DNA sequencing carried out for a specific clinical indication can significantly affect the patient's health. In an article in Am J Hum Genet[1], Majeed et al. systematically review the existing international policies for the management of such secondary findings.

[1] https://www.ncbi.nlm.nih.gov/pubmed/39299240

SEXUAL DIMORPHISM AND DIFFERENCES IN NATURAL SELECTION IN THE TWO SEXES

Many animals exhibit physical differences based on their sex—a phenomenon known as sexual dimorphism, which is driven by distinct selective pressures. Studying the forces that shape this dimorphism is particularly challenging, as traditional methods for documenting natural selection often fall short. A paper in PNAS (1) tackles this issue using a "real-time" approach, leveraging data from the UK Biobank. The authors found evidence of a life history tradeoff between survival and fecundity, with opposing effects on males and females. Their concluding remark suggests that "sex-differential selection may be an inevitable consequence of reproduction involving separate sexes."
In 1871 Darwin, in his book The Descent of Man and Selection in Relation to Sex, proposed that male and female differences arise from sexual selection, with males often evolving traits that enhance their reproductive success (fitness) through competition or attractiveness, while females prioritize traits that improve survival and care for offspring.

[1] https://www.ncbi.nlm.nih.gov/pubmed/39302970

MEASURING X INACTIVATION SKEW FOR X-LINKED DISEASES

The phenotypic expression of X-linked diseases in females heterozygous for a deleterious variant is highly variable and may be attributed to allelic skew in X-chromosome inactivation. Gocuk et al. (1) introduced a novel approach using nanopore sequencing to accurately quantify skewed X inactivation. They tested this method on two ocular X-linked diseases by sequencing three distinct tissues—blood, saliva, and buccal mucosa—since the retina is not accessible for such analysis. Their findings revealed a strong correlation between X inactivation skew and disease manifestation. The authors state that this method is applicable to all X-linked diseases.

[1]https://genome.cshlp.org/content/early/2024/09/13/gr.279396.124

HUMAN-SPECIFIC CHILDBIRTH PROBLEMS

The challenges in human childbirth are the result of three main factors: (i) the evolution of upright posture and bipedalism, which require a narrow pelvis for efficient locomotion; (ii) the fetus needs a narrow pelvis to be adequately supported; and (iii) the human head has grown significantly larger over time. Natural selection has favored a shorter gestation period, soft skull bones at birth, and brain development after birth. Nevertheless, the problems persist. Mitteroecker and Fischer further examined these concepts in a study published in Am. J. Obstet. Gynecol. (1), where they support this perspective by comparing humans with our closest relatives, the great apes. The recent paper by Pink et al. (2) addresses the same topic, expanding the analysis to include a selection of New World and Old World monkeys,

as well as lesser apes. They focus particularly on the Japanese macaque (Macaca fuscata) because, as in humans, the fetal head is large in relation to the birth canal. The lack of delivery complications (such as fetal or maternal death) in macaques can be attributed to the flexibility of the pelvis, which in humans is constrained by the upright posture. These findings are consistent with the conclusions of Mitteroecker and Fischer (1).

[1] https://www.ncbi.nlm.nih.gov/pubmed/38462258
[2] https://www.ncbi.nlm.nih.gov/pubmed/39374390

AMYLASE GENE COPY NUMBER VARIATION

Background. The first reports of Copy Number Variations (CNVs) using Comparative Genome Hybridization on microarrays were published in 2004, based on BAC/PAC DNA (Nat Genet 36:949-51, 2004; Science 305:525-528, 2004). Soon after, oligo-microarrays replaced BAC/PAC arrays. In 2006, the Sanger Centre conducted a large-scale array study (Nature 444:444-454, 2006) that revealed significant CNV variation in the amylase gene (AMY1), which is expressed in the salivary glands and plays a role in starch digestion. This discovery drew attention, and in the following year they published a study titled "Diet and evolution of human amylase gene copy number variation" (Nat Genet 39:1256-1260, 2007). The study compared populations with high-starch diets to those with low-starch diets, and found that individuals from high-starch populations had significantly more AMY1 copies on average than those from low-starch populations. Their results suggest that diet-related selection pressures influenced AMY1 copy number variation. No variation was observed in chimpanzees.

Recently, Bolognini et al. (1, 2) revisited these findings by analyzing the domain (chr. 1p21.1) containing AMY1 (expressed in salivary glands), and AMY2A/AMY2B genes (expressed in pancreas) at the sequence level across various human populations, including 533 ancient DNA samples, three Neanderthals and one Denisovan. By examining the linkage disequilibrium in these regions, they were able to distinguish different haplotypes, which allowed them to trace the evolutionary history of these genes. Their findings suggest that the advent of agriculture, around 12,000 years ago, with its starch-rich diet (primarily cereals), exerted selective pressure that favored the duplication of the AMY genes. Interestingly, no such duplications were observed in non-human primates or other animals, except for a few "commensal" species such as dogs, pigs, rats, and mice.

The Bolognini et al. paper was published in Nature, on October 17, 2024 (online on September 4). The next day, on October 18, a paper on the same subject was published by Yılmaz et al. in Science (3,4). The main difference is that Yılmaz et al. found duplications of AMY1 in three of the six Neanderthal genomes and in one Denisovan genome. They concluded that the gene duplication occurred before modern humans diverged from Neanderthals and Denisovans, approximately 800,000 years ago.

Another explanation for these findings in Neanderthals and Denisovans could be introgression—the transfer of genetic material through interbreeding. Non-African genomes contain several segments of DNA inherited from these ancient cousins, and the AMY1 gene could be part of these reciprocal exchanges.

Both papers, however, agree on the crucial role of agriculture in driving the more recent duplication of AMY genes in humans.

Incidentally: it's worth noting that the vitamin D-poor cereals-based diet played a crucial role in promoting lighter skin pigmentation.

[1] https://www.nature.com/articles/s41586-024-07911-1
[2] https://www.nature.com/articles/s41576-024-00782-2
[3] https://www.science.org/doi/10.1126/science.adn0609

EXTRA BLOOD IN PREGNANCY

Background.

In the beginning were the genes; the rest (representing the vast majority of the human genome) was junk DNA. The human genome sequencing project was not considered important, it was better to concentrate on genes! Slowly the

attitudes began to change. Then came the ENCODE project (2012), which showed that about 80% of the human genome does have a function, i.e., it is involved in gene regulation. For more on this, see Science's take at the time (1).

Duplicated transposable elements, thought of as 'junk DNA', are usually inactivated due to potential danger they can cause (disruption of genes…). However, evolution has a funny way of repurposing everything. Here is a latest example of this phenomenon.

During pregnancy, a growing baby requires a lot of extra blood—about 20% more. We know that this is partially achieved by hormonal action but that is not all.

A paper just published in Science (2) on October 24, 2024, fills the gap. When there is a need of an increased activity of hematopoietic stem cells as in pregnancy (or in cases of excessive bleeding), the hematopoietic machinery is activated by derepression of retrotransposons, including endogenous retroviruses and LINE elements.

Note. Under severe stress, some organisms actually let transposons loose as a "do or die" move—hoping that, alongside the harmful effects, something helpful might emerge. (Apologies for the anthropomorphism. That is the way evolution works).

[1] https://www.science.org/doi/full/10.1126/science.337.6099.1159

[2] https://www.science.org/content/article/pregnancy-wakes-viruslike-jumping-genes-help-make-extra-blood?utm_source=sfmc&utm_medium=email&utm_content=alert&utm_campaign=DailyLatestNews&et_rid=195247204&et_cid=5408080

THE HIGLY DUPLICATED AND HYPERVARIABLE TBC1D3 GENE

A recent post on amylase gene reported that in case of duplications of the gene, its expression is directly proportional to the gene copy number.

Genome Research just published a paper (1) on the highly duplicated and hypervariable TBC1D3 gene. Interestingly, its expression does not increase with copy number; in humans, one of the many copies is different from the others and it is human-specific. Worth a read!

[1] https://genome.cshlp.org/content/early/2024/11/01/gr.279299.124.long

INVERSION BREAKPOINTS RESOLVED USING LONG-READ GENOME SEQUENCING

The group of Anna Lindstrand focused in recent years on the study of chromosomal rearrangements, aiming to resolve derivative chromosomes at the breakpoint level using short-read genome sequencing (srGS) and, increasingly, long-read genome sequencing (lrGS).

In a paper published in Genome Res. (1), they report on twelve inversion carriers: nine analyzed using long-read genome sequencing (lrGS) and three cases where short-read genome sequencing (srGS) data were reanalyzed. By aligning both lrGS and srGS data to multiple reference genomes, nine inversions were resolved (9/12, 75%). Notably, in four cases, one inversion breakpoint was located in a genomic region missing from at least one of the human reference genomes (GRCh37, GRCh38, or T2T-CHM13), requiring a reference-agnostic analysis that included T2T-CHM13. In some instances, de novo assembly was also necessary, as long-read mapping alone was insufficient.

The clinical relevance of these findings is underscored by a case where an inversion disrupted EHMT1, resulting in a diagnosis of Kleefstra syndrome 1. The discovery that four inversions could only be mapped using specific reference genomes led us to investigate the presence and population frequencies of differential reference regions (DRRs) between T2T-CHM13, GRCh37, GRCh38, and the genomes of chimpanzees and bonobos. This investigation uncovered hundreds of megabases of DRRs.

Overall, the study highlights the critical role of reference genomes and the enhanced resolution that lrGS provides in the detection of structural variants.

[1] https://genome.cshlp.org/content/early/2024/10/30/gr.279346.124.long

EVOLUTION IN THE LAB

A study which appeared in Science (1) explores accelerating the evolution in the lab using an advanced system called OrthoRep, which enables continuous mutations of a selected gene, at a rate 1 million times higher than in nature, compressing millions of years of evolution into laboratory experiments.
The system can produce rapid and extensive genetic diversity, allowing the exploration of new biological functions and the study of the evolutionary mechanisms and forces that shape the structure and function of genes.
This paper brings to mind Richard Lenski and his long-term evolution experiment "in the bottle". The experiment began in 1988 with 12 identical populations of E. coli, which were cultured over thousands of generations in a controlled environment and freezing samples every 500 generations (two weeks). With the advent of high-throughput sequencing, Lenski was able to go back and trace the various mutations that had accumulated. A large number of studies have emerged from this experiment. One of the most famous outcomes of the experiment occurred in 2004, when one of the E. coli populations unexpectedly developed the ability to metabolize citrate. See the Science comment in 2013 (2)

[1] https://www.science.org/doi/10.1126/science.adm9073
[2] https://www.science.org/doi/10.1126/science.342.6160.790

BREAKPOINT RESOLUTION OF CHROMOSOMAL REARRANGEMENTS

Here is another paper that utilizes high-fidelity, long-read sequencing to characterize chromosomal rearrangements (1).
"Multiple breakpoints were localized to genomic regions previously recalcitrant to sequencing such as acrocentric p-arms, ribosomal DNA arrays, and telomeric repeats, and involved complex structures such as a deletion-inversion and interchromosomal dispersed duplications".

[1] https://www.cell.com/cms/10.1016/j.ajhg.2024.10.006/attachment/92a03bbb-42fb-41b5-9720-2709d7756cc1/mmc5.pdf

TANDEM REPEATS, LONG-READ SEQUENCING AND NEUROLOGICAL DISEASES

Various neurological diseases, as well as other conditions, are caused by increase in the number of tandem repeat (TR) copies (Huntington's chorea, myotonic dystrophy, fragile X syndrome…). Characterizing these expansions using short-read sequencing is challenging, as this method struggles with repetitive regions. Long-read sequencing technologies, however, are far more suitable for this task. To enhance the utility of these technologies, Zhang et al. (1) developed an algorithm called MotifScope to identify and characterize TRs more accurately.

[1] https://genome.cshlp.org/content/early/2024/11/13/gr.279278.124

SOMATIC MOSAICISM

It was once believed that our genome was identical across all cells. However, cytogenetics revealed that certain chromosomes can be lost, particularly with aging. The most commonly affected are the Y chromosome in males and the X chromosome in females.
With advancements in technology, especially single-cell characterization, it has become evident that mosaicism—variability in genetic content across cells—is not rare in normal tissues. Recently, two studies have explored this phenomenon: one examines the brain of individuals with schizophrenia (1), and the other investigates mosaicism in the placenta (2). A third study (3) offers a comprehensive review titled "*Mosaic variegated aneuploidy in development, aging, and cancer*."

[1] https://www.science.org/doi/10.1126/science.adq1456
[2] https://obgyn.onlinelibrary.wiley.com/doi/10.1002/pd.6680
[3] https://www.nature.com/articles/s41576-024-00762-6

CHROMOSOME FRAGMENTATION

Stephens et al. (1) introduced the term *chromothripsis* in their paper titled "*Massive genomic rearrangement acquired in a single catastrophic event during cancer development*." This phenomenon describes an abrupt, extensive fragmentation and rearrangement of chromo-somes. Since then, additional mechanisms of large-scale chromosomal reorganization have been identified, including chromoplexy, chromoanasynthesis, and chromoanagenesis, each arising from distinct molecular processes. These events are commonly observed in cancer due to the absence, in somatic cells, of the stringent constraints imposed by the delicate embryonic development. Two articles in *Science* explore the molecular mechanisms and specific genes associated with these complex rearrangements (2, 3), with a commentary offering further perspective (4).
Occasionally, such genomic shifts may drive significant evolutionary innovations, acting as mechanisms for rapid adaptation and diversification. This concept is supported by Vargas-Chávez et al. in their BioRxiv study, "*A punctuated burst of massive genomic rearrangements and the origin of non-marine annelids*" (5), which inspired a commentary in Science (6).

[1] https://www.cell.com/action/showPdf?pii=S0092-8674%2810%2901377-2
[2] https://www.science.org/doi/10.1126/science.adj7446?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[3] https://www.science.org/doi/10.1126/science.adj8691?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[4] https://www.science.org/doi/10.1126/science.adr7417
[5] https://www.biorxiv.org/content/10.1101/2024.05.16.594344v3
[6] https://www.science.org/content/article/earthworms-have-completely-scrambled-genomes-did-help-their-ancestors-leave-sea#:~:text=Scrambled%20genes,water%2C%20and%20then%20onto%20land.

WHY KLINEFELTER INDIVIDUALS ARE AZOOSPERMIC?

Klinefelter patients are azoospermic because their fetal germ cells (FGC) are arrested at an early stage. An article published recently in Nature (1) shows that the arrest is linked to the lack of X inactivation, resulting in an imbalance in gene expression. Genes related to pluripotency, the WNT pathway and the TGF-β pathway, are upregulated, while genes involved in FGC differentiation are downregulated.

[1] https://www.nature.com/articles/s41586-024-08104-6

NEW MUTATIONS PER GENERATION

In humans, the mutation rate per nucleotide per generation is approximately 1.59 times 10 to the negative eight that is ±48 mutations per genome per generation (1).
To address the inherent limitations in humans, López-Cortegano et al. (2) conducted experiments in mice. They used 12 inbred mouse lines derived from three commonly used inbred strains maintained for 8-15 generations in a "mutation accumulation" experiment. "Mutation accumulation" means that the lines are maintained under conditions that minimize selective pressure, often with a small number of individuals per generation. This reduces selection against deleterious mutations, enabling their accumulation. Individuals are propagated over many generations, during which new mutations accumulate.
In this way they were able to calculate:

- Single nucleotide mutations (~20 per haploid genome/generation).
- Insertions and deletions (~24.4 per genome/generation).
- Structural mutations (~1 per genome/generation).

These mutations are favored by repetitive DNA sequences (insertions, deletions, and contractions/expansions); microsatellite instability (90% of indels); insertion of transposable elements (they also mediate structural mutations); nonallelic homologous recombination (usually triggered by interspersed repeats or by transposable elements); methylated CpG sites (favoring C→T transitions).

[1] https://www.cell.com/ajhg/fulltext/S0002-9297(22)00065-9?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002929722000659%3Fshowall%3Dtrue
[2]https://genome.cshlp.org/content/early/2024/12/02/gr.279982.124

GENETIC SCREENINGS IN DIFFERENT POPULATIONS

Which genetic screenings would be useful? It depends on the population being examined, as different genetic diseases have varying frequencies. The study by Schmitz et al. (1) aims to answer the question.
From the paper: "Genomic data from over 700,000 individuals of eight ancestries in the Genome Aggregation Database (gnomAD) v.4.1.0 is utilized to estimate the frequency of genetic variants that could increase the risk of recessive conditions in the offspring. These findings provide insights for optimizing reproductive carrier screening strategies in different ancestries".

[1] https://www.cell.com/ajhg/abstract/S0002-9297(24)00413-0?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002929724004130%3Fshowall%3Dtrue

THE IMMORTAL (like Highlander)

You may have heard of the Hydra (Hydrozoa) as one of the few organisms often described as "immortal," making it a fascinating focus for research on aging. A recent study by Sahm et al. (1) sheds light on this intriguing creature.
Notably, Hydra's so-called "immortality" has been observed only in an individual taken into the lab in 1973 and maintained under controlled conditions. Thanks to its high stem cell turnover and exceptional regenerative abilities, it has shown no signs of aging in this environment. However, the story is quite different in nature, where Hydra faces significant external threats, including predation and environmental stress, limiting its lifespan to just a few weeks. This indicates that its extraordinary longevity in the lab is not an adaptation for survival in the wild but rather a consequence of idealized conditions.
The study also challenges the theory that aging is primarily driven by the accumulation of somatic mutations. Interestingly, Hydra exhibits a mutation rate slightly higher than that of humans, raising questions about the assumed link between low mutation rates and longevity. On the contrary, these mutations may have contributed to Hydra's adaptability. The authors were able to show that some mutations have undergone strong positive selection since its cultivation began 50 years ago.
Lastly, it's worth noting that lab-maintained Hydra reproduce asexually, whereas in the wild, Hydra switches to sexual reproduction under stressful conditions.

[1]https://genome.cshlp.org/content/early/2024/12/04/gr.279025.124

A SINGLE MUTATION IS ENOUGH

The title of this article, published in Science (1), speaks for itself:
"A single mutation in bovine influenza H5N1 hemagglutinin switches specificity to human receptors."
This is not the norm—usually, three or more mutations are required for such a shift. However, this example sheds new light on how easily viruses can adapt for transmission to humans.

[1] https://www.science.org/doi/10.1126/science.adt0180

GENOMIC INFORMATION TO CLINICAL CARE

Starting in 2019, Am J Hum Genet has published an annual feature identifying ten key advances in applying genomic information to clinical care that were reported in the previous 12 months of published literature (1).

[1] https://www.cell.com/ajhg/abstract/S0002-9297(24)00411-7

A CNV ASSOCIATED WITH A HIGHER COGNITIVE ABILITY

Copy-number variants (CNVs) are major contributors to neurodevelopmental disorders and are often associated with reduced cognitive performance. The authors of a paper published in Cell Genomics (1) present a novel approach to functionally aggregate rare and ultra-rare CNVs, enabling a deeper understanding of gene-dosage-sensitive processes. They identified 864 gene sets sensitive to deletions or duplications across brain and non-brain tissues.

Remarkably, the study reveals the first CNV associated with higher cognitive ability: a duplication at 2q12.3, encompassing EDAR, SH3RF3, SEPT10, and SOWAHC. This CNV has a moderate effect size, equivalent to a 6.5-point increase in IQ, without significant heterogeneity across cohorts.

This finding brings to mind the BOLA2 gene, which is duplicated between 4 and 8 times exclusively in Homo sapiens, not in any other ptimate, not in Neanderthals (2).

[1] https://www.cell.com/cell-genomics/fulltext/S2666-979X(24)00350-1?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2666979X24003501%3Fshowall%3Dtrue

[2] https://www.nature.com/articles/nature19075

THE POTENTIAL OF GWAS IN UNDERSTANDING FEMALE INFERTILITY

In earlier posts on this forum, we have highlighted studies that demonstrate the value of exome sequencing in uncovering the genetic basis of infertility. A recent article in the Am. J. Hum. Genet. (1) takes an alternative approach, utilizing Genome-Wide Association Studies (GWAS) to investigate the genetic etiology of this condition.

Through GWAS, researchers identified a rare stop-gained mutation in the TBPL2 gene using data from 22,849 women with infertility and 199,000 controls in the Finnish FinnGen cohort. This mutation disrupts a transcription factor crucial for oocyte development. Women with two mutated alleles exhibited reduced fertility, often requiring infertility treatment to conceive.

In addition to TBPL2, the study identified three age-specific genetic loci associated with infertility. Early-onset infertility (before age 30) was linked to variants in CHEK2 and the major histocompatibility complex (MHC), while late-onset infertility was associated with a long non-coding RNA gene.

The study highlights the utility of GWAS as a cost-effective tool for uncovering the genetic basis of complex conditions like female infertility.

[1] https://www.cell.com/ajhg/fulltext/S0002-9297(24)00387-2?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002929724003872%3Fshowall%3Dtrue

THE DARK PROTEOME

In humans, the number of annotated canonical protein-coding genes is estimated to range between 20,000 and 25,000. However, alternative splicing dramatically increases the complexity of the proteome, with estimates surpassing 100,000 unique isoforms.

Recent research has begun uncovering a “dark proteome,” composed of small proteins, as short as a dozen or fewer amino acids, derived from non-canonical open reading frames (ncORFs). A preprint published on BioRxiv (1) reports that at least 25% of the 7,264 identified ncORFs generate translational products, resulting in over 3,000 peptides.

The importance of these findings has been emphasized in a commentary featured in Science (2), underlining the potential implications for understanding human biology and identifying new therapeutic targets.

[1v] https://www.biorxiv.org/content/10.1101/2024.09.09.612016v1

[2] https://www.science.org/content/article/dark-proteome-survey-reveals-thousands-new-human-genes

CHROMOSOME INSTABILITY AT THE BLASTOCYST STAGE

The pioneering work by J. Vermeesch's group in 2009 (1) revealed that chromosome instability is common in human cleavage-stage embryos. The single cell analyses were conducted by microarray technology. Several confirmatory papers followed.

Handyside et al. (2024), in a study published on bioRxiv (2), performed a similar investigation across 342 cycles of Preimplantation Genetic Testing for Monogenic diseases (PGT-M), combining parental haplotyping with SNP intensity analysis. This cost-effective assay enabled the precise identification of meiotic and mitotic whole chromosome and segmental gains and losses, along with their parental origins.

The authors concluded: "Meiotic aneuploidies were predominantly whole chromosome aneuploidies of maternal origin and increased with maternal age. Mitotic aneuploidies (with normal parental haplotype patterns) were mainly segmental imbalances."

The tables included in the paper provide a rich source of data for researchers in this field.

In the Discussion, the authors address the challenges faced in PGT practice, making this study an engaging and essential read for those involved in preimplantation genetic testing.

[1] https://www.nature.com/articles/nm.1924

[2] https://www.biorxiv.org/content/10.1101/2024.11.17.623999v1

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Unitat de Biologia Cel·lular
Dept de Biologia Cel·lular, de Fisiologia i d'Immunologia
Facultat de Biociències (Edifici C)
Univ. Autònoma de Barcelona
08193-BELLATERRA SPAIN
Tel. : +34 93 58 13 728
E-mail: joan.blanco@uab.cat

Jean-Michel DUPONT
Laboratoire de Cytogénétique
Hôpitaux Univ. Paris Centre
Hôpital Cochin -
Bât Jean DAUSSET 4e
27 rue du Fbg St Jacquesl
75014 PARIS
FRANCE
Tel.: +33 1 58 41 35 30
E-mail.:
jean-michel.dupont@ aphp.fr

José M. GARCIA-SAGREDO
Pabellón Docente, Med. Genetics
Univ. Hospital Ramon y Cajal
Carretera de Colmenar Km 9.100
28034 MADRID
SPAIN
Tel.: +34 91 33 68 550
E-mail:
jgarcias.hrc@salud.madrid.org

J.S. (Pat) HESLOP-HARRISON
Genetics and Genome Biology
University of Leicester
LEICESTER LE1 7RH
UK
Tel.: +44 116 252 5079
E-mail: phh4@le.ac.uk

Thierry LAVABRE-BERTRAND
Laboratoire de Biologie Cellulaire et Cytogenetique Moleculaire
Faculté de Médecine
Avenue Kennedy
30900 NÎMES
FRANCE
Tel.: +33 4 66 68 42 23
E-mail: tlavabre@univ-montp1.fr

Anna LINDSTRAND
Clinical Genetics and Genomics
L4:03
Karolinska University Hospital
17176 STOCKHOLM SWEDEN
Tel.: +46 705436593
E-mail: anna.lindstrand@ki.se

Kamlesh MADAN
Dept. of Clinical Genetics
Leiden Univ. Medical Center
P.O.Box 9600
2300 RC LEIDEN
THE NETHERLANDS
Tel.: +31 72 51 28 953
E-mail: k.madan@lumc.nl

Konstantin MILLER
Institut für Humangenetik
Medizinische Hochschule
30623 HANNOVER
GERMANY
Tel.: +49 511 532 6538
E-mail:
miller.konstantin@mh-hannover.de

Franck PELLESTOR
Unit of Chromosomal Genetics
Arnaud de Villeneuve Hospital
Montpellier CHU
34295 MONTPELLIER cedex 5
FRANCE
Tel.: +33 4 67 33 07 70
E-mail: fpellestor@yahoo.fr or
f-pellestor@chu-montpellier.fr

Maria Rosario PINTO LEITE
Cytogenetics Laboratory
Centro Hospitalar de Trás-os-Montes e Alto Douro
Av. da Noruega
5000-508 VILA REAL
PORTUGAL
Tel.: +35 1 25 93 00 500
E-mail:
mlleite@chtmad.min-saude.pt

Harald RIEDER
Institut fuer Humangenetik und Anthropologie
Universitaetsstraße 1
40225 DUESSELDORF
GERMANY
Tel.: +49 211 8110689,
E-mail:
harald.rieder@uni-duesseldorf.de

Mariano ROCCHI
Emeritus Professor
Dip. di Biologia
Campus Universitario
Via Orabona 4
70125 BARI
ITALY
Tel.: +39 080 544 3371
E-mail: mariano.rocchi@uniba.it

Elisabeth SYK LUNDBERG
Dept. of Clinical Genetics
Karolinska Hospital
17176 STOCKHOLM
SWEDEN
Tel.: +46 85 17 75 380
E-mail:
elisabeth.syk.lundberg@ki.se

Roberta VANNI
Dept. of Biomedical Sciences
Biochemistry, Biology and Genetics Unit
University of Cagliari
09142 MONSERRATO (CA)
ITALY
Tel.: +39 07 06 75 41 23
E-mail: vanni@unica.it

Meral YIRMIBES KARAOGUZ
Gazi University Medical Faculty
Department of Medical Genetics
Besevler
06500 ANKARA TURKEY
Tel.: +90 312 2024644
E-mail: karaoguz@gazi.edu.tr

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ECC SCIENTIFIC PROGRAMME COMMITTEE

E.C.A. News

- The 2024 General Assembly of the E.C.A. with Board elections took place on Friday, 23 August 2024, at 6:00 pm at Goldrain Castle, Goldrain / South Tyrol, Italy.
- Renewal of the Board in 2024: the following members were re-elected at the General Assembly: J-M. Dupont (France), J. Garcia-Sagredo (Spain), M. Rocchi (Italy), E. Syk Lundberg (Sweden), R. Vanni (Italy).
- The 2025 General Assembly of the E.C.A. with Board elections will take place during the 15th European Cytogenomics Conference, Leuven, Belgium, 29 June - 1 July, 2025

E.C.A. Fellowships

- The **E.C.A.** offers two **Fellowships** for each of the following courses:

  European Advanced Postgraduate Course in Classical and Molecular Cytogenetics
  to be held in Nîmes (France) 24 – 30 March 2025 (see page 23)

  Goldrain Course in Clinical Cytogenetics
  to be held in Goldrain Castle (South Tyrol, Italy) 25-August – 2 Sepember 2025 (see page 24)

- The fellowships **include the course fees and the accommodation** during the lectures in Nîmes or in Goldrain but **do not include travel expenses** for either of the courses or for accommodation during the practical training for the Nîmes course. Applications with CV, list of publications and a letter of support should be addressed to the appropriate course organizer. The Educational Advisory Council of the E.C.A. will select the successful candidates.

Kind reminder

Dear E.C.A. member, please renew your membership: http://www.e-c-a.eu/

E.C.A. PERMANENT WORKING GROUPS (PWG)

PWG: MARKER CHROMOSOMES

Thomas LIEHR
Jena University Hospital, Friedrich Schiller University, Institute of Human Genetics
Postfach
07740 JENA, GERMANY
Tel: + 49 3641 93 96 850
E-mail: Thomas.Liehr@med.uni-jena.de

Isabel MARQUES CARREIRA
Cytogenetics and Genomics Laboratory,
Faculty of Medicine, University of Coimbra
Rua Larga
3004-504 COIMBRA, PORTUGAL
Tel/Fax . +351 23983886
E-mail: i_marques@hotmail.com

New achievements on small supernumerary marker chromosomes (sSMCs) research have been published, are summarized and freely available on https://cs-tl.de/DB/CA/sSMC/0-Start.html.

However, it must be noted that in recent years the number of publications on sSMCs have decreased, as an increasing number of patients with clinical symptoms are being studied by CMA-analyses as first-line test, often replacing the use of FISH techniques. At the same time, peer review assignments on sSMC studies show a severe lack of knowledge on sSMCs. Here are just a few examples:

- When a mosaic sSMC is found with chromo-some banding and a “partial trisomy of 12p” is found with CMA-analyses, the authors fail to consider Pallister-Killian-syndrome.
- In cases with pericentric duplications of a specific chromosome, the researchers do not compare their case with previously published cases.
- Even in a case of a large sSMCs, in the mega-base-size range, the authors speculate on single genes that might be responsible for the phenotype.

Accordingly, there are no actual papers of interest; all we can recommend are the books we have already mentioned:

- Book: T Liehr. Small supernumerary marker chromosomes, Basics. Epubli, 2023, ISBN 978-3758451935 – also available in German: ISBN 978-3758451669, Portuguese: ISBN 978-3758454387, Russian: ISBN 978-3758463709, and French: ISBN 978-3758458576
- Book: T Liehr. All you need to know about uniparental disomy, UPD and imprinting. Epubli, 2024, ISBN 978-3758465581 – also available in German: ISBN 978-3758465574

Finally, we just want to remind everyone that we - the coordinators - are happy to receive ideas for projects and for cooperation.

PWG CHROMOSOME INTEGRITY, STABILITY and DYNAMICS

José M. GARCIA-SAGREDO
Medical Genetics Department
Hospital Ramon y Cajal
Carretera de Colmenar Km 9.100
28034 MADRID, SPAIN
Tel: +34 91 3368550
E-mail: jgarcias.hrc@salud.madrid.org

Emanuela VOLPI
Faculty of Science and Technology
University of Westminster
115 New Cavendish Street
LONDON W1W 6UW, UK
E-mail: e.volpi@westminster.ac.uk

"The ‘Chromosome Integrity, Stability and Dynamics’ PWG will hold a satellite meeting at the next ECA conference in Leuven in 2025. The coordinators will be considering submitted abstracts falling within the remit of the PWG for invited presentations at the satellite meeting. Applying molecular cytogenetic techniques for biomonitoring and environmental studies, novel assays for DNA damage and chromosomal instability, nuclear and micronuclear biomarkers, chromosome fragility, cell-cycle errors, and genome ageing would be particularly welcome research themes this year. Should you have any queries about contributing to this PWG and/or presenting your research at the satellite meeting, please feel free to contact the PWG Coordinators, Jose' Garcia-Sagredo and Emanuela Volpi."

MINUTES OF THE E.C.A. GENERAL ASSEMBLY AUGUST 2024

Minutes of the General Assembly held on August 23rd 2024 in Schloss Goldrain, Coldrano, Italy.

All active members had been sent postal ballots and were invited to the General Assembly, only four were present onsite.

The President, Mariano Rocchi, opened the Assembly at 18:00 and welcomed those attending.

The Minutes of the General Assembly held on 3rd of July 2023 in Montpellier, France and published in Newsletter 53 from January 2024 were approved

Reports of the Committee

The General Secretary, Jean-Michel Dupont, reported the membership of the ECA. The membership includes 1307 members, 268 are active (including 42 associated/overseas members). The number has remained stable and 48 new members joined the Association in 2023 (12 from outside the EU).

In the absence of the Treasurer, Thierry Lavabre Bertrand, the General Secretary presented the financial results. Income in 2023 increased due to the Conference, mainly through new membership. However, the 2023 Montpellier Conference led to a deficit due to lower attendance by sponsors than in previous years. The overall balance is still satisfactory but the Treasurer warned that the next Conference has to have a positive balance in order to keep the financial balance of the Association on the safe side. The accounts of the Association were approved by the Assembly.

Board elections

Five members were due for replacement or re-election in 2024. A single list was received by the General Secretary before the deadline of August 11, 2024, with five candidates: JM DUPONT (France), JM GARCIA SAGREDO (Spain), M ROCCHI (Italy), E SYK LUNDBERG (Sweden), R VANNI (Italy). The voting for board members was closed and those who were not candidates, was asked to count the ballots.

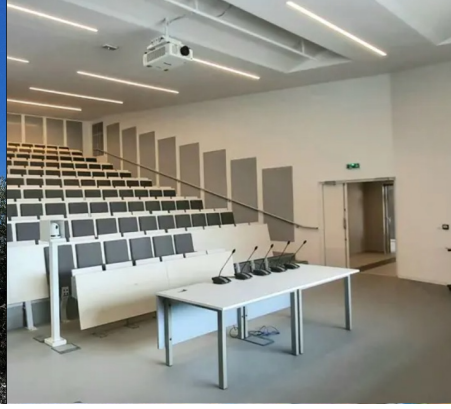
45 ballots were received, 43 voted ‘yes’, 1 ‘No’ and one ballot was not valid. The list comprising the five candidates was duly elected.

Montpellier Conference

The Conference attracted 304 participants (Europe 74.5%, World 25.5%), 104 of them had been invited. The scientific program had 13 oral presentations and 132 posters with two main topics: Clinical cytogenomics and Tumour cytogenomics. Only 11 companies were present, a figure which needs to be improved for the next conference.

No other subject being put forward, the Assembly was closed at 19:00.





Nîmes – France, March 24-30, 2025

EUROPEAN CYTOGENETICISTS ASSOCIATION (E.C.A.)

European Diploma
in Classical and Molecular Cytogenetics

Director: Professor Jean-Michel Dupont, Paris - France

http://www.biologia.uniba.it/SEC/

This course was started by Professor Jean Paul Bureau in 1997 and has been held in Nîmes under his directorship until 2017. It is designed to provide advanced training in constitutional, haematological, and oncological cytogenetics to medical graduates, pharmacists, pathologists, biologists, health professionals and researchers, with an academic qualification. The students will be trained to identify genetic abnormalities for diagnosis and prognosis, and for fundamental and applied research using both classical and molecular cytogenetic techniques. The course is co- organized by E.C.A. and two French Universities.

Registration

(September 2024 – January 31st, 2025)

You can select either

- Basic diploma: only the lectures and a final online examination (no previous experience required)
- Advanced diploma: lectures + 2 months training in a cytogenetic laboratory (6 months experience in cytogenetics required), and onsite final examination (written and oral) in Paris

For registration, please send a letter of application with your CV to the organizers, Prof. Jean-Michel DUPONT (jean-michel.dupont@aphp.fr) or to Prof. Thierry LAVABRE-BERTRAND (thierry.lavabre-bertrand@umontpellier. fr).

Registration fee is the same for both: €1034 if paid by the participant, 2034€ if paid by an institution.

Beware: the fee does not include accommodation during the lectures or the training

Accommodation

A **special** price is available for participants in the 4* Vatel hotel close to the course venue (https://www.hotelvatel.fr/en/nimes) . We highly recommend that all participants stay in this hotel where all the lecturers will be hosted in order to promote interactions during the course.

Scholarships

E.C.A. will award two scholarships covering the registration and accommodation fees. The Education Committee of the E.C.A. will select the suitable candidate.

Students whose registration is paid by a third party institution are not eligible for a scholarship

Topics

Technical Aspects: *Classical Cytogenetics:* Cell culture techniques; Chromosome staining methods (Q-, G-, C-, R-banding); *Molecular Cytogenetics:* Methods and principles of Fluorescence In Situ Hybridization (FISH); CGHarray and SNParray; Application of Massively Parallel Sequencing to Cytogenetics; Optical Genome Mapping ; Databases in Cytogenetics; *Laboratory quality assessment.*

Clinical cytogenetics: *Basics:* Frequency of chromosome disorders; Cell cycle, mitosis and meiosis, gametogenesis; Heterochromatic and euchromatic variants; Numerical chromosome abnormalities; Structural abnormalities: translocations, inversions, insertions, deletions, rings, markers; Risk assessment for balanced abnormalities; X inactivation; numerical and structural abnormalities of the X and the Y; Mosaicism; Chimaeras; ISCN 2024; *Clinical:* Phenotype of common autosomal and sex chromosome aneuploidies; Chromosome abnormalities in recurrent abortions; Cytogenetics and infertility; Microdeletion syndromes; Uniparental disomy and its consequences; Genomic imprinting; Genetic counselling and ethical issues in cytogenetics; *Prenatal diagnosis:* Indications, methods and interpretation; Risk assessment for chromosomal abnormalities; Non-invasive methods using foetal nucleic acids in maternal blood; Pre-implantation diagnosis; *Cancer* Cytogenetics: Molecular approach to cancer cytogenetics; Predisposition to cancer, Chromosome instability syndromes; Chromosome mutagenesis; Solid tumors; Clinical application in onco-haematology.

Other topics: Genome architecture; Structure of chromatin; Structure of metaphase chromosomes; Mechanisms of chromosome aberrations; Origin of aneuploidy; Evolution and plasticity of the human genome; Animal cytogenetics; Plant cytogenetics.

18th Goldrain Course in Clinical Cytogenetics

August 26 – September 1, 2025

(arrival Aug. 25, departure Sept. 2)

DIRECTORS

A. Schinzel (Zurich, Switzerland); **M. Rocchi** (Bari, Italy)

PROGRAMME COMMITTEE

A. Schinzel, M.Rocchi, J-M. Dupont, K. Miller, K. Madan, A. Baumer, E. Klopocki,

FACULTY

D. Bartholdi (Berne, Switzerland), A. Baumer (Zurich, Switzerland), P. Benn (Farmington CT, U.S.A.), J.M. Dupont (Paris, France), E. Errichiello (Pavia, Italy), E. Klopocki (Würzburg, Germany), K. Madan (Leiden, The Netherlands), K. Miller (Hannover, Germany), R. Pfundt (Nijmegen, The Netherlands), M. Rocchi (Bari, Italy), G. van Buggenhout (Leuven, Belgium), M. Vismara (Rome, Italy), J. Wisser (Zurich, Switzerland), O. Zuffardi (Pavia, Italy)

LOCATION

Goldrain Castle, Goldrain, South Tyrol, Italy

COURSE DESCRIPTION

The course is focused on phenotypic findings, mechanisms of origin and transmission, correlations of clinical patterns with chromosomal imbalance and modern ways of diagnosis of the latter. Special attention is paid to an understanding how deletions and/or duplications of chromosomal segments cause developmental defects. The course also addresses the optimal application of the diagnostic possibilities, both pre- and postnatally and including molecular cytogenetic methods for a precise determination of segmental aneuploidy.

TOPICS

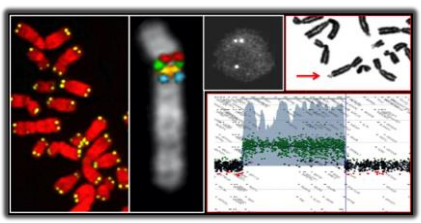
Dysmorphic findings in chromosome aberrations: formation and interpretation – The adult and elderly patient with a chromosome aberration – Follow-up studies in patients with chromosome aberrations – Clinical findings associated with chromosome aberrations – Microdeletion syndromes: clinical pictures – prenatal cytogenetic diagnosis – Mosaics and chimeras – imprinting and uniparental disomy - Epidemiology of chromosome aberrations – Chromosome aberrations in spontaneous abortions and stillborns – Harmless chromosome aberrations – Risk assessment in structural chromosome aberrations Extra small supernumerary chromosomes – Genomic variation: a continuum from SNPs to chromosome aneuploidy – Pre-implantation cytogenetic diagnosis – Ultrasound findings indicative of chromosome aberrations – Ethical issues in the context of cytogenetic diagnosis – Non-invasive prenatal cytogenetic diagnosis. ISCN - Practical exercises in cytogenetic nomenclature – Accreditation of cytogenetic laboratories - Accreditation of cytogenetic laboratories – Optimal use of available techniques in clinical cytogenetics – NGS – SNP arrays and Array-CGH: principles, technical aspects; evaluation of the results – MLPA - QF-PCR - FISH techniques and their interpretation – Optical genome mapping – Introduction and practical exercises with database for phenotypical and variant interpretation - Students presentation of cases with difficult-to-interpret chromosome aberrations. Introduction to modern genetic editing techniques. - Practical exercises will be offered with the ISCN system for chromosome aberrations and with cytogenetic, genomic, and phenotypical databases.

Students will have the opportunity to present their own observations and cytogenetic findings which are difficult to interpret, and to perform a test at the end of the course.

The **41** available spots will be allocated on **first come** - **first served** basis.
In 2024 all spots were filled by mid-April.

Full scholarships will be available (travel not included). Application deadline: **April 30, 2025**

For further questions:
mariano.rocchi@uniba.it
or
schinzel@medgen.uzh.ch



Fees: ***€1.700*** *– single room*
€1.450 *– double room*
The fee includes tuition, course material, free access to internet, accommodation for 8 nights, all meals, coffee breaks and a ½ day excursion. Travel is not included.

For more details: http://www.biologia.uniba.it/SEC/