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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. Our E.C.A. conferences will also 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 on page 7.
Please contact us (mariano.rocchi@uniba.it) if you wish to share an interesting news item or a pertinent article.

President's Address

Dear Colleagues and Friends,

It is my pleasure to invite and welcome you to the 16th European Cytogenomics Conference, which will take place in Stockholm from 4 to 6 July 2027.

Since its launch in 1997, the conference has been a major meeting point for the cytogenomics community and, more broadly, for all those interested in chromosomes and genome biology. Held every two years, it provides a unique forum to connect the latest advances in knowledge, technology and bioinformatics with clinical practice and ongoing research.

With our previous experience of a very successful conference held in Stockholm in 2009, and with the active support of the local organizing committee, chaired by Professors Elisabeth Syk Lundberg and Anna Lindstrand, we are committed to offering you another great conference.

As always, the conference will be preceded by the Permanent Working Group meetings, providing extended opportunities to present and discuss research results. There will also be the Hands-on Workshops, which were introduced in Leuven and were highly appreciated by the participants.

A renewed Scientific Program Committee, chaired by Professor Joris Vermeesch, is currently preparing an exciting scientific program. Further details will be announced later on the official website of the conference which will be launched soon.

Besides the scientific sessions, ECC 2027 will be an opportunity for networking, exchange and collaboration among colleagues from across Europe and beyond. We are pleased to welcome you to Karolinska University Hospital and Karolinska Institute, where world-leading clinical care, medical research, and education come together in a setting with a long and distinguished tradition.

Jean-Michel Dupont
E.C.A. President

European Cytogeneticists Association

SAVE THE DATE

16th EUROPEAN CYTOGENOMICS CONFERENCE

JULY 4–6, 2027
STOCKHOLM, SWEDEN

#ECA2027

www.eca2027.org

A Unique Cell with 17 X chromosomes

Kamlesh Madan

Leiden University Medical Center, Leiden, The Netherlands
1974 – 2006 VU Medical Center, Amsterdam, The Netherlands

Introduction

I would like to share this picture of a unique human cell, 61,XXXXXXXXXXXXXXXXX, with readers of the ECA Newsletter. I came across it in 1980, just a single cell, one out of 30, in a woman with a normal karyotype referred for recurrent miscarriages. To understand the significance of this cell, here is some background.

Background:

Age-related loss of the X chromosome in women has been known since the early 1960s [1,2]. Low level Mosaicism of X aneuploidy (LLX-A), involving both loss or gain of an X in cells of women of reproductive age has been extensively documented and reviewed [3-8]. LLX-A in up to approximately 10% of blood cells of women of reproductive age is without reproductive consequences.

Loss of X

Russell *et al*. [6] have shown that the process of age-related X chromosome loss (XCL) in women starts early and goes on throughout life. They have provided reference graphs showing the percentage of cells with XCL that would be regarded as normal at a given age. They have done this for a chromosome count in 30, 40, 50 and 60 cells. In 30 cells one can expect XCL in up to 6% of cells at age 30, 9% at 40, 13 % at 50 and 17% at 60 years of age. The lost X is more likely to be the inactive X [9,10]

Gain of X

Also finding of cells with an extra X (47,XXX) is age related; occasionally single 48,XXXX or 49,XXXXX cells have also been reported. Sometimes one to four Xs in these cells show chromatids that have separated early, without the primary constriction (named X fragments in earlier publications) [11,13]. Finding of cells with an X with premature centromere division (PCD) is also age related [11-13].

Mechanism

In 1975 Fitzgerald *et al.* proposed that PCD is the basis of age-related X aneuploidy [11]. X has a tendency to undergo premature centromere division [11,12]. PCD of the X occurs already in the interphase stage of mitosis [14]. The X with PCD fails to align itself on the mitotic spindle during cell division, undergoes anaphase lag and gets excluded from both daughter cells, each of which is then 45,X. The excluded X forms a micronucleus. The number of X containing micronuclei is known to increase with age [15, 16]. The mitotic laggard X can also get included in one daughter cell, which gains an X (47,XXX), while the other daughter cell loses an X (45,X)

Occasionally, in a 47,XXX cell, each of the chromatids of the X with PCD may replicate in the S phase and the chromatids may sometimes again separate prematurely. These Xs again lag behind during the following mitosis resulting in a 49,XXXXX with some Xs showing PCD. This process, which operates in vivo and in vitro, can recur in several successive mitoses [11,12] giving rise to cells with multiple copies of the X.

The cell

The cell in figure 1 could be an extreme example of the above-mentioned phenomenon. It has 17 X chromosomes, one or two normal X chromosomes and 15 or 16 Xs without the centromeric constriction.

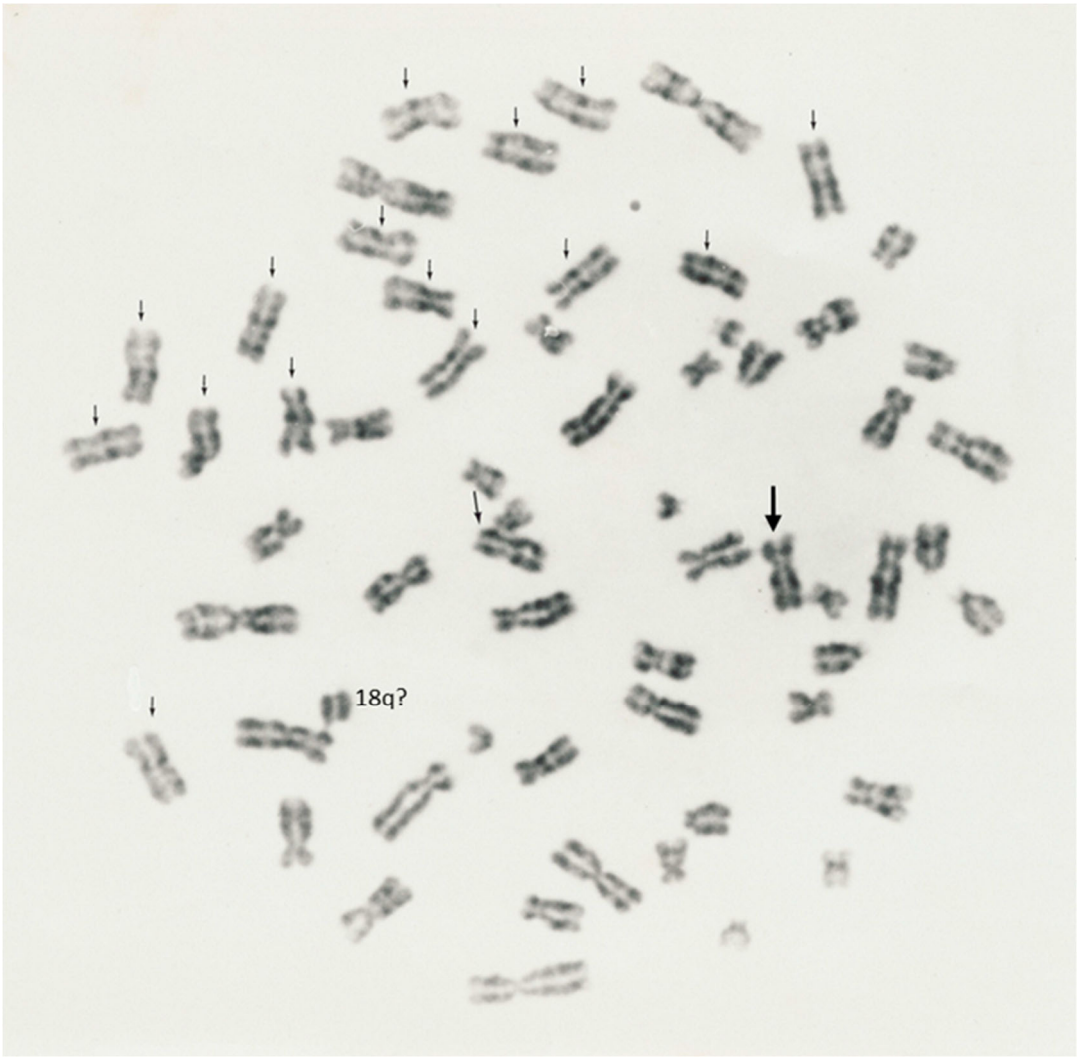

Fig 1 There are 44 autosomes (short arm of one 18 appears to have broken off). One X appears to be normal (large arrow). The X in the middle (medium arrow) could be a normal or an X with PCD like the 15 other Xs (small arrows).

Possible mechanism

Multiple copies of the X without the centromeric constriction could arise in the same way as described above [11,12], only, this time the chromatids would go through one or two more replication cycles and each time the Xs with the PCD would fail to align on the spindle due to centromeric disfunction; these Xs could get repeatedly included in the same cell. Similar mechanism of repeated replication cycles without segregation has been proposed to explain multiple copies (up to 10) of the X found in some micronuclei [17]. It is possible that some micronuclei may be retained in the cell. The chromosomes/chromatids could replicate during the S phase of several cell cycles, *in vivo* or *in*

vitro, but without being able to segregate due to absence of a mitotic mechanism in the micro-nucleus.

These authors [17] also speculate on the possibility that the membrane of the micro-nucleus may disintegrate and the multiple copies of the X chromosome that were originally confined within the micronucleus could get reincorporated into the main nucleus.

Conclusion

Whatever the mechanism, it is clear that more than one rare event, or even a series of rare events, would have to occur to produce a cell with multiple copies of the X showing the premature centromere division. This is what makes this cell an extremely rare finding.

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Literature on Social Media

E.C.A. is 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.

IMPACT OF SYNONYMOUS MUTATIONS ON RNA SPLICING

Although synonymous mutations have long been considered functionally neutral, this view has been progressively challenged over the past two decades. It is now well established that synonymous variants can affect gene expression by altering splicing regulatory elements, particularly when they occur near exon–intron boundaries or within exonic splicing enhancers and silencers. Several individual examples have demonstrated that such variants can lead to aberrant splicing and disease.
What is less clear, however, is the extent to which this phenomenon operates at a genome-wide level and how frequently synonymous substitutions contribute to functional and potentially pathogenic effects. Srinivasan et al. (1) address this gap by systematically investigating the impact of synonymous variants on splicing, showing that their contribution is far more widespread than previously appreciated. These findings challenge the traditional view of synonymous mutations as largely neutral and underscore the need to reconsider their role in the interpretation of variants and in the genetics of the disease.

https://pubmed.ncbi.nlm.nih.gov/41436921/

WE ARE ALL CHIMERAS (AND WE DIDN'T KNOW IT)

The word chimera comes from Greek mythology and evokes a creature assembled from parts of different animals. But in a very real biological sense, we are all chimeras. This is the fascinating message at the heart of the book recently reviewed in Nature, *Hidden Guests: Migrating Cells and How the New Science of Microchimerism Is Redefining Human Identity* by Lise Barnéoud.

During pregnancy, cells pass from the fetus to the mother and from the mother to the fetus through the placenta. Some of these cells do not disappear after birth, but remain in the body for decades, possibly for a lifetime. And they do not come only from the direct mother–child exchange: cells may also originate from a grandmother, older siblings, or even a twin. This phenomenon is known as microchimerism.
These "guest" cells are extremely rare, yet they have been found in every organ studied so far. Remarkably, they are not just passive bystanders. They can contribute to tissue repair, take part in immune responses, and even influence immune memory.
The book also traces the scientific history of these discoveries, from chance observations in the 19th century to modern research showing that cells exchanged in utero can persist for decades. This challenges the traditional view that all cells in a person come only from the original fertilized egg.
The implications are profound. According to classical immunology, the immune system sharply distinguishes between "self" and "non-self". Yet microchimeric cells are clearly "non-self" and still are not rejected. This opens new questions about autoimmune diseases, immune tolerance, and even transplantation medicine.
In the end, Hidden Guests is not only a book about cell biology. It is also a reflection on what it really means to be an individual. If we permanently carry cells from other people, and if our own cells can persist in others across generations, where does the boundary between "me" and "you" truly lie?
As the Nature review concludes, this is a book that weaves together science, history, and philosophy into a compelling narrative.

Book Reference (English and Original French)

Barnéoud, Lise. Hidden Guests: Migrating Cells and How the New Science of Microchimerism Is Redefining Human Identity.
Translated from the French by Bronwyn Haslam., Greystone Books, 2025.
ISBN: 978-1778402661.

Original French edition:
Les cellules buissonnières: L'enfant dont la mère n'était pas née et autres folles histoires du microchimérisme (Premier Parallèle, 2023).

LACTASE PERSISTENCE

For decades, lactase persistence has been the textbook example of gene–culture coevolution: when humans started herding cattle and drinking milk, the ability to digest lactose in adulthood supposedly became a major nutritional advantage, and natural selection drove the relevant variants to high frequency. Indeed, the region around LCT shows one of the strongest signals of positive selection in the human genome, with extreme extended homozygosity. See Schlebusch et al. (1)

In recent years, however, this simple story has been questioned. Archaeological and genetic evidence showed that people were using milk thousands of years before lactase persistence became common, and some authors suggested that selection at the LCT locus might have been driven by something else (for instance immune-related genes in the same region), rather than by milk consumption itself.

A new large-scale study published in bioRxiv (2) focusing on South Asia brings the story back into sharp focus. By analysing ~8,000 present-day and ancient genomes from India, Pakistan and Bangladesh, the authors show that the classic Eurasian lactase persistence allele (-13.910*T) arrived in South Asia via Steppe pastoralist ancestry. In most South Asian populations, its present-day frequency is explained almost entirely by ancestry, not by local selection.

But two striking exceptions stand out: the Toda in South India and the Gujjar in Pakistan, both traditional pastoralist groups whose subsistence has long revolved around milk and dairy products. In these two populations, the lactase persistence allele reaches frequencies comparable to Northern Europe and shows clear, independent evidence of very strong recent positive selection. The estimated selection coefficients are among the highest known in recent human evolution.

In other words: where people truly depended on milk as a staple resource, natural selection strongly favoured lactase persistence. Where milk was only one component of a mixed subsistence economy, it did not.

As Johannes Krause (Max Planck Institute for Evolutionary Anthropology) nicely puts it: “To me, it’s a nail in the coffin to the idea that it wasn’t milk, but something else, that has driven its frequency.”

This study elegantly reconciles archaeology, population genetics and evolutionary theory: lactase persistence is not a universal story of selection wherever milk is used, but a highly context-dependent one. Yet, when human survival really hinges on dairy, milk alone is more than enough to leave one of the strongest footprints of selection in our genome.

[1] https://pubmed.ncbi.nlm.nih.gov/22948027/
[2] https://www.ncbi.nlm.nih.gov/pubmed/41278663

GENE DRIVE CAPABLE MOSQUITOS

A gene drive is a genetic mechanism that causes a particular gene to be inherited much more often than the normal 50% predicted by Mendelian rules, allowing it to spread rapidly through a population. Mechanisms of this kind also exist in nature (for example meiotic drive elements, selfish genetic elements, and transposons), but today they can also be engineered artificially using CRISPR.

The idea behind the Nature paper by Habtewold et a. (1) is not to eliminate mosquitoes, but to genetically modify them so that they can no longer transmit malaria, and then use a genetic mechanism to spread this trait through natural populations (gene drive).

First, the researchers engineered mosquitoes to produce two small anti-parasitic molecules. These molecules interfere with the development of the malaria parasite inside the mosquito. As a result, even if the mosquito feeds on infected blood, the parasite usually fails to reach the salivary glands, which are essential for transmission to humans. In practice, the mosquito can still bite, but it almost never becomes infectious.

Second, they use a “gene drive” system. Normally, a gene has a 50% chance of being inherited. A gene drive biases this process: using CRISPR-based molecular machinery, the modified gene is copied onto the other chromosome, so it is inherited by nearly 100% of the offspring. This allows the trait to spread very rapidly through a population, even if it provides no direct advantage to the mosquito.

In principle, the entire system (the antimalarial genes and the gene-drive machinery) could be packaged into a single genetic construct that would spread autonomously. However, for safety reasons, the researchers deliberately did not do this. Instead, the system is split into two parts. One mosquito line carries the anti-malaria genes but no drive. Another line carries the CRISPR machinery. Only when the two are crossed does the gene drive operate, forcing the anti-malaria genes to be inherited by almost all descendants.

This makes the system much more controllable and safer to test.
The key advance of this study is that the system was tested using blood samples collected from malaria-infected children in Tanzania, rather than using only laboratory parasite strains. The results show that in genetically modified mosquitoes, the parasite almost never reaches the salivary glands, meaning transmission would be essentially blocked.
Artificial gene drives have never been released into the wild. Once such a system starts spreading in a natural ecosystem, nobody can reliably predict what will happen in the long term, nor how it might interact with ecology and evolution. For this reason, gene-drive systems are currently kept under strict containment.
Most researchers agree that gene drives should be considered only in extreme situations, where the potential benefit is enormous and no reasonable alternatives exist. The most often cited case is the control of devastating human diseases such as malaria, dengue, or Zika, when other methods (insecticides, drugs, vaccines, environmental control) prove insufficient.
Another widely discussed application is the control of invasive species, especially in geographically limited ecosystems such as islands, for example rats or mice that are responsible for the extinction of native birds and reptiles.
Even in these cases, it is likely that the first real-world applications will not use fully self-propagating global gene drives, but rather self-limiting or threshold-dependent systems, designed to remain local and, in principle, reversible.
Gene drive will probably be used only when the risk of not using them is clearly greater than the risk of using them. Until then, they remain one of the most powerful and carefully contained tools ever developed in evolutionary genetics.

[1] https://www.ncbi.nlm.nih.gov/pubmed/41372414

PALINDROMES, HAIRPINS, AND COMPLEX REARRANGEMENTS: THE CASE OF 16P13.3

Genomic palindromes are DNA sequences arranged as inverted repeats, meaning that the two strands contain mirror-image sequences. Such structures are intrinsically unstable because the DNA can fold back on itself and form secondary structures, such as hairpins or cruciforms. These non-B DNA conformations interfere with normal DNA replication and repair, can stall or collapse replication forks, and are well known to promote double-strand breaks (DSBs). In short, palindromic architecture creates a physical fragility of the DNA molecule.
This principle has been beautifully illustrated by the work of Beverly Emanuel's group and others on recurrent translocations mediated by short AT-rich palindromic repeats (PATRRs), most famously the t(11;22). In those cases, relatively small palindromes form hairpin or cruciform structures, break, and are then mis-repaired, leading to highly recurrent, stereotyped balanced translocations, often arising during meiosis.
The situation at 16p13.3 described by Fasham et al. (1) is conceptually related but structurally very different. Here, the rearrangements are driven by a much larger palindromic architecture, spanning hundreds of kilobases and embedded in a region rich in segmental duplications. Such a large palindrome is again expected to form secondary structures and to be prone to breakage or replication fork collapse, but the repair does not typically produce a simple translocation. Instead, because of the local genomic architecture and the abundance of homologous sequences, the outcome is a variety of complex intrachromosomal rearrangements.
In practice, this means that the instability of the 16p13.3 palindrome is resolved by error-prone repair or replicative mechanisms (such as template switching), generating complex copy-number structures, most often inverted duplications and duplication–triplication architectures, rather than simple reciprocal exchanges.
The study shows that this locus behaves as a highly unstable, palindrome-driven rearrangement hotspot, explaining why patients present with a characteristic spectrum of complex duplications involving 16p13.3. Importantly, these copy-number variants cause a recognizable and severe clinical phenotype, marked by early-onset progressive ataxia, cognitive decline, and cerebellar atrophy.

[1] https://www.ncbi.nlm.nih.gov/pubmed/41349538

BREAKAGE–REPLICATION/FUSION PROCESS

Genomes are frequently shaped by several mechanisms that generate massive structural complexity. The most relevant ones are breakage–fusion–bridge (BFB), chromothripsis, and what a recent paper in Nature Genetics by Zhang et al. (1) calls the "breakage–replication/fusion"

cycle. These mechanisms are related, but are not the same.
BFB (breakage–fusion–bridge) is a cyclical process: a broken chromosome end fuses to another end, forms a dicentric chromosome, breaks again during mitosis, and repeats the cycle. This process generates inverted duplications and amplifications, and it is very common in cancer, as suggested by the abundance of foldback junctions in tumor genomes.
Chromothripsis, instead, is primarily a catastrophic fragmentation event: a chromosome (or a chromosome arm) is shattered into many pieces in a single crisis and then stitched back together in a chaotic order. This nicely explains the famous oscillating copy-number patterns, but by itself it does not naturally explain copy-number gains, high-level amplifications, or complex insertions.
Zhang et al. propose a third concept: the breakage–replication/fusion cycle. The key idea is that if a broken DNA end enters S phase and gets replicated before being repaired, a single end can generate two "sister" ends, which can then fuse in different ways. Breakage–replication/fusion is not a new concept, but it is the first time that this long-known phenomenon is formalized as a general mechanism with clear genomic signatures and recognized as a major driver of structural complexity in cancer genomes, human disease, and genome evolution.
This has several important consequences:
replication of one broken end can produce two adjacent, parallel breakpoints
fusion of these replicated ends can directly generate duplications, foldbacks, and amplifycations
in the same cycle, short insertions derived from ssDNA can be incorporated at the junctions
In this framework, chromothripsis can be the initiating fragmentation event, but much of the subsequent complexity, including segmental gains and amplifications, can be built by breakage–replication/fusion cycles acting on the fragments. And many structures that have traditionally been interpreted as products of multi-generation BFB cycles may, in fact, arise from replication–fusion of broken fragments in a much more direct way.
So perhaps we should think less in terms of a single, isolated "chromosome catastrophe", and more in terms of what broken DNA ends do when they are allowed to replicate.

[1] https://www.ncbi.nlm.nih.gov/pubmed/41482535

GENES AND DEATH: THE EVOLUTIONARY TRADE-OFF

Mutations, sexual reproduction, and death are the cornerstones of evolution. But is death a programmed necessity or an evolutionary accident?
Organisms like the Hydra (specifically strain 105) have seemingly evaded aging during their 50 years in controlled laboratory settings; however, in the wild, death remains an almost inevitable and universal law of nature.
It is often suggested that evolution selected "genes for death" to benefit the species, but from a Darwinian perspective, this is a contradiction: natural selection favors individual survival and reproduction, not self-destruction.
A recent study by Sanchez et al. in Nature (1) resolves this paradox through the lens of antagonistic pleiotropy. The researchers identified a genetic axis in mice, Foxo1 and its effector Trim63 (MuRF1), that acts as a double-edged sword: In Youth: These genes are essential for disease tolerance. During severe infection (sepsis), they protect the heart from pathological remodeling and multi-organ injury, ensuring the individual survives long enough to reproduce. In Old Age: The same mechanism becomes maladaptive. In older mice, Foxo1 and Trim63 switch roles, driving the very cardiac damage and pathogenesis that leads to death.
This confirms a key rule of evolution: traits that provide a massive survival advantage during our reproductive prime are favored by selection, even if those same traits become the "executioners" that make us decrepit later in life. Death, then, is not the goal, but the price we pay for the defenses that kept us alive when it mattered most.

[1] https://www.ncbi.nlm.nih.gov/pubmed/41535469

GENETIC MUTATIONS: WHEN THE SAME GENE TELLS TWO DIFFERENT STORIES

Genetic mutations can fundamentally alter how a protein behaves: they can lead to a complete loss of function (LOF) or, in rarer cases, to an increased or persistent activity, known as gain of function (GOF). Generally, loss-of-function mutations tend to be recessive, requiring two affected copies of the gene, while gain-of-function mutations often act in a dominant manner.

The phenotypic outcomes of these two mechanisms can be so strikingly different that, without molecular investigation, it would be nearly impossible to guess that the same gene is responsible for both conditions.
A perfect example of this is the recent study by Bertola et al.(1) regarding the ATOH1 gene:
Recessive Loss-of-Function (LOF): When both copies of the ATOH1 gene are "broken," the result is a severe neurodevelopmental disorder. Patients exhibit profound hearing loss and significant brain underdevelopment, specifically severe cerebellar and pontine hypoplasia, leading to major cognitive and motor deficits.
Dominant Gain-of-Function (GOF): In contrast, specific mutations at the end of the gene (C-terminal) create a "hyper-stable" protein that doesn't degrade when it should. This leads to a much milder and distinct phenotype: a recognizable brainstem malformation, mild motor symptoms, and only mild-to-moderate hearing loss.

[1] https://www.cell.com/ajhg/abstract/S0002-9297(25)00487-2?dgcid=raven_jbs_aip_email

PLASTICITY OF THE XIST REGULATORY LANDSCAPE IN PRIMATE EVOLUTION

Evolution of X-chromosome inactivation mechanisms in primates has proven to be significantly more dynamic than previously assumed. A recent study published in Science Advances by Cazottes et al (1) provides a detailed comparative analysis of the X-chromosome inactivation center in humans, rhesus macaques, and marmosets. The authors employed a complex approach, including high-resolution chromatin conformation capture (Capture Hi-C), transcriptome analysis (RNA-seq), and transcript visualization via RNA-FISH. They discovered that a HERVK family retrotransposon integrated into the X-chromosome inactivation center within the macaque lineage. Using CUT&RUN profiling, researchers identified four CTCF binding sites within this insertion, which establish a new topological boundary in the 3D genome organization. This boundary effectively isolates the neighboring genes CHIC1 and NAP1L2 on the active X chromosome from the regulatory influence of the XIST domain. To confirm the functional significance of this element, authors utilized the CRISPR-Cas9 system for the targeted deletion of the HERVK insertion. This manipulation led to a "humanization" of the 3D architecture of the locus in macaques and the activation of ectopic contacts. The authors suggest that macaque-specific boundary between chromatin domains on the active X chromosome protects CHIC1 and NAP1L2 genes from ectopic interactions with putative enhancers located between the HERVK retrotransposon and the XIST gene. This study demonstrates the role of mobile elements as key genome architects capable of reshaping the chromatin landscape.

[1] https://www.science.org/doi/epdf/10.1126/sciadv.adw5839

HOW CELLS FIX THEIR OWN DEFECTS

For decades, geneticists have been intrigued by a paradox: some individuals carry severe mutations in essential genes yet show no signs of disease. This unexpected resilience is often explained by transcriptional adaptation (TA). When a gene is mutated, the cell does not simply lose the corresponding protein. Instead, it actively degrades the defective messenger RNA (mRNA). Somehow, this degradation triggers the activation of related genes, or paralogs, which can compensate for the missing function. Until recently, the mechanism linking RNA decay to gene activation in the nucleus was unclear.
El-Brolosy et al. (1) have identified the missing link in this cellular backup system. The crucial signal is not the mutation itself, but the specific mRNA decay products, small fragments generated from the defective transcript. These fragments act as signaling molecules. A key player is the protein ILF3, which binds these RNA fragments in the cytoplasm and transports them into the nucleus. There, the ILF3-bound fragments help locate and activate compensatory genes with similar sequences.
This mechanism is most effective for mutations that produce a faulty mRNA, such as nonsense mutations. In these cases, the destruction of the abnormal mRNA is what initiates the compensatory response. By contrast, if a gene is completely deleted, no mRNA is produced. Without mRNA to degrade, no signal fragments are generated, and the backup system remains silent.

[1] https://www.science.org/doi/10.1126/science.aea1272

DARWINIAN EVOLUTION OF TUMORS

The idea that tumors evolve through Darwinian processes had long been proposed, but it was the advent of single-cell analysis that finally provided direct experimental evidence. In 2011, Navin et al. (1) showed, using single-cell genomic analysis, that tumor evolution follows a Darwinian process. By resolving copy-number variation at the level of individual cells, his team reconstructed clonal expansions and phylogenetic relationships within tumors, using analytical approaches borrowed from evolutionary genetics.
Now, Ashford et al. (2) extend this evolutionary perspective further. Studying lung tumors, they identify a hallmark feature of Darwinian evolution: the diversification and potential neofunctionalization (acquisition of a new function) of duplicated genes and paralogs. Their analyses suggest that gene duplication can expand the adaptive landscape of cancer cells, enabling functional innovation that may enhance tumor fitness.
Together, these studies reinforce a powerful concept: tumors are not static masses of cells but evolving ecosystems, shaped by variation, selection, and innovation.

[1] https://www.nature.com/articles/nature09807
[2] https://genome.cshlp.org/content/early/2026/02/18/gr.278663.123

TRANSPOSABLE ELEMENTS (TE) IN CANCER AND IN EVOLUTION

A recent study of tumors with exceptionally high LINE-1 (L1) activity was published in Science (1). In just ten highly active tumors, more than 6,000 somatic L1 insertions were identified using long-read sequencing. Most were the expected 5′-truncated insertions. However, a small but significant fraction proved far more consequential. Rather than simply inserting into new loci, some L1 events bridged distant chromosomal breaks, generating deletions, inversions, duplications, and reciprocal translocations between non-homologous chromosomes. These rearrangements arise early during tumorigenesis and were propagated through subsequent clonal expansions, thus, supposedly, making a substantial contribution to the evolutionary trajectory of the tumor.

This same grammar that governs structural variation in tumors operates in the germline. The mechanism is the same; only the clock changes, it just runs much faster in cancer.
Recombination between non-allelic transposable elements, generating deletions, copy number variants, and chromosomal rearrangements, has been extensively documented by Lupski and colleagues in the human population (2).
When a deletion generated by repeat-mediated recombination becomes fixed in a population, it effectively disappears from the radar of present-day population studies. To uncover these “ghost” events, Batzer and colleagues (3) compared the human and chimpanzee genomes. They identified hundreds of human-specific deletions, totaling roughly 400 kb of DNA, mediated by Alu–Alu recombination. Many of these occurred within or near genes, and some removed functional exons that were present in our common ancestor.
Across tumors, populations, and species divergence, the underlying mechanism remains strikingly consistent. Transposable elements provide dispersed homologous substrates; DNA repair pathways resolve breaks between them; rearrangements arise. Selection then determines their fate.

[1] 10.1126/science.aee4513
[2] 10.1101/gr.229401.117
[3] 10.1086/504600

REPEAT EXPANSION IN THE NORMAL HUMAN POPULATION

Repeat expansions in the germline and in somatic tissues are classically studied because they cause disease. More than 60 inherited disorders are due to pathogenic repeat expansions, many of them involving trinucleotide repeats.
A new study in Nature (1) takes a different perspective. Instead of focusing only on disease-causing expansions, it asks a broader question: what is the background level of repeat instability in the general population?
The authors analyzed whole-genome sequencing data from more than 900,000 individuals, combining two extraordinary resources: the UK Biobank (~490,000 participants) and the All of Us Research Program (US, ~415,000 participants).
The authors systematically examined over 356,000 polymorphic short tandem repeats across the genome, quantifying both germline mutation rates and somatic expansions in blood. The result is a population-scale map of repeat instability, revealing that many repeats are dynamic even in

people without diagnosed repeat-expansion disorders.
In other words, repeat expansion is not only a rare pathogenic event. It is a widespread, measurable, genetically modulated biological process shaping human genomes throughout life.

[1] 10.1038/s41586-025-09886-z

GENES ESCAPING X-INACTIVATION

In biology, things are often far more complex than we once imagined, and DeCasien's work brings this into sharp focus through the lens of genes that escape X chromosome inactivation (XCI).
While it was traditionally believed that XCI was a relatively uniform process and that genes in the pseudoautosomal regions (PAR) completely escaped inactivation to be expressed from both sex chromosomes, this research reveals a much more nuanced reality. DeCasien (1) demonstrates that XCI actually extends into these PAR areas, influencing genes like CD99 and PLCXD1 and explaining why many of them unexpectedly show higher expression in males.
The study further challenges the long-held assumption that higher expression in females is a definitive marker of a gene escaping inactivation. It turns out that many genes previously labeled as "escapers" based on sex-biased expression are actually subject to XCI, while others that do escape show no significant difference between sexes. This intricate landscape is heavily dictated by the 3D architecture of the genome; genes grouped within the same Topologically Associating Domains (TADs) tend to share similar escape patterns. Ultimately, the interplay between varying XCI intensity and sex-specific enhancer activity creates a sophisticated regulatory balance that shapes how our sex chromosomes function across different tissues.

[1] 10.1186/s12864-026-12611-3

MEIOTIC RECOMBINATION AND ANEUPLOIDY

The relationship between reduced meiotic crossover and aneuploidies in females is well known. Carioscia et al., in a paper published in Nature (1), investigated this relationship in a very large PGT study, comprising over 139,000 IVF embryos, a scale that allows the study of inviable aneuploidies that never reach live birth and provides statistical power unavailable to earlier work.
The central new contribution is demonstrating that common genetic variants shape both recombination rate and aneuploidy risk simultaneously. The strongest signal is a haplotype spanning SMC1B, encoding a meiotic cohesin subunit, where a promoter-proximate SNP reduces ATF1 transcription factor binding and lowers SMC1B expression, a non-coding regulatory mechanism validated experimentally with an electrophoretic mobility shift assay. Transcriptome-wide analyses additionally implycate C14orf39, CCNB1IP1, and RNF212 in aneuploidy risk. These genes were previously connected only to recombination phenotypes.
The paper also shows that several of these same variants associate with age at menarche and menopause, suggesting a shared genetic logic linking meiotic fidelity and female reproductive lifespan. Finally, the authors tackle an evolutionary paradox: if these alleles reduce fitness, why are they common? Their modelling argues that the loose connection between embryo euploidy and realized fitness — mediated by environment, behaviour, and parental care — is sufficient to let risk alleles drift to intermediate frequencies despite negative selection pressure.

[1] 10.1038/s41586-025-09964-2

RETHINKING EMBRYO SELECTION IN PGT-A

A recent paper in Reproductive BioMedicine Online (1) explores whether it is time to rethink how we interpret chromosomal abnormalities detected during preimplantation genetic testing for aneuploidy (PGT-A).
The authors argue that current approaches may lead to the unnecessary discard of potentially viable embryos because they do not clearly distinguish between meiotic aneuploidies, which affect the entire embryo, and mitotic abnormalities, which arise later and often remain confined to the trophectoderm.
By combining genome-wide SNP parental haplotyping (karyomapping) with allelic intensity analysis, it is possible to determine the origin of chromosomal alterations and differentiate meiotic from mitotic events. This distinction is clinically relevant: embryos showing only mitotic imbalances with normal biparental inheritance may still retain developmental potential and

could be considered for transfer with appropriate genetic counselling.
The work highlights the importance of adopting more informative genomic approaches to reduce the risk of discarding embryos that might lead to healthy live births.

[1] 10.1016/j.rbmo.2026.105504

ANOTHER EXAMPLE OF HOW GENOMIC BACKGROUND CAN MODULATE PENETRANCE

Huntington's disease (HD) is caused by an expanded CAG repeat in the HTT gene, a highly penetrant mutation with predictable, devastating consequences. Yet onset can vary by decades among carriers.
A new PNAS study (1) points to LIG1, the gene encoding DNA Ligase 1. A rare missense variant, K845N, substitutes a lysine for an asparagine in the oligonucleotide-binding domain of LIG1 and is associated with a 7–8 year delay in motor onset in HD patients.
The mechanism: K845N increases the enzyme's ability to discriminate against mismatched DNA substrates - particularly promutagenic 8-oxoG:A mispairs - thereby enhancing repair fidelity and slowing the somatic CAG repeat expansion that drives HD progression. Mouse knock-in models confirmed that the orthologous K843N variant significantly suppresses somatic expansion in striatum and liver.

[1] 10.1073/pnas.2518854123

CAN A MOUSE BE CLONED INDEFINITELY?

When Wakayama's work on indefinite recloning of mice was published in 2013 (1), it had the impact of a lightning bolt on the scientific community. That paper appeared to shatter every established dogma. It suggested that, through the use of Trichostatin A (TSA) for epigenetics reprogramming, a way had been found to make a genetic lineage potentially immortal, overcoming the biological limits of cellular decay.

In March 2026, however, a more in-depth study published by the same team has produced opposite results (2); see also a commentary in Nature (3). The experiment lasted a full 20 years. While the first study had focused on the cell's "software" (epigenetics), this new work went on to examine the integrity of the "hardware" (the DNA itself). Recloning of mice continued for over 30,000 attempts, going well beyond the 25 generations of the 2013 experiments. And that is where the surprise emerged: recloning is not infinite. The lineage terminated at the 58th generation. Despite the clones appearing healthy and living as long as normal mice, their DNA was silently accumulating enormous, lethal structural mutations. As early as the 27th generation, the success rate began to collapse, until total extinction.
The conclusion stands as a perfect antithesis of the one from ten years prior: serial cloning in mammals has an insurmountable biological ceiling. Notably, when these "terminal" clones were mated with normal males, meiosis (sexual reproduction) managed to "clean up" most of those genetic errors, allowing healthy offspring to be born, a finding that calls to mind the work titled "Sexual selection protects against extinction" appeared in Nature in 2015 (2648.pdf).

[1] http://dx.doi.org/10.1016/j.stem.2013.01.005
[2] https://doi.org/10.1038/s41467-026-69765-7
[3] https://doi.org/10.1038/d41586-026-00945-7
[4] https://doi.org/10.1038/nature14419

ONE GENE, MANY FACES

A commentary in Trends in Genetics (1) puts the spotlight on one of the most complex phenomena in human genetics: a single gene that manifests across apparently unrelated disorders.
GRIN2A encodes a subunit of the NMDA receptor, a key player in glutamatergic signaling in the brain. Over the years it has been linked to epilepsy, language impairment, and, more recently, schizophrenia. But how can phenotypes so different all trace back to the same gene?
The answer, at least in part, lies in how patients are studied. Lemke et al. (2) recontacted a cohort of carriers of pathogenic GRIN2A variants, many of whom had originally been recruited for epilepsy and aphasia, and found that roughly one in five also carried psychiatric diagnoses, particularly associated with loss-of-function variants. A finding that had simply been invisible in earlier studies, because the recruitment criteria weren't designed to look for it.
It is a powerful reminder: genotype–phenotype relationships are not fixed properties of genes; they also reflect the methodological choices of those who study them. Broadening the bounda-

ries of observation, both over time and in phenotypic depth, can radically change the picture.

[1] https://doi.org/10.1016/j.tig.2026.02.004
[2] https://doi.org/10.1038/s41380-025-03279-4

GGC REPEAT EXPANSIONS AND THE DISCOVERY OF HIDDEN TOXIC PROTEINS

Trinucleotide repeat expansions are a well-established cause of over 60 genetic disorders, but their pathogenicity often remains a mystery when they occur in "non-coding" regions. While traditional models focus on RNA toxicity or loss of function, a new study published in Nature Genetics (1) reveals a surprising twist in the tale of Oculopharyngodistal Myopathy (OPDM) and Oculopharyngeal Myopathy with Leukoencephalopathy (OPML).
The researchers discovered that these GGC expansions are not actually in silent regions. Instead, they are embedded within previously unrecognized open reading frames. This means that sequences are translated into entirely new, toxic polyglycine-containing proteins. These new proteins aggregate into the p62-positive inclusions that are the hallmark of these diseases, directly causing muscle and neuronal degeneration.

[1] https://doi.org/10.1038/s41588-026-02507-z

SMALL SUPERNUMERARY MARKER CHROMOSOMES (sSMCs)

Saether et al. (1) used long-read genome sequencing (lrGS) combined with the T2T-CHM13 assembly to characterize 10 small supernumerary marker chromosomes (sSMCs), which are hard to resolve with standard methods. The authors managed to resolve 9 out of 10 at base-pair resolution, identifying breakpoint junctions and inferring how they formed.
Simple sSMCs tend to form through microhomology-mediated end joining (MMEJ) or microhomology-mediated break-induced replication (MMBIR), while the complex ones show signs of chromoanasynthesis and breakage–fusion–bridge cycles. Haplotype analysis pointed to trisomy rescue as a key formation mechanism in four cases, including all three complex sSMCs. Mosaicism rates across cases ranged from 13% to 100%, raising interesting questions about how this variability shapes both the phenotype and the ability to detect breakpoints. Nearly all simple sSMCs had at least one breakpoint within a centromere, consistent with centromeric instability playing a central role in their formation. In four of the 28 breakpoint junctions, the breakpoint was located in genomic sequence present in T2T-CHM13 but absent from GRCh38; a reminder of why the new reference genome matters.
Case RD_P274, a ring of chromosoe 10, remained unresolved due to breakpoints in highly repetitive acrocentric p-arm regions, highlighting that even lrGS has limits, and that cytogenetics and pangenome references will continue to play an important complementary role.
Deeper functional analysis of the genes within these segments and a richer clinical follow-up linking molecular complexity to patient outcomes, will be key to unlocking the full diagnostic and counseling potential of this approach.

[1] 10.1101/gr.281175.125

REJECTION OF THE OTHER AS WELL AS REJECTION OF THE SELF, HAVE A ROLE IN EVOLUTION

We often think of self/non-self discrimination as an immunological concept. The major histocompatibility complex (MHC) is the best example: this highly polymorphic genomic region allows the immune system to distinguish "me" from "not me," triggering rejection of foreign tissues and pathogens. But evolution has gone further: in the context of reproduction, it has repeatedly invented ways to reject the self.
Take flowering plants. Many species carry self-incompatibility systems, typically governed by a single highly polymorphic locus (the S-locus), that allow the pistil to recognize and reject pollen carrying the same genetic identity as the plant itself. It is, in essence, a molecular veto against selfing. This system has been repeatedly dismantled during plant domestication: when breeders wanted to fix a desirable trait and needed inbreeding to stabilize it, self-incompatibility became an obstacle, and selection, natural or artificial, simply got rid of it. See grapes, peas (Mendel used self pollination).
Move to the nervous system, and you find yet another version of the same idea. Neurons use surface proteins, most famously the Dscam family, to avoid making synaptic connections

with their own dendrites. A neuron, in other words, can recognize itself and actively refuse to connect. This self-avoidance is essential for the proper wiring of neural circuits: without it, a cell's processes would collapse onto each other rather than spreading out to sample the environment.
And now, a paper just published in PLOS Biology adds a remarkable new chapter to this story, this time in primates. Petersen et al. (1) studied olive baboons (Papio anubis) and found that the female vaginal tract can discriminate between sperm based on the genetic makeup of the male. After mating with males who are genetically more similar, particularly at the MHC, females showed stronger vaginal immune responses and a more pronounced drop in vaginal pH, both conditions that are hostile to sperm survival. The effect is subtler than outright rejection, but the logic is the same: the female reproductive tract appears to create a less favorable environment for sperm that are, genetically speaking, too close to home.

[1] 10.1371/journal.pbio.3003699

What about Homo sapiens? If you want to dive deeper, check out these papers:
Wedekind et al. 1995 10.1098/rspb.1995.0087
Fitzpatrick et al. 2020 10.1098/rspb.2020.0805
Colaco et al. 2015 10.1186/1477-7827-4-S1-S10

WHY SO MANY DIFFERENT TRANSCRIPTS

When the Human Genome Project was nearing completion, expectations were high. How many genes does Homo sapiens carry? Estimates ranged from 80,000 to 150,000, with some voices pushing toward 200,000. The reasoning was intuitive: we are complex, we are unique, our genome must reflect that. The answer was deflating: somewhere between 20,000 and 25,000 protein-coding genes. About the same as a mouse. Not far from a worm.
Biology quickly found a way to restore our sense of exceptionalism. Never mind gene number. Human cells produce a remarkable diversity of transcripts through alternative splicing. We might share the same gene catalogue as a rodent, but we were running far more sophisticated software on the same hardware. Complexity rescued from the jaws of humility.
Then came ENCODE. In 2012, the project declared that roughly 80% of the human genome shows biochemical activity and should therefore be considered "functional." The concept of junk DNA was pronounced dead. Everything was there for a reason.
A new paper by Mi et al., published in PLOS Biology [(1), and a commentary (2)], adds another chapter to this recurring story. The question is simple: why do large-bodied species like humans have so many alternative transcripts? The answer is not flattering. Most of that transcript diversity is molecular noise, errors in RNA processing that natural selection is too weak to eliminate.
The explanation comes from population genetics. Species with small effective population sizes, and humans qualify because we are large, long-lived, and slow to reproduce, experience weaker natural selection. Mildly harmful errors accumulate not because they are useful, but because chance overwhelms selection. Mi et al. show, across 67 animal species, that transcript diversity scales predictably with small population size. And the extra transcripts look like mistakes because they are mistakes: they are rare, carry weak splice sites, and contain premature stop codons.
What is striking, looking back, is how persistent our tendency is to read molecular complexity as a mark of distinction. Each time genomics has handed us a mirror, we have found a way to see confirmation of our uniqueness. And each time, a more careful evolutionary reading has suggested a simpler, less flattering explanation.

[1] 10.1371/journal.pbio.3003671
[2] 10.1371/journal.pbio.3003686

INVERSIONS

Chromosomal inversions anchor genes inside the inverted segment by suppressing recombination, effectively "locking" beneficial allele combinations together and preventing them from being reshuffled during meiosis. These genomic regions are often referred to as "Supergenes." A recent study by Akopyan et al. in Science [1] illustrates this principle in a marine fish adapting along a steep thermal gradient. Inversions maintain the advantageous adaptation despite extensive gene flow.

What about humans?

A well-known example is the **17q21.31 inversion**, a large genomic segment common in populations of European descent, described by Stefansson et al. in 2005 [2]. This region exists in two primary forms (H1 and the inverted H2). By suppressing crossover during meiosis, the H2

lineage has remained genetically distinct for over 2 million years. Women carrying the H2 variant tend to have more children, suggesting this inversion is maintained by positive selection on fertility.
Other examples:
High-altitude survival: Inversions on chromosome 2 help preserve clusters of hypoxia-related genes that allow Tibetan populations to thrive in low-oxygen environments [3].
Immune defense: A major inversion on **chromosome 8 (8p23.1)** maintains a high density block of defensin genes, equipping local populations with a specialized genomic toolkit to combat region-specific pathogens [4].
This last inversion at 8p23.1 was described by Giglio et al. [5] as a polymorphism present in ~26% of Europeans, where heterozygosity predisposes to severe chromosomal rearrangements. The same structural variant that locks in immune defensins also carries a genomic cost for the next generation. A perfect example of an evolutionary trade-off that maintains the inversion polymorphism at high frequency in the European population.

[1] 10.1126/science.ady6774
[2] 10.1038/ng1508
[3] 10.1371/journal.pone.0017002
[4] https://pubmed.ncbi.nlm.nih.gov/10375637/
[5] https://pubmed.ncbi.nlm.nih.gov/11231899/

GENE KNOCKOUTS IN HUMANS

In the mouse, knocking out a gene has long been the standard way to find out what it actually does. In humans, deliberate gene knockouts are obviously off-limits, but nature sometimes does the experiment for us. In populations where consanguineous marriages are common, long runs of homozygosity enrich the pool of rare variants carried in biallelic state, producing living, phenotyped adults in whom both copies of a gene are inactivated. Pakistan and Bangladesh (~60% first-cousin marriages) are among the most informative settings, and the large diaspora from these regions in the UK has made British South Asians a particularly attractive cohort for this kind of genetics.
Saleheen et al. (1) first laid out this rationale in PROMIS (Pakistan Risk of Myocardial Infarction Study), a Pakistani case-control cohort, uncovering homozygous loss-of-function (LoF) mutations in >1,300 genes and sketching the roadmap for a "human knockout project."
Heng et al. (2) then showed in the British Pakistani and Bangladeshi Genes & Health cohort (G&H project) that this same autozygosity unmasks 185 recessive loci for common diseases; signals routinely missed by additive genome-wide association studies (GWAS).
The new Nature Genetics paper (March 2026) from the G&H team delivers the full exome resource: whole-exome sequencing of 44,028 participants linked to longitudinal electronic health records from the UK National Health Service (NHS), now publicly available.
Key findings:
a) 2,991 genes with biallelic predicted loss-of-function or predicted damaging genotypes, 546 of them novel human knockouts.
b) >100 novel gene–phenotype associations from exome-wide association on 645 traits derived from electronic health records (EHR) and meta-analyses with UK Biobank.
c) Drugs targeting genes with adult human knockouts are ~2.2× more likely to progress beyond phase 1 clinical trials, a compelling argument for naturally occurring human LoF variants in drug target validation.
From PROMIS to G&H: proof of concept → recessive signals beyond GWAS → an open exome resource already delivering novel biology and drug-target insight. For rare-variant and translational genetics in non-European ancestries, G&H is becoming hard to ignore.

[1] https://www.nature.com/articles/nature22034
[2] https://www.cell.com/ajhg/fulltext/S0002-9297(25)00141-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002929725001417%3Fshowall%3Dtrue
[3] https://www.nature.com/articles/s41588-026-02553-7

THE INACTIVE X AS A FEMALE PROTECTOR

Autism affects three to four males for every female, and the same male bias runs through a long list of paediatric and congenital autosomal disorders: ADHD, intellectual disability, congenital heart disease, Hirschsprung disease, pyloric stenosis, clubfoot, and others. The underlying mechanism of this Female Protective Effect (FPE) has remained elusive.
In a Nature Genetics Perspective (April 2026), Maya Talukdar and David C. Page (1) propose a simple unifying explanation: the inactive X chromosome (Xi), considered transcriptionally

silent since Mary Lyon's 1961 work, is the hidden protector.
The argument rests on three points:

1. Xi is not silent. At least 60 protein-coding genes escape X-inactivation and are transcribed from Xi alongside Xa, giving females a higher total dosage than males (whose Y-linked homologues are often functionally divergent).
2. These Xi-expressed genes are dosage-sensitive global regulators of chromatin (KDM6A, KDM5C), transcription (ZFX), translation (DDX3X), and ubiquitination (USP9X) — the very pathways disrupted in autism.
3. Higher baseline dosage buffers autosomal mutations. Females can tolerate deleterious variants that in males push the system past threshold. Xi acts as a genetic suppressor of autosomal mutations.

The same framework is then applied by the authors to 17 other male-biased paediatric disorders (Table 1 in the paper), each showing consistent FPE signatures (higher familial recurrence when the index case is female; the Carter effect).
The framework remains hypothesis-generating rather than a primary study, but it ties together a remarkable amount of scattered evidence under one experimentally testable mechanism.
It is worth stressing that the disorders discussed here are autosomal, not X-linked. The mechanism proposed is that Xi expression buffers autosomal mutations. It has nothing to do with classical X-linked inheritance.

[1] https://www.nature.com/articles/s41588-026-02534-w

THE FALL OF A DOGMA: PROTEIN-TEMPLATED DNA SYNTHESIS

1956–1958: A. Kornberg — DNA synthesis from a DNA template, following Watson–Crick base pairing.
1970: Temin and Baltimore — DNA synthesis from an RNA template (Reverse Transcriptase).
DNA synthesis from a protein template? A heresy against the dogma.
April 2026: the heresy becomes reality. Deng et al. report a bacterial enzyme that uses its own amino acid structure as the template for DNA synthesis (1).
Technically, this mechanism is part of a bacterial defense system (DRT3) in which the enzyme Drt3b produces short, alternating dinucleotide repeats. The conceptual weight of this discovery lies not in the length of the sequence, but in the process: the enzyme does not "read" a sequence of nucleotides. Instead, it uses its own amino acid structure and active site residues as a blueprint to assemble DNA. By mimicking the role of a traditional template, the protein itself dictates the genetic sequence. It is a profound conceptual shift that demonstrates life has evolved fundamentally new ways to produce genetic information, effectively rewriting the "Central Dogma."

[1] https://www.science.org/doi/10.1126/science.aed1656

MICROARRAYS AND SOMATIC MOSAICISM

or: How software can revolutionize old microarrays data.

Deep genome sequencing remains the gold standard for detecting somatic clonal mosaicism, but its cost keeps it out of routine use. C. Terau has found a way to extract this information from standard DNA microarrays that already exist by the millions (1).
The key is MoChA (Mosaic Chromosomal Alterations), a specialized software tool that detects mosaic mutations, the subtle changes occurring in only a fraction of cells as we age, which are linked to future risks of blood cancers and cardiovascular disease.
This new "digital lens" can re-analyze the vast archive of microarray data already in existence. A compelling example of how smart bioinformatics can transform routine diagnostic tools into powerful research instruments, without generating a single new sample.

[1] https://www.nature.com/articles/s41576-026-00948-0

SEX CHROMOSOMES AND HEALTH

The X and Y chromosomes are not just "genetic instructions" for reproduction; they are active drivers of human health. Key examples include why certain drugs, such as statins, cause more side effects in women, and how the loss of the Y chromosome in aging men is linked to heart disease. A Nature Feature article (April 2026) maps out the current state of the field (1).

https://www.nature.com/articles/d41586-026-01256-7

WHY DO FERTILIZED EGGS KEEP PARENTAL GENOMES APART

After fertilization, the egg and sperm do not immediately merge their chromosomes. The maternal and paternal genomes remain enclosed in two separate pronuclei for roughly 10–12 hours in mice and 16–20 hours in humans. This prolonged separation has long been considered a mechanical byproduct of fertilization. A new study in Nature shows it is functionally essential (1)
To test this, the authors developed a novel ICSI approach: by injecting the sperm adjacent to the maternal chromosomes rather than away from them, they generated zygotes where both parental genomes are enclosed in a single enlarged pronucleus from the start (1PN). The result: without a rival pronucleus to compete with, the single structure grows too large, disrupting histone trimethylation patterns and sharply reducing developmental potential to term, even though early cleavage looks normal in vitro.
The finding is counterintuitive: the two pronuclei don't cooperate, they compete for cytoplasmic resources, and that competition is what keeps epigenetic regulation on track. It is a striking example of intragenomic conflict co-opted as a developmental mechanism.
Clinically, 1PN zygotes arise in 2–8% of IVF/ICSI cycles and are increasingly used in transfer. This study provides the first mechanistic explanation for their lower success rates, and hints at possible pharmacological rescue.

[1] https://www.nature.com/articles/s41586-026-10417-7

3D LAMPBRUSH CHROMOSOMES ORGANIZATION IN CHICKEN OOCYTE

Understanding how chromosomes fold in 3D space is one of the central questions in modern cell biology. Lampbrush chromosomes, with their spectacular chromomere–loop architecture, offer a uniquely accessible window into this problem.
A new study in Nucleic Acids Research by Lagunov et a. (1) presents the first genome-wide Hi-C (chromosome conformation capture) analysis of lampbrush chromosomes, integrating single-nucleus Hi-C, RNA-seq, NOMe-seq (Nucleosome Occupancy and Methylome sequencing), FISH mapping, and polymer simulations. The authors show that chromatin domains in lampbrush chromosomes are formed independently of CTCF (a key chromatin insulator protein that demarcates domain boundaries in somatic cells). Instead, their boundaries are defined by the orientation of transcription units, with convergently oriented gene pairs acting as insulating barriers. Active transcription repositions SMC (Structural Maintenance of Chromosomes) complexes and stiffens chromatin, driving the extrusion of lateral loops away from the chromosome axis. A biophysical model quantitatively reproduces these features, providing a unified mechanistic framework for lampbrush chromosome architecture.

[1] https://academic.oup.com/nar/article/54/7/gkag316/8653609

AMYLASE GENE COPY NUMBER AND POTATOES

An earlier post explored the correlation between AMY1 (salivary amylase) gene duplications and high-starch diets. The AMY1 gene is expressed in saliva and initiates the digestion of starch.
A clear confirmation of this diet-duplication link comes from a study by Scheer et al. (1), recently published in Nature Communications (2026), which found that indigenous Peruvian Andean populations harbor the highest AMY1 copy numbers worldwide. The expansion dated to approximately 10,000 years ago, coinciding precisely with the domestication of the potato in the Southern Andes.

[1] https://doi.org/10.1038/s41467-026-71450-8

GERMLINE IMMORTALITY

Every generation is born biologically young, even when parents are old.
A new essay in PLOS Biology by Chiavellini and Sebastiano (1) argues that the answer lies in the oocyte.
Despite residing in an aging ovary within an aging organism, the egg executes a remarkable molecular reset before passing the genome to the next generation. Global epigenetic reprogramming erases age-associated drift accumulated over a lifetime; a mitochondrial bottleneck selectively amplifies high-functioning organelles and filters out dysfunctional ones; autophagy clears damaged proteins at the moment of fertilization. No other adult cell type routinely performs this coordinated renewal. The authors call it a

blueprint for rejuvenation, and draw a direct parallel to experimental approaches such as partial reprogramming, which attempt to recreate in somatic tissues what the oocyte does naturally.

The reset operates across three layers simultaneously: the epigenome, the organelles, and the proteome. It is also tightly regulated, not haphazard. Certain genomic regions resist complete demethylation, preserving stability. The ovarian niche itself contributes, selecting through atresia the most competent oocytes for reproduction. And crucially, the oocyte does not act alone: the cytoplasmic machinery that reprograms both parental genomes after fertilization is entirely of maternal origin, including the elimination of paternal mitochondria. The egg is not just a vehicle for DNA, it is the engine of biological renewal.

But this reset has a fundamental limit. The oocyte resets the epigenome, the mitochondria, the proteome. It does not rewrite the DNA sequence itself. Genomic mutations accumulate in the parental germline and are faithfully transmitted to the offspring. As discussed in an earleir post, serial cloning experiments showed exactly this: oocyte-mediated reprogramming occurred at every generation, yet underlying DNA mutations continued to accumulate until the lineage collapsed at generation 58 (2).

This is where sexual reproduction acts as the complementary mechanism. Meiosis and recombination reshuffle variation; selection then acts on the result. As shown experimentally in Tribolium flour beetles, populations with strong sexual selection — male competition, female choice — purge deleterious variants far more effectively than those reproducing without it (3). The oocyte resets what each generation inherits at the molecular level; sexual selection filters the DNA sequence itself across generations. Together, they explain what the germline actually is: an unbroken chain of living cells that reaches back, without a single interruption, to the origin of life 3.5 billion years ago.

[1] https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3003804
[2] https://www.nature.com/articles/s41467-026-69765-7
[3] https://www.nature.com/articles/nature14419

MATTER ARISING — NATURAL PARAMUTATION IN MAMMALS FINALLY CAUGHT IN THE ACT

Paramutation has long been a curiosity of plant genetics: an allele that, when present alongside its homolog in a heterozygous cell, alters the methylation state of it, and this altered state is then inherited by the next generation, independent of DNA sequence. Maize geneticists have known this since the 1950s. Mammalian bio--logists have largely treated it as someone else's problem.

A paper just published in Nature Genetics (1) changes that. The key methodological enabler is long-read Oxford Nanopore sequencing, which reads genetic sequence and DNA methylation simultaneously on the same DNA molecule. **Because a single long read can span multiple SNPs, each read can be unambiguously assigned to a specific parental haplotype. This makes it possible to determine, for every CpG site in the genome, whether its methylation state is of maternal or paternal origin**. Short-read bisulfite sequencing cannot do this: it destroys haplotype information and forces averaging across alleles.

Using Oxford Nanopore sequencing across three generations of mice, the authors mapped epigenetic inheritance genome-wide and confirmed the first naturally occurring intergenerational paramutation in a mammal, at the Capn11 locus, with two additional highly likely cases involving strain-specific transposable elements.

The broader picture is equally striking: roughly 7% of autosomal epigenetic inheritance patterns are non-Mendelian. That is not a rounding error. It has direct implications for incomplete penetrance, transgenerational effects of environmental exposures, and the still-underexplored space between genetics and phenotype.

Mendel's laws remain a good first approximation. But at 7% of autosomal loci, the exceptions are too frequent to ignore.

[1] https://www.nature.com/articles/s41588-026-02604-z

TWO CLOCKS, ONE BODY: A NEW MAP OF MAMMALIAN AGEING

The serial cloning experiments discussed in two earlier posts have recently been joined by a new paper that reframes them. The new paper, published in Nature (1), offers a molecular map of mammalian ageing precise enough to show, in retrospect, exactly what those experiments were measuring — and what they were missing. The earlier posts now read as two chapters of a larger story.

The paper does something that had never been done at this scale: it integrates more than 11,000 transcriptomes from over 25 tissues across four mammalian species — mouse, rat, macaque, and human — to build a unified molecular portrait of ageing and mortality. The result is not a single clock but a modular architecture: 28 co-regulated gene expression modules, each tracking a different biological subsystem, from inflammation and interferon signalling to mitochondrial respiration and chromatin remodelling. The most striking finding is that the mortality-associated transcriptomic signature is conserved across species and cell types — and that it can be reversed. Reprogramming, cell immortalisation, heterochronic parabiosis, and early embryogenesis all attenuate or erase it. Epigenetic age, the paper makes clear, is a state, not a sentence.

This brings into sharp focus a distinction that two earlier papers from the Wakayama laboratory illuminate with unusual clarity. In 2013, that group reported serial recloning of mice through 25 generations using somatic cell nuclear transfer with trichostatin A (TSA) as an epigenetic reprogramming agent (2). Efficiency did not decline. Body weight, lifespan, and fertility remained normal. No accumulation of epigenetic abnormalities was detected. The conclusion — that serial cloning might continue indefinitely — was bold, but the data supported it. What the experiment had demonstrated, without framing it in those terms, was a repeated, successful reset of precisely the transcriptomic ageing signature that the Nature paper now maps so carefully: each round of nuclear transfer was, in effect, a rejuvenation of the epigenetic layer.

The sequel, published in Nature Communications in 2026 by the same group after twenty years of continued experiment (3), tells a different story. Cloning was continued through 58 generations before the lineage finally collapsed. And here the two levels diverge completely. Epigenetic reprogramming kept working: histone modification profiles in 51st-generation embryos were indistinguishable from those of first-generation clones. The transcriptomic clock was being reset at every cycle. But the DNA sequence itself — the hardware beneath the software — was silently accumulating damage that no reprogramming could touch. Whole-genome sequencing revealed approximately 3,700 single-nucleotide variants from generation 1 to 57, plus large structural variants including chromosome translocations and loss of an entire X chromosome. The cloned mice looked normal, lived normally, and died normally — until the mutational load crossed a threshold and the lineage simply ended.

The two levels, in other words, are genuinely parallel and genuinely non-intersecting. The epigenetic/transcriptomic level is malleable: it can be measured by molecular clocks, modulated by dietary or pharmacological interventions, and reset by reprogramming. The mutational level is a ratchet: it accumulates with each cell division, leaves no trace in gene expression profiles, and cannot be erased by any known biological mechanism short of meiosis. When the near-final-generation cloned females were mated with normal males, a small fraction of embryos survived — rescued by meiotic recombination and fertilisation. The experiment thus provides, almost accidentally, a direct demonstration of why mammals reproduce sexually: not merely to generate variation, but to purge a mutational debt that clonal reproduction accumulates without limit.

The practical implication is sobering. The molecular clocks built in the Nature paper — transcriptomic, epigenomic, proteomic — measure the reversible layer with impressive precision. But they are blind to the other layer. An intervention that dramatically lowers your clock age while leaving somatic mutation burden untouched may be doing something real and valuable at one level, while the underlying genetic text continues to erode at the other. Both currencies of ageing are real. Neither is sufficient on its own. And the most honest reading of these three papers together is that we now have a clearer map of what can be reversed — and a much clearer view of what cannot.

[1] https://doi.org/10.1038/s41586-026-10542-3
[2] http://dx.doi.org/10.1016/j.stem.2013.01.005
[3] https://doi.org/10.1038/s41467-026-69765-7

NATURE vs NURTURE

Nature vs. nurture is one of the oldest and most loaded debates in science: how much of who we are, especially our intelligence, comes from our genes versus our environment? It's a topic that's not just academically complex, but socially and politically charged, since the answers we settle on shape how we think about inequality, education policy, and opportunity.

It's also a field where caution is warranted. Psychology and neuroscience have a well-documented replication problem. The Open Science Collaboration group (1) found that only about **a third of psychology studies could be reproduced**. This refers especially to brain research linking brain measures to behavior or cognition because these studies often relied on samples that were far too small to detect the tiny effects involved.

It appears that a new study just published in Science (2) could be a milestone precisely because it was designed with these concerns in mind. It draws on thousands of children, splits the data into discovery and replication samples, and then re-tests its main findings in two completely independent datasets of tens of thousands of adults.

The researchers scanned the brains of thousands of 9–10-year-olds and tested 649 environmental, social and behavioral factors against brain structure and function. The single strongest, most reliable association with the brain wasn't IQ it was the socioeconomic status of the child's neighborhood. And here's the twist: once they accounted for socioeconomic status, the classic "brain-IQ" link that decades of neuroimaging research has reported, largely fell apart. **95% of those associations weakened, and 70% became statistically non-significant.** Brain models trained to "read" IQ from scans turned out to actually be picking up signatures of stress, sleep quality and arousal linked to socioeconomic conditions, not some intrinsic biological marker of intelligence. The pattern held up in adults too.

Does this settle nature vs. nurture? Not quite. Genes still clearly matter, and socioeconomic status explains at most ~16% of brain variability, leaving most of it unexplained. But it's a powerful reminder that the environment a child grows up in leaves deep, measurable marks on the developping brain, and that some of what looked like "the biology of intelligence" may really be the biology of inequality. As the authors put it: socioeconomic opportunity is not destiny, but it clearly shapes the starting line.

[1] https://www.science.org/doi/10.1126/science.aac4716
[2] https://www.science.org/doi/10.1126/science.aee6213

THE EQUILIBRIUM OF THE MUTATION RATE

Every organism needs mutations to evolve. Too many mutations would be catastrophic. But too few would be just as bad - perhaps worse. Without a steady supply of new variants, populations would indeed lose the raw material needed to adapt to changing environments. The mutation rate is therefore not a flaw in the system. It is the system.

Porubsky et al. (1) have calculated, thanks to long-read sequencing, that every time a human being has a child, the newborn's genome carries an average of about 75 new point mutations, contributed roughly equally by each parent.

De Manuel and colleagues (2) looked for the mutation rate beyond humans. Measuring germline mutation rates across dozens of animal species, from nematodes with generation times of just three days, to whales that reproduce every two decades, they found that the rate per base pair per generation barely changes: it stays within roughly one order of magnitude (~10-9 to 10-8) across the entire animal kingdom. A mouse passes along fewer absolute mutations per generation than a human, but the per-bp rate is comparable. So does a fruit fly, a stickleback, a chimpanzee.

Three orders of magnitude in generation time and one order of magnitude in mutation rate is not a coincidence. It is a signature of natural selection actively maintaining an equilibrium. Species that drift too far above it, pay a fitness cost in deleterious mutations; those that drift too far below it, lose evolutionary flexibility. The result, across radically different life histories and environments, converges on roughly the same solution.

Understanding how selection enforces this balance, through the interplay of DNA repair fidelity, damage tolerance, and population size, is now one of the central questions in evolutionary biology. But the fact that such a balance exists, and that it is shared so broadly across the tree of life, is itself a remarkable discovery.

[1] https://www.nature.com/articles/s41586-025-08922-2
[2] https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3003799

WHY DO WE AGE AND DIE?

Biologists have been arguing about it for seventy years, and they still don't agree.
Three main theories have been on the table since the 1950s.
The first, due to Peter Medawar (1), says aging is essentially evolutionary negligence. In the wild, most animals die young — from predation, starvation, disease. So natural selection barely sees what happens to old individuals. Harmful genetic variants that only cause damage late in life simply accumulate in the genome, invisible to selection. Aging, in this view, is what happens when no one is watching.
The second, proposed by George Williams (2), is darker. Some genes are good for you young and bad for you old. They get selected because the reproductive benefit early outweighs the survival cost later. You're not just passively aging; evolution actively traded your old age for your reproductive success. A Faustian bargain encoded in your DNA.
The third, by Tom Kirkwood (3), is the most pragmatic. The body is a disposable soma. Energy is finite. You can invest it in reproduction, or in maintaining the machinery of the body. Evolution, reliably, favored reproduction. The biological systems keeping you alive were never built to last forever; they were built to get you to reproductive age and a bit beyond.
Three theories. All plausible. All partially supported by observations. But for decades, what was missing was direct genetic evidence, specific variants, specific mechanisms, specific windows of time in which each theory actually operates.
That's exactly what a study recently published in Nature by Arends et al. (4) set out to do.
The researchers followed 6,400 genetically diverse mice from puberty to natural death, measuring survival day by day. Then, using a method that maps mortality across successive survival cohorts, essentially asking which genes matter at 400 days, which at 600, which at 800? They identified 59 genomic loci that modulate aging and lifespan.
And here is where it gets interesting.
Some loci show sign reversals: an allele that reduces mortality at young ages increases it at old ages. That's antagonistic pleiotropy. Williams was right: the Faustian bargain is real, and it's written at specific addresses in the genome.
Others, 30 loci they call Soma, mediate a direct trade-off between body mass during reproductive life and subsequent lifespan. Bigger, heavier mice die earlier. Kirkwood was right too: the energy invested in growth is energy not invested in longevity.
And some loci only become relevant late in life, well past the reproductive phase, exactly where Medawar predicted selection would go blind. Mutation accumulation, confirmed at the genomic level.
What this study shows, for the first time with this resolution, is that all three mechanisms operate simultaneously, but in different genes, at different ages, and differently in males and females.
Aging is not a single thing. It is not a program. It is not a clock. It is the sum of evolutionary compromises that made sense when selection pressures were about surviving to reproduce, not about living to 90.
The question "why do we age?" turns out to have three answers, all true, all running in parallel, all written into the same genome.

[1] Medawar, P.B. (1952). An Unsolved Problem of Biology. H.K. Lewis & Co., London.
[2] https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1558-5646.1957.tb02911.x.
[3] https://www.nature.com/articles/270301a0
[4] https://www.nature.com/articles/s41586-026-10407-9

CHROMOSOME 21 CENTROMERE SIZE AND DOWN SYNDROME

Small chromosome 21 centromeres had been proposed as a risk factor for non-disjunction in mothers of children with Down syndrome — a hypothesis consistent with mouse data showing that larger centromeres, with stronger kinetochores, are preferentially retained in the egg during female meiosis. A new paper in Am J Hum Genet (1) puts this hypothesis to rest. Comparing completely assembled chromosome 21 centromeres from eight trisomy 21 families with those of over 280 population controls, the authors found no enrichment of small centromeres in trisomy 21 cases ($p = 0.72$).

However, they did find a subset of mothers among the trisomy 21 families in whom the size of the centromere in the two chromosomes 21 differed by more than tenfold, an extreme asymmetry not observed in any control individual. This imbalance may impair homologous pairing during maternal meiosis I and predispose to non-disjunction in a minority of families.

[1] https://www.sciencedirect.com/science/article/pii/S0002929726001977

AI IN MEDICINE: A DOUBLE-EDGED SCALPEL

Artificial intelligence is reshaping medicine at a remarkable speed. It reads imaging, flags anomalies, supports diagnosis, and in many settings outperforms human specialists on specific tasks. The promise is real.
BUT
A study published in The Lancet Gastroenterology & Hepatology (1) should give us serious pause. Across four endoscopy centres in Poland, researchers found that continuous exposure to AI-assisted colonoscopy reduced the quality of standard, non-AI-assisted procedures. Adenoma detection rates dropped from 28.4% to 22.4% — a statistically significant 6-point fall — simply because endoscopists had grown accustomed to the AI doing the watching for them.
This is the deskilling effect: automation erodes the very cognitive skills it was meant to support. Fifteen out of nineteen experienced endoscopists performed worse once the AI was switched off. The study suggests AI-induced deskilling may have direct patient-relevant consequences in clinical medicine.
Unchecked, AI may quietly degrade the competence we thought it was enhancing.

[1]https://www.thelancet.com/journals/langas/article/PIIS2468-1253(25)00133-5/abstract

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Job Opportunity

The Department of Medical Genetics at Liège University Hospital (CHU de Liège), Belgium is recruiting a Medical Cytogeneticist for the position of Deputy Head of the Cytogenetics Laboratory.

https://www.jobs.chuliege.be/cms/c_225711/fr/cytogeneticien-chef-de-laboratoire-adjoint-h/f/x-service-de-genetique/cytogeneticist-deputy-head-of-laboratory-m/f/x-department-of-medical-genetics

ERRORS IN BIOLOGY EXTEND WELL BEYOND DNA MUTATIONS.

We usually think about errors in terms of mutations in DNA. But DNA replication and transcription are actually the most accurate steps in gene expression.

One overlooked error is the "nonsense error": a ribosome falls off the mRNA before finishing the protein, wasting the energy spent on a useless, incomplete chain. A study in PLOS Genetics (1) modeled this per codon in yeast and found the drop-off rate varies enormously, especially for codons resembling stop codons. Yeast genomes seem adapted to manage this cost, avoiding risky codons near the 5'-end of coding sequences and in highly expressed genes.

A related story: slow codon decoding doesn't just risk dropped ribosomes, it can also mark the mRNA itself for destruction. A Spotlight in Trends in Genetics (2) describes how a newly found factor, DHX29, senses sluggish decoding at nonoptimal codons and flags the mRNA for decay, working alongside a second reader, CNOT3, that watches for slow arginine codons elsewhere on the ribosome.

Same root cause, two outcomes: slow decoding can cost a protein or cost the whole transcript. Errors and inefficiencies in *reading* the code turn out to matter as much as mutations in it.

[1]https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1012162
[2] https://www.cell.com/trends/genetics/fulltext/S0168-9525(26)00149-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952526001496%3Fshowall%3Dtrue

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E.C.A. News

- The 2026 General Assembly of the E.C.A. with Board elections will take place on Saturday, 29 August 2026, at 5:00 pm at Goldrain Castle, Goldrain / South Tyrol, Italy.
- Elections 2026 – renewal or re-election of five board members: A. Lindstrand (Sweden), K. Miller (Germany), F. Pellestor (France), J. Blanco Rodriguez (Spain), M. Yirmibes Karaoguz (Turkiye).
- Only one list has been received by the President, with the following candidates: A. Lindstrand (Sweden), K. Miller (Germany), F. Pellestor (France), J. Vermeesch (Belgium), E.Volpi (United Kingdom)

E.C.A. Fellowships

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

  European Diploma in Classical and Molecular Cytogenetics
  to be held in Nîmes (France) 15-21 March 2027 (see page 34)

  Goldrain Course in Clinical Cytogenetics
  to be held in Goldrain Castle (South Tyrol, Italy) August 2027
  (The course was fully booked for 2026, an early application for 2027 is recommended)

- 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.

For details see http://ww.biologia.uniba.it/SEC/

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

NIPT survey in Europe – Prenatal Permanent Working Group, 15th ECC, Leuven, July 2025

Rosario Pinto Leite (Porto, PORTUGAL), Jean-Michel Dupont (Paris, FRANCE)

The Permanent Working Group on Prenatal diagnosis focused on the implementation of NIPT services in Europe, 10 years following the widespread use of this technology in health services.

There were 108 responses to the online survey from 19 countries. However, as the vast majority of respondents were from three countries (Spain, France and Portugal, see fig.1), it was not possible to perform any statistical analysis.

Fig. 1: Origin and number of respondents

The replies to the survey were divided as far as possible into those that were from clinicians (57replies) and those from laboratory specialists (51 replies). The survey was on four main topics: Organization of the health Service, Techniques used in the laboratory, Handling of the results and Role of NIPT in detecting maternal malignancies.

1) Health service setting

Overall, two-thirds of respondents work in a public setting but samples are sent out to both public (47%) and private laboratories (42%). Most of them rely on Guidelines for NIPT, mostly national. Only 6 respondents had no Guidelines to rely on (Fig. 2).

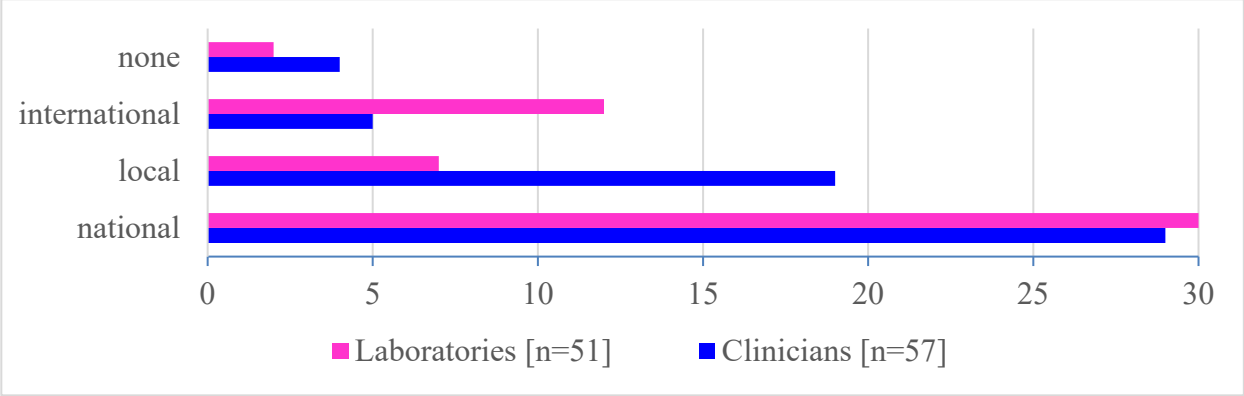

Fig 2: Does your institute have formal guidelines regarding NIPT screening?

NIPT is included in the public health system for reimbursement, at least in part, in majority of the cases, but with various regulations across Europe. In up to 40% of cases, there is either no reimbursement or NIPT is covered by private insurances or a combination of various systems (see Table 1).

Private insurance + Public healthcare system	1,8%
Patient, Private insurance, Public healthcare system	3,6%
Patient + Private Insurance	7,1%
Patient + Public healthcare system	10,7%
Patient	17,9%
Public healthcare system	58,9%

Table 1: How is the NIPT fee covered at your institute?

In almost every country, informed consent is mandatory to run the test which is performed in 63% of cases at first trimester and 37% at second trimester. The main reason for referral for NIPT is an intermediate risk after maternal serum marker screen, but 10% of respondents use NIPT as a first-tier test (fig. 3).

Other specific reasons for referral are: previous history of genetic disorder, ultrasound findings including soft markers, maternal medical history (obesity, autoimmune condition…)

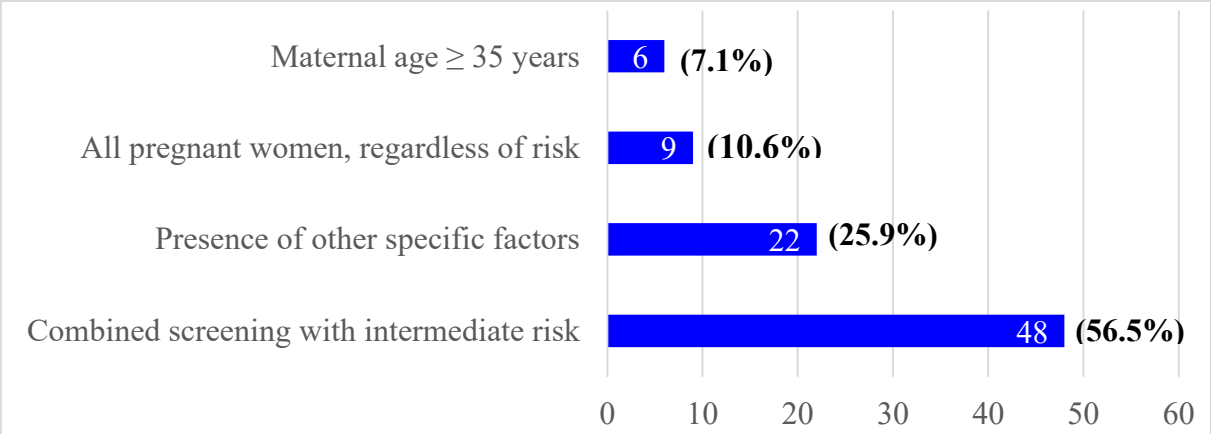

Fig 3: What are the criteria used in your lab/department to offer NIPT?

Along with targeted analysis, whole genome screening is more widely used, with the final choice depending on patients' decision following informed consent, but it can also depend on specific risk factors or national regulations (fig. 4).

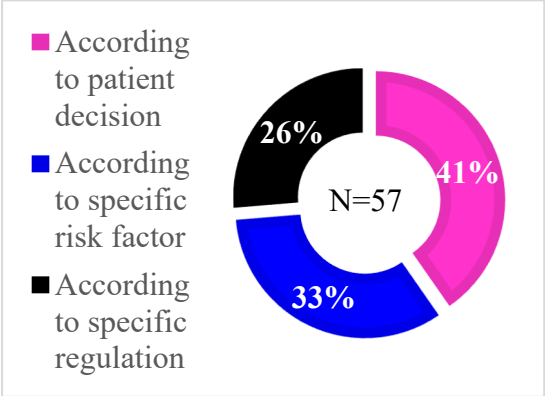

Fig 4: If several NIPT panels are available to patients, how is the choice made?

2) Wetlab organization

Most of the respondents who perform NIPT in their lab, work in medium size settings, running 1,000 to 5,000 samples a year (fig. 5). Unfortunately, very few large laboratories responded.

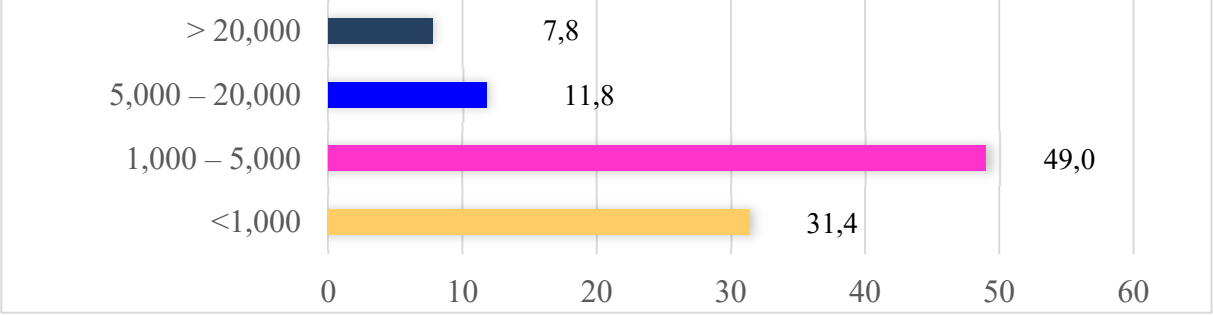

Fig 5: If you perform NIPT in your lab, how many tests do you perform per year?

Short read sequencing is by far the main technology used for NIPT, and most frequently whole genome analysis method is offered (fig.6).

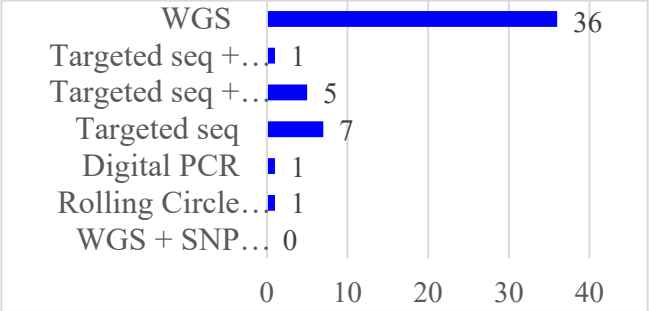

Fig 6: Which technology do you use?

Almost 90% of laboratories use commercially available tests. As expected, the proportion of laboratories testing for Rare Autosomal Trisomies and CNVs is in accordance with the proportion of labs using Whole Genome Sequencing technology; only 27% of laboratories include microdeletion testing in their NIPT panels (fig. 7).

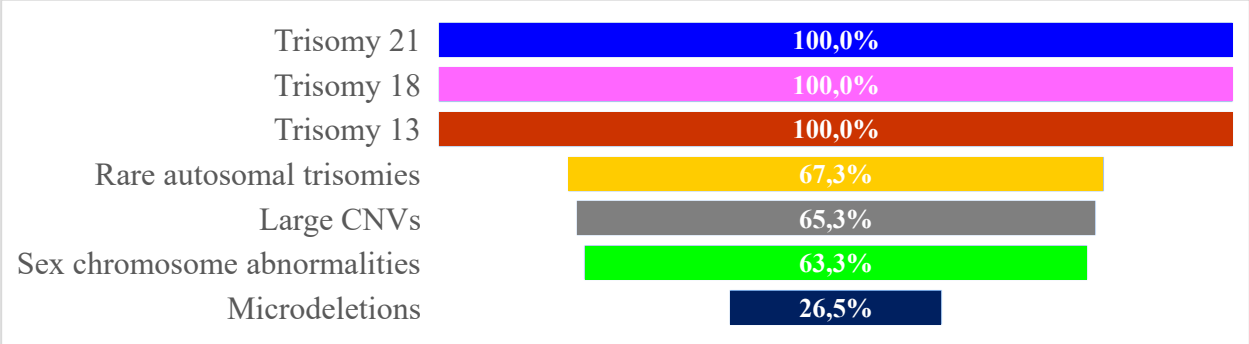

Fig 7: Chromosome anomalies included in your NIPT panels?

NIPT is now a robust technique with a low failure rate, less than 1% of samples in most laboratories. The main reported reason for test failure is a low fetal fraction (fig.8).

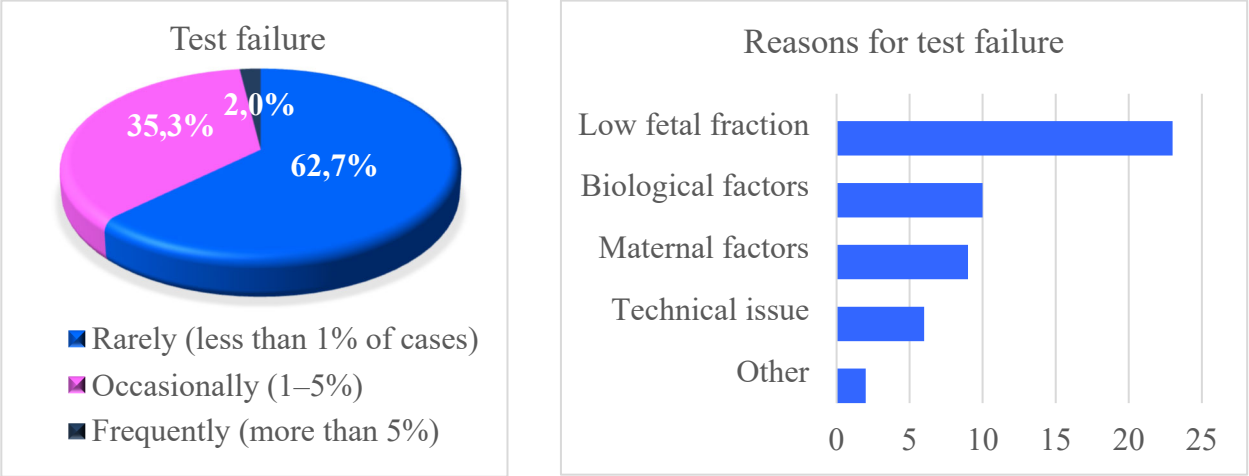

Fig 8: Inconclusive results

3) Handling of the results

In most cases, the referring physician or Genetic counsellor is responsible for communicating the result to the patient (fig. 9). In other cases, this is done by either laboratory specialists or midwives.

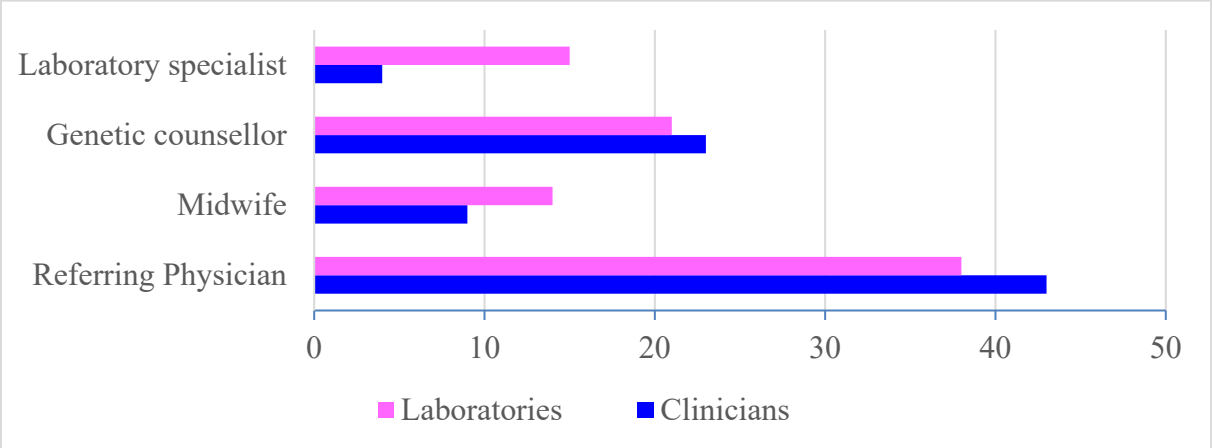

Fig 9: Who is responsible for communicating the result to the patient?

In case of an inconclusive result, the test is mostly repeated on a new blood sample. Some laboratory specialists repeat the test on the same sample while clinicians may opt for an invasive procedure (table 2). If the second NIPT on a new sample fails, 80% of respondents proceed to an invasive procedure.

	Lab survey	Clin survey
Repeat the NIPT test on a new blood sample	35	37
Repeat the NIPT test on the same blood sample	7	12
Recommend proceeding to diagnostic testing	4	4
Other	3	4

Table 2: What is your preferred approach when NIPT results are inconclusive?

If NIPT is positive for a chromosome anomaly, the standard procedure for laboratory specialists as well as clinicians is to ask for confirmation with an invasive sampling before taking any decision (fig.10). Some report that confirmatory sampling is performed only where termination of pregnancy is an option.

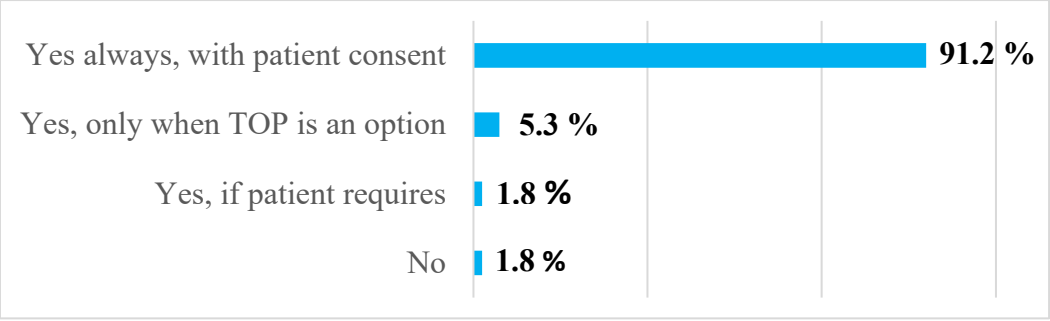

Fig 10: Confirmation of positive results

4) Maternal Malignancies

Large scale implementation of NIPT led to the discovery that cell free DNA could also include tumor DNA in case of occult maternal malignancy. However, how this observation could help in the follow-up of these women and improve their outcome is still highly debated. Absence of consensus on this topic is reflected by the high variability of answers from the survey, with striking differences depending on whether the respondent is a clinician or a laboratory specialist.

The good news is that most (90.1%) involved professionals are aware of this hot topic. However, because of the lack of consensus, handling of these situations is very variable: clinicians are more prone to counsel patient about potential implications while laboratory specialists tend to just report inconclusive or abnormal result (fig.11). Obviously, consensus is needed here to harmonize the reporting.

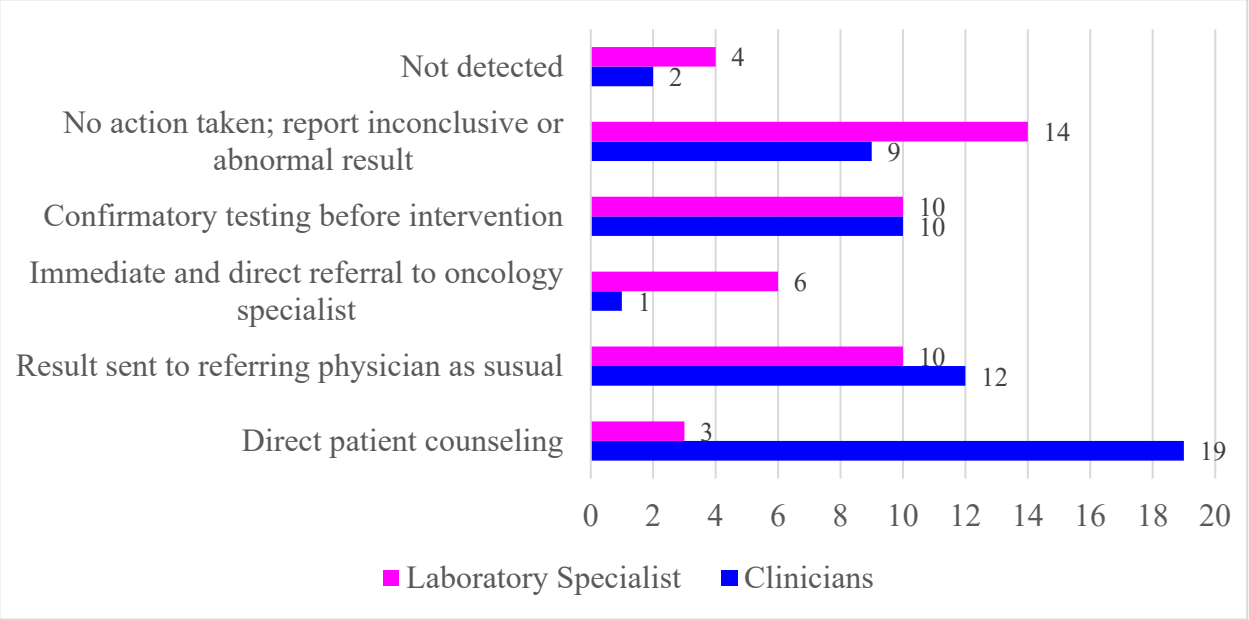

Fig 11: Reporting of results suggestive of maternal malignancy

The difficulty in including this topic in pre-test counselling and following up of screened-positive patients probably explains the discrepancy between the opinions of the laboratory specialists and the clinicians concerning the inclusion of maternal malignancy screening in routine NIPT. Most clinicians think it should not be included, while 50% of laboratory specialists are just unsure at present of the best choice (fig.12).

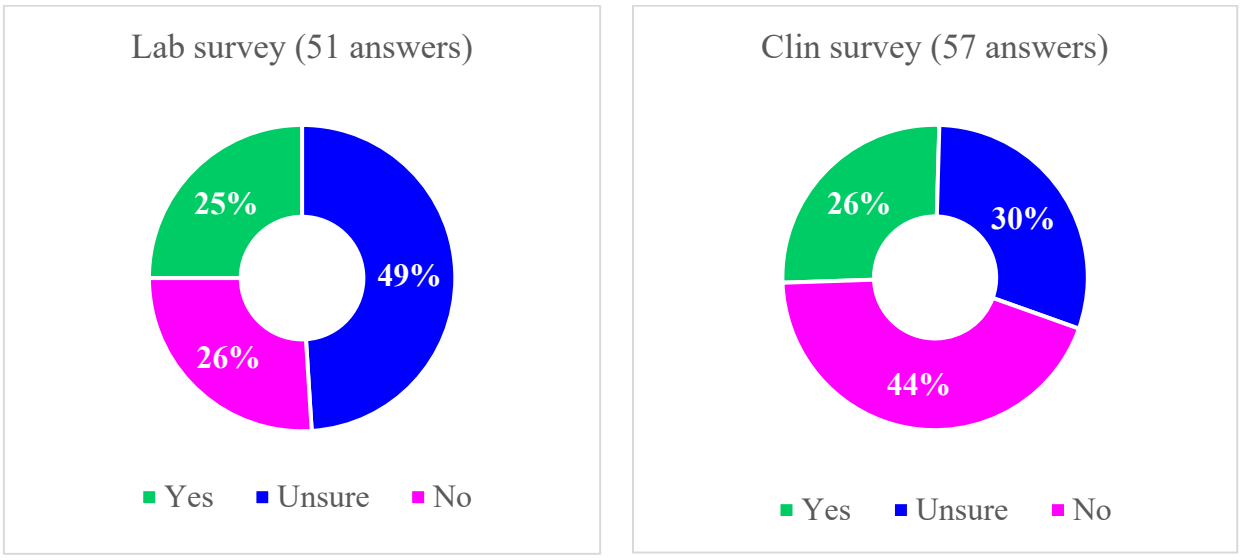

Fig 12: Do you think routine screening for maternal malignancies should be integrated into NIPT protocols?

Conclusion

This survey, although not fully representative of the field in Europe, confirms that NIPT is now a part of standard care in prenatal setting, with roughly similar management of pregnancies across institutions. Whole genome sequencing is the overwhelmmingly dominant technology; in two-thirds of the institutes it is also used for rare autosomal trisomies and CNVs.

Whether maternal malignancy screening should be included is still a matter of debate; further studies on the definition of suspicious results and follow-up strategies for patients are needed to reach a consensus.

PWG Neoplasia

Co-ordinators:
Paola Caria, University of Cagliari
Sabrina Tosi, Brunel University London

In this communication, I would like to draw the attention of the members of the Neoplasia Working Group on Solid Tumors to an opportunity for collaboration within the project "Biology and Genetics of Familial Papillary Thyroid Carcinoma (fPTC)."

Our research group is investigating the biological and genetic mechanisms underlying Familial Papillary Thyroid Carcinoma (fPTC), a rare hereditary form of thyroid cancer.

To strengthen this project, we are expanding our collaborative network and warmly invite research groups and clinical centers with access to families affected by this rare disease to join the study.

We are particularly interested in collaborating with groups able to contribute families with two or more first-degree relatives diagnosed with papillary thyroid carcinoma, in the absence of other known hereditary cancer syndromes predisposing to thyroid cancer.

Researchers interested in participating are warmly invited to contact us to discuss the collaboration and receive further information on eligibility criteria, study procedures, and data/sample sharing. We would also be pleased to meet interested colleagues during the upcoming Neoplasia PWG meeting at the ECA Conference, Stockholm, 4–6 July 2027.

Contact:
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University of Cagliari
Email: paola.caria@unica.it

Minutes of the E.C.A. Board meeting Nîmes, 28 March 2026

Present:
Jean-Michel Dupont (President); Mariano Rocchi (General Secretary), Kamlesh Madan (First Vice-President), Pat Heslop-Harrison (Second Vice President), Roberta Vanni.
Present on-line:
Frank Pellestor (Treasurer); Claudia Haferlach; Jana Drábová; Konstantin Miller; Anna Lindstrand; Jose M Garcia Sagredo, M Rosario Pinto Leite, Elisabeth Syk Lundberg
Present on line as guest: Joris Vermeesch (Scientific Programme Committee); Pinar Akbulut (Dekon)

AGENDA
The President opened the meeting at 18.15 and welcomed those attending. The resignation of Juan Blanco Rodriguez as a board member was accepted and he was thanked for his services to the Association. The President noted with regret the passing of Honorary Members of the Association, Professors Albert Schinzel and Malcolm Ferguson-Smith.
1) Report of the President and the General Secretary
There are 1376 members, of which 182 are active. The number is stable; the global distribution was presented.
2) Treasurer's Report
There was a deficit for the year 2025 but the Association account balance remains healthy. The Board agreed that a bank account should be opened at Caisse d'Epargne in Montpellier; some of the funds will be transferred from Société Générale in Paris to ensure easy access for the Association.
3) 2027 ECC
After considering four Venues, Stockholm was chosen for the next ECC. Pinar Akbulut (Dekon) presented information about the venue: The Karolinska University Hospital. There is one main hall and several theatres of appropriate size. Several smaller rooms are available for parallel sessions, company meetings or overflow for larger talks. The space for exhibitions and posters is quite appropriate. There is an option for lunch symposia in a nearby building.
The Board agreed to hold the ECC at the Karolinska University Hospital, Stockholm from 4-7 July 2027.
Dinner and Social venues were presented by Pinar Akbulut. Some good restaurants were mentioned. Hotels were also considered, including both nearby and more distant venues.
The Budget was presented with conservative estimates. The registration costs were considered, in comparison with other Society meetings. The possibilities of a party or a networking event was considered. Company sponsorships were also discussed, including the pre-conference company workshops and lunch-symposia.
Joris Vermeesch was appointed chair of the Scientific Programme Committee (SPC) and memberships for SPC will be reviewed.
4) Permanent Working groups
Structures of the PWGs were reviewed.
5) Education
The structures, contents, sponsorship and attendance at the two ECA courses: Scuola Europea di Cytogenetica – Goldrain and the Nîmes course were discussed. Both are well attended and fit different needs for students with different backgrounds.
6) Election of Board members will take place at the next General Assembly.
There will be a regular renewal of five board members according to the statutes. The president received one list before June 15, 2026 as required by the statutes.
7) Miscellaneous
It was agreed that any ideas for improving the Association and the Conference are welcome.
8) The next meeting and General Assembly will be held in Goldrain on Saturday 29 August 2026.

The president closed the meeting at 19.55.



Nîmes – France, March 15-21, 2027

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/

The Course 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. It is taught by about 20 leaders from major cytogenomics groups involved in research and applications across Europe who will train the students to identify genetic abnormalities for diagnosis and prognosis, and for fundamental and applied research using both classical and molecular cytogenetic techniques. The course, co- organized by E.C.A. and two French Universities, was started by Professor Jean Paul Bureau in 1997, and has been held in Nîmes under his directorship until 2017.

Registration

You can select either (September 2026 – January 31st, 2027)

- 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. Franck PELLESTOR (f-pellestor@chu-montpellier.fr).

2026 Registration fee may be adjusted: €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 three scholarships covering the registration and accommodation fees. The Education Committee of the E.C.A. will select the suitable candidates.

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.