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E.C.A. Newsletter

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No. 53 January 2024

Contents	*Page*

E.C.A. on Facebook

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

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

You will find a selection of interesting Facebook posts in this Newsletter starting at page 84.
Please contact us (mariano.rocchi@uniba.it) if you wish to share an interesting news item or a pertinent article.

President's Address

Dear ECA members and friends,

First and foremost, I extend my warmest wishes for a wonderful and successful 2024 to all of you and to the entire ECA community.

On 2023, four years after the Salzburg conference, we had the pleasure of meeting in person in Montpellier. The decision to host an "in-person" conference materialized late due to the uncertainties caused by the lingering effects of the Covid pandemic. As we look ahead, optimism is on the rise, and we have been diligently focusing on selecting a suitable venue for the 2025 ECA conference. I had committed to announcing the chosen location by the end of 2023, and an ECA team has worked tirelessly to fulfill that promise. To this end, we have personally visited potential locations, and although the decision-making process is taking a little longer than expected, we are just days away from finalization. I will promptly communicate the decision via email. It will also be published on the ECA website (https://www.e-c-a.eu/EN/).

In this ECA newsletter you will find updates on ECA activities. The newsletter also includes ECA posts from its Facebook page since the previous issue (https://www.facebook.com/Cytogeneticists). These posts consist of summaries of intriguing articles related to cytogenomics and biology in general. Your contributions are highly encouraged; please contact mariano.rocchi@uniba.it.

ECA courses

The Nîmes course (European Diploma in Classical and Molecular Cytogenetics) is scheduled for March 18-24, 2024. Registration closes on January 31, 2024; details at http://www.biologia.uniba.it/SEC/. ECA is offering two scholarships for the course, covering registration and accommodation fees. For more information and registration, please contact Prof. Jean-Michel Dupont (jean-michel.dupont@aphp.fr) and/or Prof. Thierry Lavabre-Bertrand (thierry.lavabre-bertrand@umontpellier.fr).

The Goldrain Course in Clinical Cytogenetics (http://www.biologia.uniba.it/SEC/) whic is held at the Goldrain castle in South Tyrol, Italy, was founded by Prof. Albert Schinzel. ECA has been providing substantial organizational support since last year and is also offering two scholarships to cover registration and accommodation fees. Additional scholarships will be provided by the European Society of Human Genetics (E.S.H.G.). For further details, please contact Prof. Albert Schinzel (schinzel@medgen.uzh.ch) and myself (mariano.rocchi@uniba.it).

Thank you for your continued support and engagement with ECA. Wishing everyone a productive and fulfilling year ahead.

Kind regards,

Mariano Rocchi
E.C.A. President

14th European Cytogenomics Conference Montpellier

Workshops and discussion meetings of Permanent Working Groups

PWG Quality Issues, Training and Cytogenomics and ISCN Workshop
Coordinators: Martine Doco-Fenzy, Jean-Michel Dupont

After a short introduction by **Martine Doco-Fenzy**, **Melody Tabiner** gave a presentation of External quality assessment. External Quality Assessment is defined as a system for objectively checking the performance of a service according to international standards, using an external agency or facility. The aims and importance of genomics EQA were presented, these include benchmarking the quality of genomics services, identifying imperfect practice and ultimately improving quality of care for patients. Additional benefits include building public confidence and promoting quality across national borders, as well as professional training and evidence of competency. The processes involved in the delivery of EQA were described and examples of how EQA can improve quality were discussed. These include the observed reduction in errors with regular EQA participation, identification of substandard reagents, support for poorer performers and educational resources for all. GenQA's new online individual training and competency tool, GENie, was also introduced.

Ros Hastings gave a short overview of ISCN 2020 and the online Forum which can be used for ISCN queries. This was followed by an overview of the planned nomenclature changes for ISCN 2024 including a new chapter on genomic mapping. Finally, the talk concluded with educational resources (webinars and YouTube) available to everyone virtually provided by GenQA in addition to the ISCN workshops run by GenQA.

Jean-Michel Dupont led an interactive training session with short questions about the ISCN nomenclature.

Marie Berengère Troadec presented her work titled: Towards a decision-making tool for the identification of chromosome structural abnormalities in conventional cytogenetics: Development of a prototype for the detection of del(5q) deletion based on artificial intelligence (selected abstract 1053).

PWG Neoplasia
Coordinators: Paola Caria, Harald Rieder, Roberta Vanni

There were a number of abstracts by authors of abstracts submitted to the conference. The first was titled "Donor cell acute myeloid leukaemia after haematopoietic stem cell transplantation for chronic granulomatous disease" given by **Francesco Pasquali** (I). He reported about a boy who developed an acute myeloid leukemia in donor cells of his sister two years after haematopoietic stem cell transplantation (HSCT) for chronic granulomatous disease (CGD), an inherited disorder of the phagocytes. The donor cell leukemia (DCL) was characterized by a translocation t(9;11)(p21;q23). This case was the first with DCL after HSCT for CGD and demonstrated that, apart from malignant hematological neoplasias, DCL may also occur in patients after HSCT for non-malignant hematological disorders.

Kalliopi Manola (G) presented the paper entitled "Ring chromosomes in hematological malignancies are mainly associated with myeloid malignancies and complex karyotypes". She showed that ring chromosomes are very rare in hematological neoplasms, and they were observed mainly in complex karyotypes and in elderly patients with myeloid malignancies. The most common origin of ring chromosomes was from chromosome 11, often accompanied by KMT2A amplifications. The most frequent additional abnormalities were marker chromosomes, -5/del(5q), and -7/del(7q).

Uliana Karnaukhova (UA) presented the talk "Cytogenetic groups of pediatric acute myeloid leukemia from Ukraine". She demonstrated that rearrangements of the 11q23/KMT2A locus with different partner chromosomes were most common. In three cases disruption of the 11q23/KMT2A locus occurred as a result of chromosomal inversions or insertions. Patients with translocations t(8;21) and t(15;17) were almost equally prevalent. Additionally, 14% of the patients with chromosome abnormalities had complex karyotype changes or a clonal karyotype evolution.

Victoria Marcu (IL) presented the paper titled "Validation of the Optical Genomic Mapping (OGM) for cytogenomic testing in hemato-oncology – Sheba experience". She showed that OGM had to be carried out by very experienced laboratory professionals. OGM detected chromosomal aberrations and aneuploidies that were diagnosed by karyotype and FISH in all cases. Moreover, additional chromosome abnormalities were identified by OGM in half of the cases. The detection limit of OGM for copy number variations and for single genomic variants was set at 10%. By comparing the results of an inter-laboratory test using OGM consensus was demonstrated in all pathogenic changes, which showed high reproducibility of the results of OGM. **Bob Argiropoulos** (CA) gave a talk titled "Laboratory Validation and Clinical Implementation of an RNA sequencing-based Prognostic Assay for Multiple Myeloma". He showed that this assay is highly accurate and reproducible. Clinical implementation of the RNAseq assay for multiple myeloma had already taken place and 624 clinical samples had been successfully investigated. After a short break the meeting continued with the presentation titled "Mutation of the PIK3CA gene in breast cancer" which was given by Gulsi Smgulova (KZ). She reported that PIK3CA gene mutation testing may help to develop an appropriate treatment strategy for patients with certain types of breast cancer (BC). I.e., PIK3CA mutations were more frequent in luminal B type of BC. The PIK3CA gene mutations were detected in primary tumors so it may be assumed that these mutations were involved in tumor pathogenesis. In addition, she stated that the investigation of PIK3CA gene mutations in liquid biopsies may help to initiate and to monitor a mutation directed cancer treatment. "Detection of promoter methylation as well as deletion of MGMT gene in patients with glioblastoma using methodologically different approaches" was the title of the talk presented by **Halka Lhotska** (CZ). She demonstrated that the methylation of the promoter of the MGMT gene was confirmed in 38% of patients. The MS-MLPA MGMT_215 probe had the best ratio of sensitivity and specificity for the detection of MGMT deletions. She showed that the 5´ and 3´ends of the MGMT promoter were methylated most frequently, and that there was a high concordance of 84% among MS-MLPA and metSeq results. The last talk of the session was titled "Report on the implementation of an early cancer identification and prevention programme among the population of the central Poland" and was given by **Tadeusz Kaluzewski** (PL). He reported that the introduction of the National Cancer Control Program (NCCP) was a breakthrough for genetic diagnostics in hereditary cancer predisposition syndromes (HCPS) in Poland. He pointed out that the scope of the genetic testing in the NCCP should be improved further and that there is a need to educate physicians from other specialties than clinical geneticists in the counselling and treatment of families with a hereditary cancer predisposition syndrome.

Finally, it was an outstanding pleasure to announce Paola Caria from the Department of Biomedical Sciences, Biochemistry, Biology and Genetic Unit - University of Cagliari, Italy, to the audience as a co-ordinator of the Permanent Working Group Neoplasia.

PWG Prenatal Diagnosis
Coordinators: Rosário Carvalho Pinto Leite, Jean-Michel Dupont

The focus of the working group was to get an overview of the main technical strategies used nowadays in prenatal diagnosis, with special emphasis on array and exomes approaches. As usual the PWG session was well appreciated and attended by 60 colleagues.

Jean Michel Dupont started the session and provided an overview of available microarray guidelines in prenatal diagnosis: ECA Guidelines 2011, ACMG 2013, ACOG and SMFM 2018, and ESHG 2019. Consensus data was presented for strategy of use (CMA should be a first tier test in case of abnormal ultrasound), laboratory setting (validation of the platform, type of array to use, CGH versus SNP, reference DNA to use, quality controls), microarray analysis (need for a back-up culture, parental sampling, minimum resolution), validation of results (strategy for validation of CNVs, interpretation and classification according to ACMG 5 tiers), reporting of CNVs (standardized report complying with ISO 15189, technical information on CMA platform used, ISCN string, detailed explanation of the abnormality and the relationship with clinical findings) and genetic counselling (pre and postnatal tests).

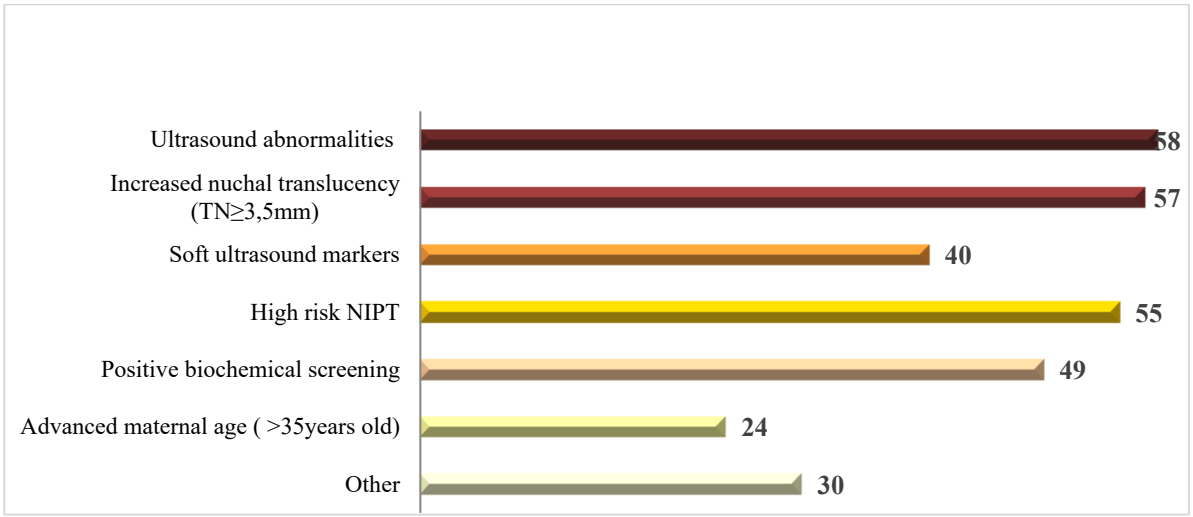
In an attempt to investigate the laboratory methodologies employed in prenatal diagnosis, a survey was distributed to ECA colleagues working in the field. Designing the survey proved challenging due to potential diverse responses based on various variables. To address this, an "other" option was included for colleagues to provide alternatives. The goal was to obtain a single response per laboratory.

Rosário Pinto Leite presented the survey results, with 58 responses received, comprising 48 from state laboratories and 10 from private laboratories. While optional, 32 responses indicated a predominant presence from Southern Western Europe, with notable contributions from countries such France (14), Portugal (6), Spain (5), and one response each from Belgium, the Czech Republic, Slovenia, Iceland, India, Serbia, and Sweden.

Results of the survey

Question 1: Concerning the first question: “What are the indications for the analysis of a Prenatal Diagnosis sample that you receive in the laboratory?” (Graph1)

Responses revealed that ultrasound anomalies were a universal indication, followed by increased nuchal translucency, positive NIPT, and positive biochemical screening. Only 24 laboratories reported still receiving samples based on advanced maternal age. "Other" responses varied, including indications linked to cytogenetics such as familial translocation, previous fetal aneuploidy, but also suspected infection, or a history of monogenic disease.



Graph1

Question 2: The next question was: What is the first-line test that your laboratory does/recommends? (Graph2).

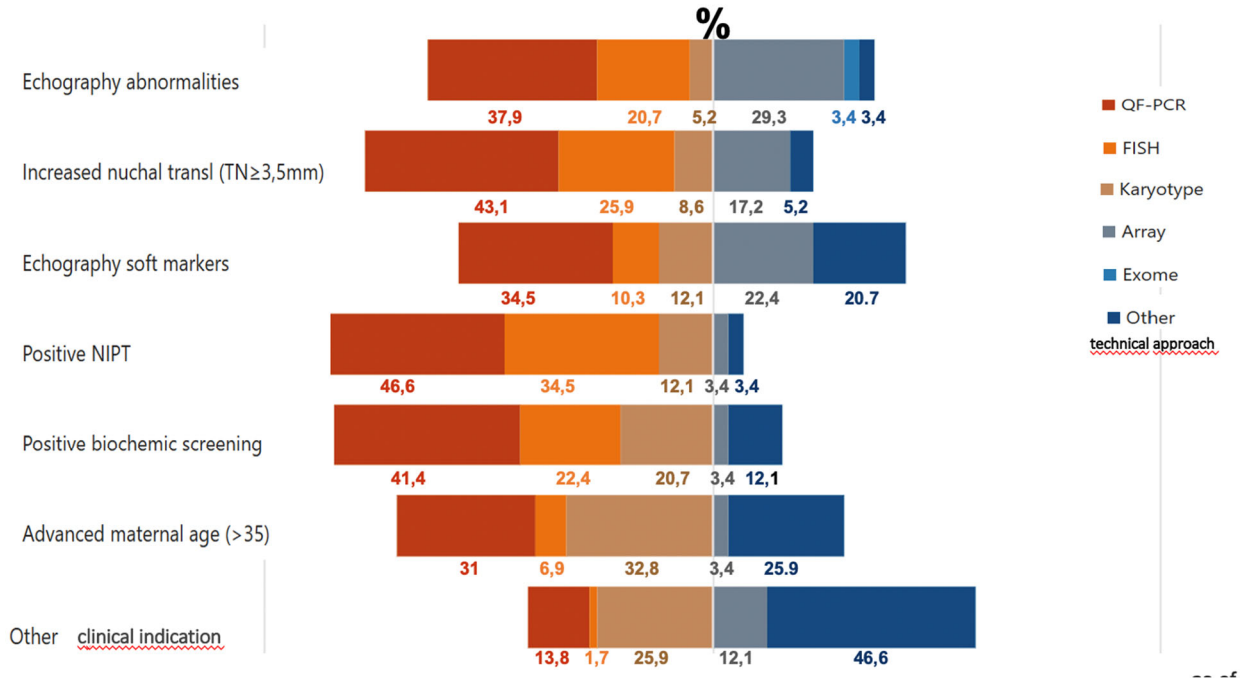
QF-PCR emerged as the predominant method, followed by FISH, for nearly all clinical indications, including echographic anomalies, nuchal translucency, ultrasound soft markers, positive NIPT, and positive biochemical screening.

The array exhibited notable prevalence in three indications: echographic anomalies, nuchal translucency, and echographic soft markers.

Karyotyping was predominantly used in cases of advanced maternal age (approximately thirty-three percent) and positive biochemical screening. For the presence of echographic soft markers and positive NIPT, the frequency was about twelve percent, while for echographic anomalies and nuchal translucency, it was less than ten percent.

Exome sequencing was reserved for special cases, with many laboratories not adopting this particular technical approach.

For each clinical indication, there is the possibility of "other" technical approach, and the responses vary. One laboratory adopts a unique approach, performing prenatal BoBs. Others follow a dual approach, such as combining QF-PCR and karyotyping. Additionally, some laboratories do not handle samples with soft marker indications. Notably, we emphasize the significant finding that 13 laboratories do not receive samples indicating advanced maternal age.



Graph 2

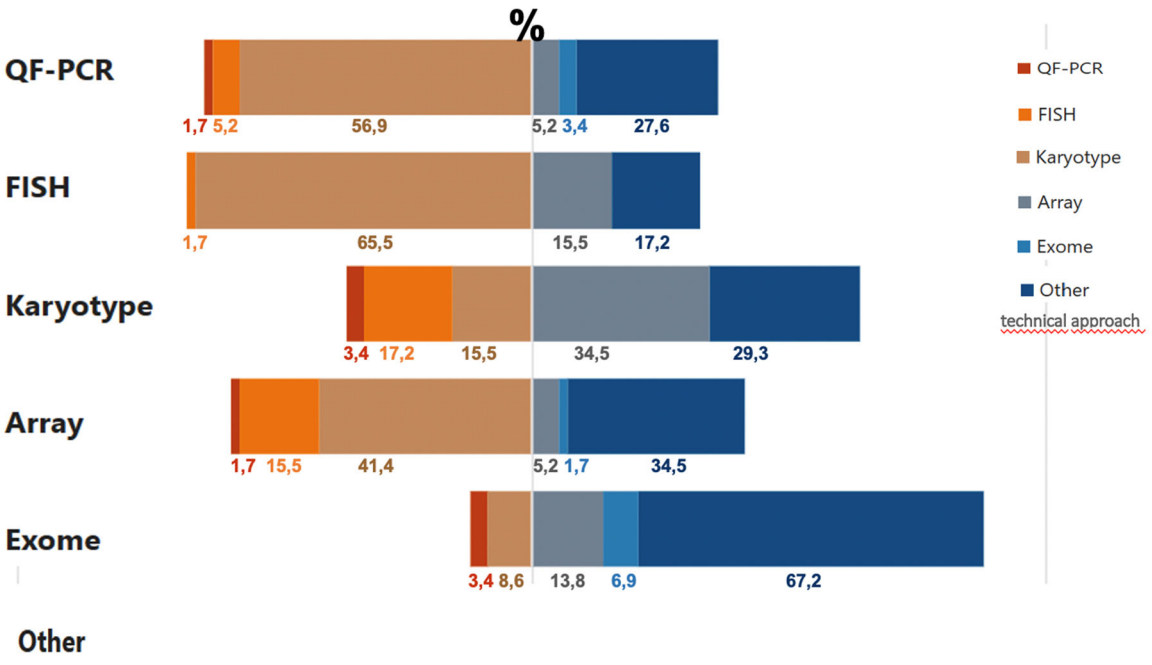
Question 3: The third question focused on the laboratory procedure following a positive outcome with a specific technique: What is the second-tier test that your lab does if a positive result was obtained in first tier test? (Graph 3)

When a positive QF-PCR or FISH result occurs, the most commonly employed technique is karyotyping. Responses to the "other" question for these two indications often indicated a decision not to perform QF-PCR/FISH tests.

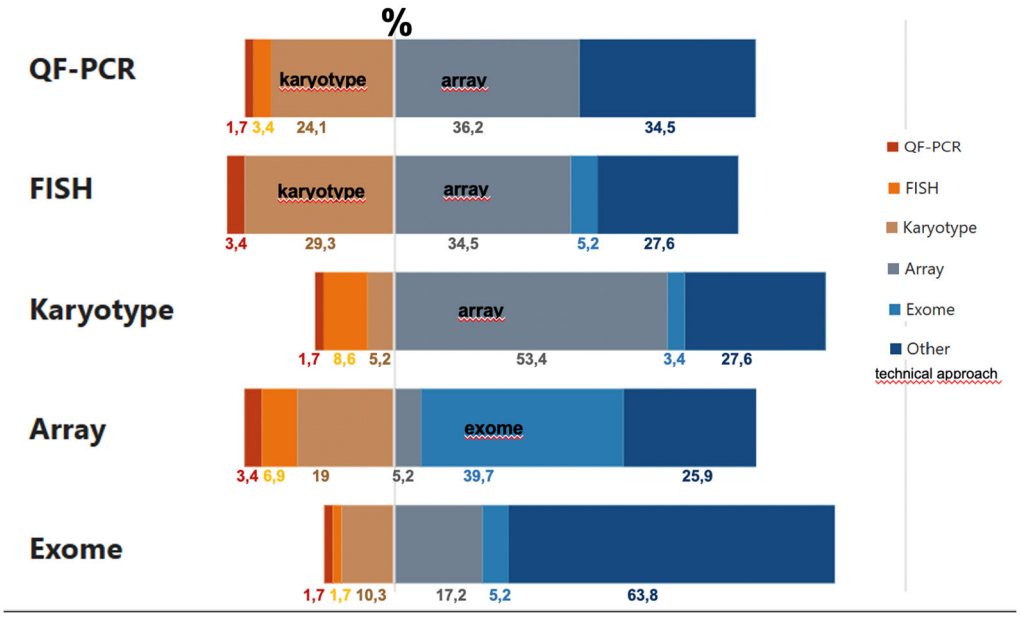
In cases where the karyotype is positive, there is a subsequent confirmation process involving either an array (34.5%) or FISH (17.2%). In the "other" category, responses frequently centered around the decision not to perform karyotyping.

Regarding the array, there is a significant incidence of concurrent karyotyping (41.4%), followed by FISH (15.5%). In the "Other" category, various responses were observed, including some laboratories chose not to pursue any additional technical approach.
Concerning Exome, some labs opt for array (13.8%) or karyotype (8.6%). In the "Other" option, responses varied, with some labs choosing not to pursue any further actions, while others indicated the possibility of conducting Sanger sequencing. Some laboratories also mentioned not pursuing the exome.
Regardless of the diverse responses in the "other technical approach" category, the underlying theme is that the chosen approach depends heavily on the specific clinical indication.

Question 4: Concerning the next question: what is the second tier test that your lab does if a negative result was obtained in the first tier test? (Graph4).
The responses align with expectations. For both QF-PCR and FISH, the prevailing technique following a negative result is array, with karyotyping as the subsequent choice. The answers to the "other" question for these two indications are similar from those provided in the previous responses (it is not the first test, it is not performed, or it is confirmed through array or karyotype).
Examining responses related after a negative karyotype, the predominant technique is array. Some responses mention FISH, alternative karyotype analyses, or, to a limited extent, the exome. The "other option" indicates either the non-performance or non-validation of karyotyping. Depending on the indication, respondents may opt for specific techniques.
After a negative array, approximately forty percent of respondents indicate the use of the exome, followed by karyotyping and other analyses for a smaller fraction. In this context, the "other" option aligns with the prior approach: either abstaining from repetition or not conducting it.
Regarding exome negative result, some laboratories preformed karyotyping, while others rely on the array. The notable 64% incidence in the option “others” results from the majority of laboratories practicing this technique without subsequent confirmation.
Upon analyzing the responses in the "Other" category, it becomes evident that the choice of an additional technique hinges primarily on the clinical indication.



Graph3



Graph 4

Question 5: Moving to the fifth question, our objective was to precisely understand the role of cytogenetics in prenatal care. Only four laboratories consistently perform conventional cytogenetics in all prenatal cases. The other responses indicate that conventional cytogenetics is employed primarily when there is a history of a structural chromosomal anomaly, making it the initial approach.
As a second-line test, three laboratories noted their practice of doing conventional cytogenetics for all requests, while twenty laboratories mentioned its use to confirm specific results based on the clinical indication. Responses in the "other" category align with those indicating a cessation of this technique, consistent with prior answers.

Question 6: The final question was: Is maternal cell contamination ruled out before prenatal diagnosis?
A total of 24.1% of the laboratories stated that they consistently perform this check on amniotic fluid, with 48.3% doing so on chorionic villi. Also, 41.4% exclude maternal contaminations during amniocentesis only if a DNA test was conducted, and 29.3% follow a similar protocol for chorionic villi. In the "other" category, colleagues provided additional insights for both techniques. For amniotic fluid, the decision seems to depend on factors such as the sample's degree of bloodiness, while for chorionic villi, it hinges on the XX result.

The results of the survey led us to the conclusion that karyotyping is diminishing in significance within the prenatal laboratory. The array technology has become the predominant technique, especially in cases of ultrasound anomalies. QF-PCR or FISH are the primary first-tier approaches in the majority of the laboratories.

Two communications were selected among the abstracts of the conference.
The first communication was by **Céline Dupont** from Robert Debré Hospital in Paris who shared their experience with Whole Exome Sequencing (WES) in a prenatal setting.35 cases were analysed in trio or quartet where standard cytogenetic tests (including chromosome microarray) were normal. Pathogenic or likely pathogenic variants were present in 21% of cases with a failure rate of ≈6%. In most cases, the result was available before the end of the pregnancy allowing for a better follow-up.
Joris Vermeesch from Leuven University presented the project of a European Network on Cancers in pregnancies. Now that NIPT is widely

used in many countries, it appears that some cases show multiple chromosomal changes usually not associated with placental constitutional anomalies. Rather, they may be indicative of a maternal tumor occurring in about 1/10000 pregnancies.
Within the context of the Horizon CAN.HEAL project they are creating a consortium to (a) provide guidance to labs encountering such cancers, (b) provide a second opinion (c) enable a prospective study to prove the clinical validity and utility to report cancers in pregnancy, (d) create EU guidelines on how to work in a clinical context and (e) obtain longitudinal data. Joris Vermeesch invited any lab that is interested in participating to contact him or Liesbeth Lenaerts (joris.vermeesch@kuleuven.be) (Liesbeth.lenaerts@kuleuven.be).

PWG Clinical and Molecular Approaches to Cytogenetic Syndromes & Cytogenomics
Coordinators: Anna Lindstrand, Damien Sanlaville, Joris Vermeesch

The two permanent working groups, Clinical and Molecular Approaches to Cytogenetic Syndromes and Cytogenomics have been fused. So this was the first meeting of the new PWG. The rationale for the fusion is obvious: the cytogenomics working group used to focus on genomic technologies and the molecular approaches was focusing on technology to detect cytogenetic syndromes. Both aims have now come together in common technologies. At the high end, we have left the era of single locus methods and are fully in the genomics era, where whole genomes are scanned in search for structural variation. However, while we are entering this era, methods to study structural variation from whole genome scanning techniques have not yet fully matured. At best, we can state that we are at the start of clinical implementation but that competing technologies and bioinformatic pipelines compete to become the standard of care.

Needless to say that the working group meeting was again a huge success. With a full room of attendees – a rough estimate would be a 100 participants - and a great speaker line-up the expectations were high. We started with a presentation by **Vasheghani Farahani Faezeh** on the use of Optical Genome Mapping to scan for fertility disorders. A major cause of fertility problems are balanced translocations. Because of the difficulty in detecting balanced translocations, karyotyping remains the method of choice in most cytogenetic and fertility genetic laboratories. Significant structural rearrangements were identified in all known control samples, and in over 50% of the 60 tested samples. Optical mapping allows for the detection of such balanced translocations with the exception of Robertsonian translocations. It seems as if it is only a matter of time before OGM will be able to detect also Robertsonian transloctions

Different speakers presented the challenges and the approaches to detect structural variation from whole exome or whole genome sequencing data. There is no one-size-fits-all approach for reliable detection of CNVs from WES or WGS data. On the contrary, many different approaches combining capture kits and bioinformatics approaches are being tested for their detection. **Vladimíra Vallová** presented her work describing different strategies for the detection of copy-number variations from exome sequencing data. She tested two different capture designs and five different read-depth based CNV calling strategies: Human Core Exome (HCE) from Twist Biosciences (CNVRobot (CNVR), in-house pipeline (IHP)) and SureSelect All Exon v7 (SSEL) from Agilent Technologies (Circular Binary Segmentation (CBS), Hidden Markov Model (HMM), ExomeDepth). Of the twenty rare CNVs tested, three strategies (CNVR and IHP for HCE and ExomeDepth for SSEL) were able to identify all 20 rare larger CNVs. The CBS- and HMM-based strategies (SSEL) missed some of the CNVs. **Annelies Dheedene** presented a CNV detection approach in WES data for the detection of CNVs in patients with neurodevelopmental disorders.

The value of ExomeDepth was evaluated. With over 15 cases with a pathogenic intragenic CNV reported, the CNV detection on WES data has the potential to increase diagnostic yield. Several patients harbor a pathogenic deletion in compound heterozygous state with a pathogenic SNV. Both smaller and larger CNVs were detected. The team started using ExomeDepth as part of the routine WES diagnostics, but warned: confirmation of all CNVs by an independent technique remains a necessity, as also many false positive calls are made. **Nicolas Chatron** presented the French work on the analysis of balanced structural variants from short genome sequencing data. Using MANTRA, they typically retain an average of 5-15 variants consistent with Mendelian inheritance for analysis. Among these, it is crucial to distinguish classical cytogenetics rearrangements from „sequence structural variants“ (e.g. mobile elements), as their genomic consequences differ significantly. To streamline the manual curation process, we recommend considering only (i) de novo variants, (ii) genedisrupting variants affecting a predefined gene list based on the phenotype, and (iii) variants in trans with another prioritized variant (SNV, CNV, etc.). This approach minimizes the workload for trained cytogenomics specialists to a maximum of 2 variants (zero for more than 90% of cases) that require read alignment inspection and formal interpretation. This approach is valuable, but also underscores the need for the development of common guidelines.

There were four talks discussing other cytogenetic aspects. First, **Vincent Gatinois** presented his work on the presence of the mothers cells in the offspring. Those cells can be considered chimeric in the offspring. Breastmilk contains maternal cells primarily consisting of epithelial cells but also of myeloid and lymphoid cells up to 6% of stem cells. Those cells can be transmitted to the offspring. The team shows female cells in 57.9% (22/38) of male offspring. The older mother’s age was inversely associated with female cell density.

The microchimeric cell transfer from mother to child during breastfeeding was strongly suggested although not demonstrated. However, the persistence of microchimeric cells of maternal origin was associated with previous breastfeeding, suggesting tolerogenic properties of these cells.

In addition, we had three speakers presenting case reports of rare microdeletion/duplication disorders. **Leona Morozin Pohovski** presented the first case report of a patient with three copies of distal 16p12.1p11.2 and four copies of the proximal 16p11.2, inherited from both parents. Could this be the first report of a recessive disorder not caused by a loss-of-function of two alleles, but rather of tetrasensitivity of a microduplication locus? **Anna Lengyel** presented the phenotype of 14q1.2 microdeletion syndrome. **Anna Lokchine** presented rare intrachromosomal CNVs as a cause of Primary Ovarian Insufficiency. Premature ovarian insufficiency (POI) is a major cause of female infertility. Currently, over 80 genes are reported to be responsible for POI. She reported the first case of intragenic compound heterozygous deletions in *FSHR* in a POI patient and presented on other cases of POI caused by CNVs
I would like to end this report by making two requests to the readers:

(1) considering the plethora of methologies to detect structural variation in WES and WGS data and the consequently different outcomes, it may be warranted to start a discussion on guidelines, quality parameters and expected outcomes. Candidates, please contact me.

(2) **Great job opportunity!** Being working group leaders for over 10 years, we would welcome new candidates to take over. The WG leaders can invite speakers, make the line-up for the working group presentations, suggest topics to collaborate on and, as suggested, take the lead in creating guidelines, reviews, future collaborative projects, etc…

PWG Animal, Plant, and Comparative Cytogenetics
Coordinators: **Pat Heslop-Harrison, Trude Schwarzacher**

The Workshop of the Permanent Working Group PWG for Animal, Plant and Comparative Cytogenomics filled an afternoon slot with exciting discussions and thoughtful presentations, notable for the quality not only of chromosomes but also of explanatory graphics. The vitality of modern cytogenomics was evident, with eleven countries represented: Poland, Russia, Ukraine, Austria, Germany, Taiwan, UK, Croatia, Romania, Italy, and Portugal, unfortunately with French contributors unable to join.

PWG Chromosomes' Integrity, Stability and Dynamics
Coordinators: Jose Garcia-Sagredo, Emanuela Volpi

A special buoyancy was in the air at the 14th ECA conference in Montpellier, a beautiful French city with an ancient University at the heart of Europe. It was most likely the fortunate combination of a stellar line-up of eminent yet approachable international speakers, the solid research and novel developments presented, the many early researchers from different parts of the world, and the friendly size of the conference with opportunities for informal mingling which rendered the atmosphere at the conference so upbeat. The French hospitality and sunny weather made it even more enjoyable! After the pandemic, meeting in person again felt almost like a new beginning, providing the perfect context within which to convene for the first time the newly named "Chromosomes' integrity, stability and dynamics" PWG (formerly "Genetic toxicology and mutagenesis").

The renaming of the PWG has been brought about by the need convey the broadened scope of our permanent working group that is to bring together members of the ECA with shared interests in chromosomal dysfunctionalities, from mechanistic aspects to cytogenomic outcomes and diagnostic applicability in human disease. Following consultation with the ECA Board of Directors and their deliberation, the new name was officialised in 2022.

As the PWG Coordinators and convenors of the satellite meeting, we had a really challenging time selecting abstracts for presentation as there were so many excellent examples of research submissions potentially aligned with our themes, but limited time available on the Saturday afternoon before the official start of the Conference. Our first presenter was **Eliane El Achkar** from Egypt, now based in Paris, who spoke about her work on the molecular characterisation of two replication stress-induced breakage hotspots at the common fragile site FRA11D harbouring cancer and neurological genes.

Following Eliane's talk, as per tradition, we had several presentations on the ever fascinating and seemingly never-fully-exhausted topic of chromosomal instability (CIN) in stem cells leading to discussion on the need for consensus on karyotypic analysis as part of routine quality control pipelines. The first presentation was by **Mateus de Oliveira Lisboa** from Brazil. Mateus talked about CIN in mesenchymal stromal cells from acute myeloid leukaemia (AML) patients, a collaborative research project between the Pontificia Universidade Catolica do Parana, where Mateus studies, and Sabine Mai's group at the University of Manitoba in Canada. The second presentation was by **Nikoletta Selenti** from the Aghia Sophia Childrens Hospital Laboratory of Medical Genetics in Athens (Greece) on CIN in iPSC cultures derived from dermal fibroblasts. **Anna Schachner** from the Medical University in Vienna (Austria) presented how Optical Genome Mapping - the new cytogenomic technique everybody is talking about - can be applied to monitor fine structural genomic stability in long term cultures of iPSC. Finally, **Radhia M'Kacher**, a scientist and entrepreneur from Paris, explored in her talk CIN as a biomarker in routine screening programmes in the cytogenetic clinic. There was time for questions and answers after each talk, and

inevitably a round of commemorative group pictures. It was an auspicious start for the newly renamed PWG and we look forward to reporting on future developments and activities.

PWG Marker Chromosomes
Coordinators: Thomas Liehr, Isabel Marques-Carreira

The permanent working group (PWG) on Marker Chromosomes was held on the first day of the 14th ECA-conference 2023 in Montpellier, France. The session was very well attended as usual, with a full room of interested cytogeneticists from all over Europe (Fig 1 and 2). **Isabel Carreira** (Faculty of Medicine, University of Coimbra. Portugal) briefly introduced the topic of the PWG and outlined the program. There were six presentations: two recorded ones from Thomas Liehr who was unable to attend in Person, two that had been selected from the abstracts submitted to the conference, and two discussions of clinical cases of small supernumerary marker chromosomes (sSMCs) identified during routine diagnostics. **Thomas Liehr** gave an overview of what is known about sSMCs and the techniques that are usually used to characterize them. There are 3,3 million human carriers of an sSMC worldwide, 70% of which are clinically normal. He presented the main shapes of sSMCs, the subtypes, and the mechanisms underlying their origin. Most sSMCs are derived from chromosome 15 but sSMCs derived from all chromosomes have been found, Genotype-phenotype correlation are made using many different techniques, with arrayCGH being the first-tier test. The clinical outcome for sSMCs is hard to predict, as a consequence can be correlated with: (i) differences in size of euchromatic DNA; (ii) uniparental disomy of sSMC sister chromosomes (iii) differences in mosaicism since more than 50% of sSMC are in mosaic form. He referred to the sSMC home page (https://cs-tl.de/DB/CA/sSMC/0-Start.html) where one can search for every chromosome reported with marker chromosomes. In this page one can also find a link to other sub-pages such as: uniparental disomy, chromosomal heteromorphisms, constitutional chromosome breakpoints, karyotypes of tumor cell lines and the multicolor fluorescence *in situ* hybridization. **Cristina Perez** from the Genetics Department-Cytogenetics and Cytogenomics, Barcelona Central Lab, presented 2 cases: one from a 3yr old female with developmental language disorder with a sSMC of 13q11q12.12 and an 11yr old female with an autism spectrum disorder and *attention deficit hyperactivity disorder and a* complex karyotype with different cell lines with 4 SMCs that had originated from chromosomes 4, 5, 8 and 13. Several techniques were used to characterize their size and origin: FISH, MLPA and arrayCGH. Both cases were also successfully characterized using a single workflow with Optical Genome Mapping. **Joana Melo** from the University of Coimbra presented the importance of arrayCGH in the detection and characterization of sSMCs in 4 cases: two from prenatal diagnosis where the sSMCs were detected by karyotyping and characterized by arrayCGH as an isochromosome 18p and an sSMC derived from chromosome 6. The other two postnatal cases referred for developmental delay and dysmorphism were detected by the arrayCGH and showed a dup of ~7Mb in 6q and a 7 Mb Dup at 20q. Karyotype showed that the latter two were ring chromosomes**. Esther Cuatrecasas** from the Cytogenetics Lab in the Hospital Sant Joan de Deu in Catalunya presented a case of an 11-month old patient with a bilateral iris and chorioretinal coloboma, strabismus and bilateral preauricular pits and skin tags. ArrayCGH was normal; NGS and reanalysis of NGS did not find variants or changes in the copy number that could be considered pathogenic. At 3 years and 8 month the patient was referred to the Genetics Service; the karyotype showed a low-level mosaic: 47,XX,+mar[6]/46,XX[44]dn. MLPA on this patient for the cat eye syndrome region showed a positive result. This case demonstrated that the combination of the phenotype with the karyotype was important to detect this low-level mosaicism. **Isabel Carreira** from the Faculty of Medicine of the University of Coimbra presented three cases and showed how the different technologies

complemented each other to give a more accurate genotype-phenotype correlation. In case 1 with a prenatal karyotype 48,XYY,+mar, the characterization of the sSMC showed the centromeric region of chromosome 22 as well as a small duplication in one chromosome 22; the risk for that fetus was, therefore, changed from low to high risk. In case 2 of a child with developmental delay a dup on the proximal region of chromosome 15 and a dup of 21qter was found by arrayCGH; karyotyping, however, showed that the extra chromosome was a result of a 3:1 segregation of a maternal t(15;21). Case 3 was a result of prenatal diagnosis performed because of advanced maternal age. It was a mosaic karyotype with 4 cell lines: one with 46,XY, another with 45,X and 2 cell lines with one and 2 sSMCs respectively. FISH showed that the sSMCs were derived from the Y chromosome. Against expectations a baby girl was born and the karyotype on the blood confirmed the 4 cell lines and showed 4 extra ones with 2 and 3 sSMC, all derived from the Y chromosome. Finally, Thomas Liehr presented the most complex sSMC that has ever been detected in a 41yr old patient with infertility hypothyroidism, rheumatism, degenerative spine and schizoaffective disorder. The karyotype was 47,XY,+mar. The arrayCGH showed that 5 chromosomes were involved in this sSMC. Microdissection showed that the marker was discontinuous, complex and mostly neocentric. In parallel this marker chromosome was analyzed also by Optical Genome Mapping. In the end this marker was shown to be composed of 7 euchromatic segments derived from 5 chromosomes (8; 9; 14; 15; 21). This is the first case of an obviously chromothripsis-related sSMC composed of 7 euchromatic blocks derived from 5 different chromosomes and with a neocentromere.

Overall, a broad spectrum of different sSMCs, detected during our routine pre- and postnatal studies was presented. We thank all the speakers for giving excellent presentations and the geneticists that attended and contributed to the discussion.

Conference Opening lecture
Chair: Mariano Rocchi and Franck Pellestor

Eva R. Hoffmann: Aneuploidy in the Maternal Germline

Sunday 1 July

Plenary session 1 - Mosaicism: from Preimplantation Embryos to Aging
Chairs: Joris Vermeesch and Elisabeth Syk Lundberg

The first session of the meeting involved different aspects of the common but important issue of mosaicism, defined as the presence of two or more cell lines with different chromosomal content within the same organism. The session included three invited speakers and one selected oral presentation.

The first speaker **Antonio Capalbo** from Reproductive genetics, Rome, Italy gave a talk on mosaicism in preimplantation embryos found after trophectoderm biopsy and PGT-A. With the advent of high-resolution methods such as next-generation sequencing, mosaicism has risen to become the third most common cause of "aneuploidies" in PGT-A (up to 20%). However, there is substantial evidence that mosaicism has been largely overestimated and non-selection studies have revealed that euploid and putative mosaic embryos have similar implantation, miscarriage, and live birth rates. As a result, the ongoing activities in PGT-A are focused on developing proper outcome measures, explicit frameworks for validating the technology prior to clinical usage, and evidence-based reporting standards.

The next talk by **Malgorzata I. Srebniak** from Erasmus MC, Rotterdam, The Netherlands, addressed the problem of mosaicism in prenatal

diagnosis. Mosaicism is a common phenomenon in fetal development. The earlier the fetus is investigated the more cases of mosaicism are uncovered. Nowadays, with the use of non-invasive prenatal testing (NIPT) and the genotype-first approach, it is more difficult to interpret mosaicism. Especially when mosaicism is encountered in an apparently normal pregnancy. The presentation addressed the current questions on follow up investigations after abnormal NIPT results.

The third talk was presented by **Lars A. Forsberg** from Uppsala Biomedical Centre, Uppsala, Sweden, who gave a talk on hematopoietic loss of chromosome Y and higher mortality in men. Mosaic loss of chromosome Y (LOY) in blood leukocytes of men increases the risk for all major causes of human death, including cardiovascular diseases, various forms of cancer and Alzheimer's disease. Using standard technologies such as genotyping arrays, LOY is detectable in more than half of 70+ year old men, and single cell-based analyses suggest that this is an inevitable consequence of living. It has been described that LOY drives a profibrotic disease mechanism in mice, involving up-regulated TGFβ1-signaling by LOY-leukocytes, leading to increased fibrosis in other organs, associated with organ failure. Treatment of mice with TGFβ1-inhibitors reversed the LOY-induced fibrosis and restored organ function. In the future, stratification of men based on LOY in blood could enable anti-fibrotic treatments in fields such as cardiology, oncology and geriatrics, using TGFβ1-inhibition in preventive as well as therapeutic purposes.

The last talk was a selected oral presentation by **Cornelia Daumer-Haas** from Humangenetik und Praenatal-Medizin MVZ Gmbh, Munich, Germany, who presented a very interesting case with normal array-CGH results in a patient with short stature and global developmental delay carrying a de novo ring chromosome 2p and a chromosome 2q derivative with a neocentromere. Fra(X) analysis, array-CGH and whole exome sequencing showed normal results. The diagnosis was made by conventional karyotype analysis revealing a complex karyotype with 47 chromosomes in most of the cells: A ring chromosome 2p and a derivative chromosome 2q with a neocentromere formation. In addition, cells without a ring and a cell with a large, likely dicentric ring could be found, pointing to mitotic instability. The abnormal cell lines were probably responsible for the patient's phenotype. With array-CGH and whole exome analysis alone, the diagnosis would have been missed.

Plenary session 2 - Cancer Cytogenomics
Chairs: Roberta Vanni and Harald Rieder

Due to unforeseen circumstances, Professor Felix Mitelman, who was to chair this sessionn was unable to attend; Professor Harald Rieder graciously took on the responsibility of chairing it in his absence.

The session included two invited speakers and one selected oral presentation.

During her lecture titled "Replication Stress Generates Distinctive Landscapes of DNA Copy Number Alterations and Chromosome Scale Losses in Cancer," the first speaker, **Sarah McClelland** from London, UK, discussed the mechanisms of chromosomal instability.

Based on single-cell genomics and cell biology approaches, she presented findings that shed light on the mechanisms causing genomic alterations by mitotic dysfunction and on the mechanisms that convert replication stress to genome evolution during cancer,

Her research group developed a model system that, by sabotaging the mitotic segregation of a specific chromosome, induces aneuploidies in a targeted manner. This system allows for creating a population of daughter cells enriched for chromosome-specific segmental aneuploidies. In addition, they used the single-cell approach to detect focal copy number alterations (CNA) caused by replication stress within a single-cell cycle. This approach is useful in understanding how cancer genome evolution is impacted by replication stress. By examining the distinct CNA landscapes produced by different inducers of

replication stress, precise copy number signatures can be derived for specific replication stress mechanisms. A comprehensive understanding of the mechanisms driving tumor chromosomal instability and evolution would help clarify therapy resistance in cancer patients.

The second invited speaker, **Uri Ben-David**, from Tel Aviv, Israel, presented a talk titled "Cancer Aneuploidy: From Evolutionary Pressures to Cellular Vulnerabilities", to explain how aneuploidy promotes cancer development and progression. Distinct recurrent patterns of aneuploidy have been observed across tumor types, suggesting a selection for specific aneuploidies during tumorigenesis in a lineage-dependent manner. Interestingly, stem cells tend to acquire the same aneuploidy that characterizes tumors of the same tissue origin. This implies that specific fitness advantage of an aneuploidy depends on the cellular context. In fact, in cancer cells the impact of aneuploidy on adaptation varies depending on the cellular context: aneuploidy usually has a negative adaptative value, making it likely to be selected against during cellular environment fluctuations. This observation prompted Ben-David's group to investigate whether aneuploidy increases drug sensitivity. Specifically, they explored whether high levels of aneuploidy made cancer cells more vulnerable to certain genetic or chemical perturbations, which could help identify cellular weaknesses. They demonstrated that aneuploid cancer cells are more sensitive to perturbations in the core components of the spindle assembly checkpoint than are euploid cells and that the sensitivity of the cancer cells to inhibition is exposure-time-dependent, transitioning from resistance to sensitivity with prolonged exposure. This apparent paradox was explained by the observation that KIF18a, a kinase spindle-related regulator protein, was underexpressed in aneuploid cells, consequently making the cells unable to converge on a viable metaphase plate after spindle assembly checkpoint inhibition. When KIF18a is expressed in lower levels, it leads to aneuploid cells with spindle aberrations. If the spindle assembly checkpoint is blocked, cells can quickly overcome the arrest, which can initially result in resistance. However, over time, the cells acquire multiple mitotic aberrations that lead to cell death and proliferation arrest.

During her presentation, titled "Optical Genome Mapping for Multiple Myeloma Evaluation of the Technology in a Clinical Laboratory," **Christina Srouji** from Haifa, Israel, presented her findings on the evaluation of Optical Genome Mapping (OGM) as an alternative for FISH-test in cases of multiple myeloma. Samples with >25% multiple myeloma cells detected by immunophenotyping were considered. According to the study, OGM is highly consistent with routine FISH testing. It has the potential to identify new abnormalities that are significant for the diagnosis and treatment of multiple myeloma. As a result, it could be considered as a replacement for current cytogenetic tests as the primary method of testing for multiple myeloma.

Concurrent Session 1 - Recent Advances in Cytogenomics
Chairs: Franck Pellestor and Harald Rieder

The technological developments experienced in recent years in the fields of Cytogenetics and Cytogenomics gave rise to a very interesting session which brought together 3 speakers perfectly highlighting the innovative aspects in terms of chromosomal analysis.
To begin this session, **Alexander Hoischen** from the Department of Human Genetics and Internal Medicine at Radboud University Medical Center presented the Optical Genome Mapping (OGM) technology developed by the company Bionano, for the high-resolution analysis of structural variants (SV), both in the field of constitutional cytogenetics and somatic cytogenetics. Through several examples, Alexander Hoischen clearly showed how OGM could be effective and precise for the diagnosis of structural anomalies, including rearrangements of increased complexity observed in the context of research on rare diseases. His presentation indicated the possi-

bility of developing systematic patient-parent trio studies for the characterization and the assessment of *de novo* SVs.

The next guest speaker, **Antonio Raussell**, bioinformatician at the Imagine Institute and the INSERM UMR 1163 unit at Paris Cité University, addressed the place of Artificial Intelligence (AI) in Cytogenetics and presented several new bioinformatics strategies developed by his team to improve the clinical interpretation of the increasingly numerous copy number variants (CNVs) which are revealed by genome sequencing techniques. His presentation focused on rare pediatric diseases and in particular on the interest of developing a clear clinical interpretation of small CNVs identified in non-coding regions of the genome. Three bioinformatics tools were presented: the CNVxplorer web server developed for functional clinical interpretation of non-coding CNVs through the pooling and analysis of genomic, epigenomic and phenotypic data. The second approach described was a machine learning approach called CNVscore. It was created and trained on different datasets of pathogenic and non-pathogenic CNVs. The originality of this approach is that it associates pathogenicity estimates with uncertainty scores, thus making it possible to evaluate the adequacy of potential alternative models for the identification of CNVs.

Finally, the third and final presentation came from the selection of the abstract submitted by **Gil Nifker** from the Physical Chemistry laboratory at Tel Aviv University. His presentation showed how OGM technology could be adapted to research investigations and circumvent the limitations of short-read sequencing, particularly for the study of SVs and CNVs located in genomic regions rich in repetitive elements. Dr. Gilfer's team has developed a procedure for fine analysis of the genome by combining the fluorescent marking of targeted genomic regions using an *E. coli* Dam methyltransferase (DAFCA) and the use of OGM technology. This combined approach makes it possible to generate chromatin accessibility maps composed of large DNA fragments and thus to carry out combined analyzes of SVs and associated chromatin structure.

This session on new developments in AI and OGM technology was followed by a large audience and gave rise to interesting questions and discussions, highlighting the growing interest of cytogeneticists in OGM technology and the development of bioinformatics tools.

Concurrent Session 2 - Beyond Genome Sequencing: the Epigenetic Signature
Chairs: Orsetta Zuffardi and Joan Blanco

This session was dedicated to exploring various scenarios where the analysis of epigenetic alterations can serve as both a complementary approach and, in certain instances, a potential alternative for diagnosing specific types of genomic disorders.

Bekim Sadikovic, from Western University in Canada, delivered a compelling presentation centered on the use of DNA methylation profiles as a tool for the diagnosis of large structural copy number variants. He introduced the concept of "episignatures" characterized by recurring and reproducible DNA methylation patterns intricately linked to common genetic or environmental factors within specific disorder populations. Dr. Sadikovic illustrated how episignatures emerge as highly sensitive and specific biomarkers, helping in deciphering complex clinical and genetic scenarios. He proposed that the integration of episignatures into clinical practice holds promise for the diagnosis, prognosis, and treatment of individuals grappling with a wide array of genetic conditions, ultimately paving the way for more precise and personalized healthcare interventions.

In the second presentation, **Karen Temple** from University Hospital Southampton delved into the world of Multi-locus imprinting disorders. During her talk, Prof. Temple used several case examples to help us understand this topic better. She explored how employing a multi-testing approach can enhance the chances of making accurate diagnoses. She also investigated whether testing for multiple genes could

streamline the diagnostic process or uncover unexpected findings, making it a more efficient way to diagnose classical and less common clinical imprinting disorders. One particularly intriguing aspect of her presentation was her explanation of how these multi-locus disorders arise due to changes in genes related to the subcortical maternal complex (SCMC). These genes play a crucial role in maintaining the maternal imprint in the oocyte and early embryo, which in turn affects the likelihood of these disorders recurring in future pregnancies. This insight adds a layer of complexity to our understanding of these disorders and their implications for patients.

Following these two prominent talks, the session continued with an oral presentation coming from a selected abstract. **Mathilde Geysen**, from the Catholic University of Leuven, highlighted the utility of long-read sequencing in detecting both structural and epigenetic variations. While the data presented were preliminary, her results demonstrated the potential of this approach in effectively identifying such variations.

Plenary session 3 - Newly Emerged Technologies in Cytogenomics
Chairs: Pat Heslop-Harrison and Emanuela Volpi

The session on emerging technologies focussed on use of synthetic oligonucleotide pools. The pioneer of the method for chromosomal in situ hybridization, **Brian Beliveau** (University of Washington) gave a superb talk on his labs latest work. He showed how to maintain and visualize spatial 3D genome organization with multiplexed imaging - a method complementary and giving entirely different information from sequence-based approaches - with a new tool, SABER, Signal Amplification by Exchange Reaction. He also have presented another valuable resource, PaintSHOP, for designing in oligonucleotide-based FISH probe sets (both available at https://www.beliveau.io/tools). Following his talk, there was a discussion session lead by **Emanuela Volpi** and **Pat Heslop-Harrison** (UK). The social media handle of Brian, @Oligopain, perhaps summarizes some of the experiences. The session did show the wide range of valuable results from cytogenomic uses of oligopaints including translocation detection and characterizing chromosomal organization across species, and the huge interest in applying the approaches.

Monday 3 July

Plenary session 4 - Clinical Cytogenomics I
Chairs: Damien Sanlaville and José Garcia-Sagredo

The fourth plenary session of the conference was devoted to clinical cytogrnomics I. There were three speakers and two selected abstracts. During this exciting session, several different aspects of this field were presented.

In the first talk, **Anna Lindstrand** from the Department of Molecular Medicine of Kaolinska Institut, Sweden addressed Complex Genomic Rearrangements (CGRs) as an Underestimated Cause of Rare Diseases because CGRs are often missed during routine genetic screening testing. She emphasized that identifying CGRs requires detection of copy number variants, phasing multiple breakpoint junctions in cis, and detecting and resolving structural variants within repeats. During her talk she demonstrated how combining cytogenetics and new sequencing methodologies can be successfully applied to study the genomic architecture of CGRs and to access their clinical relevance as well as their impact in rare genetic diseases.

The next talk by **Orsetta Zuffardi**: from the Department of Molecular Medicine of Pavia University, was titled: Distal Germ-Line Deletions in Mosaic With Copy-Neutral Loss of Heterozygosity: Something to Be Considered in Genetic Counselling. The assumption is that the presence

of multiple cell lines within the same individual is now considered the rule not only in persons suffering from genetic diseases but also in healthy people.

She pointed that in the last ten years a new condition has emerged: it is the presence in healthy or almost healthy persons of unbalanced rearrangements, mainly distal deletions, in mosaic form with revertant cell lines in which the imbalance is eliminated by somatic recombination. The new mosaic cell lines are characterized by Copy Neutral Loss of Heterozygosity (CN-LoH) and segmental uniparental disomy (seg-UPD). The imbalance can be inherited by affected offspring in whom other revertant events create new mosaic CN-LoH cell lines. In these families phenotype-genotype relationship is not predictable a priori and this phenomenon should be taken into account during genetic counselling.

Brunella Franco from Telethon Institut of Genetics and Medicne of Federico II University, Naples gave a talk titled: From Gene Disruption to Missense Variants: how Different Types of Variants Influence the X-Linked Inheritance Model. One of the two X-chromosomes in females is inactivated in the early blastocyst stage to achieve gene dosage compensation between the sexes. This X inactivation (XCI) randomly affects the maternal or the paternal X. However, in few instances, non-random XCI may take place thus modulating the phenotype observed in female patients carrying mutations in X-linked genes or structural abnormalities of the X-chromosome. It has been estimated that about 25-30% of X-chromosome genes escape XCI. Recent data has revealed a high degree of heterogeneity in the levels of XCI between individuals and between different tissues of the same individual. During her talk she presented several clinical examples such as X-linked dominant male-lethal disorders to discuss this topic.

A talk selected from the abstracts by **Niels Tommerup,** from Danish Cytogenetic Central Registry Study Group, was titled: The Burden of Long Range Position Effects in Balanced Chromosomal Rearrangements. The risk of early onset developmental disorders in carriers of *de novo* balanced chromosomal rearrangements (BCRs) is estimated to be 26.8% due to direct gene truncation or long range position effects (LRPE). In a systematic study of >700 simple two-way rearrangements in affected and healthy BCR-carriers, 21.3% of the BCRs directly disrupted a known autosomal dominant developmental disorder gene. This shows that they identified an enrichment of noncoding BCR breakpoints in specific topological domains (TADs). They also identified six genomic features enriched in TADs preferentially disrupted by noncoding BCRs in affected cases versus controls and used these features to build a model to predict TADs at risk for LRPEs across the genome. They observed a significant excess of cases where both breakpoints truncated a predicted high-risk TAD, suggesting that dual loss/gain of regulatory elements in two high-risk TADs may be a common morbidity mechanism. Finally, they estimate that LRPE may be at least as frequent a mechanism underlying early DD in BCRs as direct gene truncation.

Finally, **Marlene Ek** from Karolinska Institutet Molecular Medicine gave a talk: Multiomic Profiling Unravels Disease Mechanisms in Complex Chromosomal Rearrangements and Marker Chromosome Carriers. In clinical cytogenetic laboratories, in order to fully understand the complexity of a specific event and to infer underlying mechanisms and clinical consequences, one needs to pinpoint breakpoint junctions and resolve the structure of the derivative chromosome. She used combinations of short-read, linked read and long-read genome sequencing to characterize DNA samples from over 50 carriers including inversions, translocations, rings and markers as well as complex rearrangements. By multiomic analysis of these cases, she was able to identify disease causing genes and other disease mechanisms such as disturbed long-range interactions. Furthermore, the detailed analysis of breakpoint junctions show that different mutational processes may cause similar rearrangements such as both translocations and inversions being generated from either replicative or non-replicative mechanisms. Finally, they showed that chromosomal rearrangements often involve more complexities than the cytogenetic investigations indicate.

Concurrent Session 3 - Clinical Cytogenomics II
Chairs: Orsetta Zuffardi and Martine Doco-Fenzy

The first talk 'Structural Variants in Clinical Practice Using Genome sequencing' was given by **Nicolas Chatron** who showed how to obtain molecular diagnosis after the current gold-standard molecular tests for genetic diseases have failed. Through several examples, he showed that the identification and correct interpretation of structural variants, either balanced or unbalanced, cannot rely solely on the chromosomal micro-array or the short-read genome sequencing. Indeed, the limitations created by repetitive DNA and GC-rich regions also require the use of long-read genome sequencing.
In her talk titled 'Constitutional Chromoanagenesis: From Diagnosis to Genetic counselling' **Caroline Schluth-Bolard** showed how the events of chromoanagenesis though usually sporadic may also be familial with the asymptomatic or paucisymptomatic parent transmitting the complex rearrangement to off-spring in an unbalanced manner. Thus, chromo-anagenesis can be associated with a normal phenotype and normal fertility, even in males. Whole genome sequencing may be the only way to identify this type of event when there is no imbalance.

The last presentation was of an abstract 'Systematic X-inactivation Studies of Sequence Resolved Balanced X Chromosomal Rearrange-ments' submitted by **Sanam Khan**. She presented some examples of X/autosome trans-locations highlighting how DNA sequencing may explain the behavior of the X chromosome inactivation, sometimes inconsistent with the seemingly balanced state of rearrangement

Concurrent Session 4 - Animal and Plant Cytogenomics I
Chairs: Tony Heitkam and Trude Schwarzacher

We discussed the latest developments across animal and plant cytogenomics in two conference sessions and a workshop, with speakers pre-senting diverse work ranging from bioinformatics to chromosome studies, and encompassing evolutionary, biodiversity and hybrid studies. Our first speaker was to be **Mathieu Rouard**, from the nearby Institutes in Montpellier, and his talk (presented by **Pat Heslop-Harrison**) discussed the Banana Genome Hub, a remarkable tool for comparative analysis of genome evo-lution in the range of diploid species in the Musaceae genome based on high-quality, chromosome-scale genome assemblies (with various species including 2n=9, 10 and 11), complemented by chromosomal studies. The detailed analysis of how chromosomes have evolved over time in the sections of the Musa genus and sister genera Ensete and Musella (the assembly of which was announced in the talk) showed how their chromosomes have been shaped by complex processes of inter and intraspecific hybridizations as well as reciprocal translocations. **Brankica Mravinac** (Croatia) then focussed her talk on the chromosomal and sequences organization of satellite DNA in the 33 species of Tribolium flour beetles. Assembly of the satellitome (making up about a third of their genomes) is a challenge but use of the graph-based clustering approach of RepeatExplorer with Illumina sequencing showed evolutionary patterns of shared and species-group-specific tandemly repeated sequences, complemented by in situ hybridization to show chromosomal organization. Long-molecule sequencing, parti-cularly in T. feemani and its sterile hybrid with T. castaneum, showed dominance of DNA transposons in both species, but 20% of genome, mostly major satellite DNAs , and the Y sex chromosome proved challenging to assembly. The satellites may play a role in the postzygotic reproductive isolation of the hybrids. Brankica presented evidence for a range of satellite DNA amplification models including gene-conversion, unequal crossing-over, transposition, and extrachromosomal circular DNAs eccDNAs. Unrelated sequences of abundant centromeric satellite DNAs indicate amplification bursts that

caused the largest genomic differences between the species. **Filomena Adega** (UTAD Portugal) discussed the genomes of the largest and most diverse groups of mammals the bats, Chiroptera, with 1400 species and typically genomes 2Gb in size. Bats have a long life span for small mammals, and her data showed the extreme variation in these genomes. There is strong evidence for recent activity of transpsosons, and large karyotypic diversity across species in Portugal, shown by physical mapping of repetitive elements in the genomes. The non-LTR retrotransposon, LINE-1. was scattered along chromosomes and accumulated in pericentromeric heterochromatic regions, with high abundance in the X chromosome. SINEs, in contrast, were more dispersed in these genomes and excluded with from the Y chromosome, with some accumulation in terminal regions. Filomene concluded by showing how bats are prone to horizontal transfer of sequences and activity of retroelements during speciation events, being highly influenced by behaviour characteristics and environmental conditions, leading to different rates of recombination, genome variation and diversification. Active transposons are forces for gene regulation, adaptation, genome diversity and evolution

Plenary session 5: Nuclear Organization and Diseases
Chairs: Jean-Michel Dupont and Emanuela Volpi

The fifth plenary session of the 14th ECA conference was dedicated to nuclear organisation, a theme with a perhaps less applied connotation than mainstream cytogenomics yet of crucial conceptual relevance for modern genetics and chromosome biology. Particularly for those of us within the ECA mostly concerned with molecular diagnostics and increasingly focussed on linear sequence analysis, it is always inspiring to be reminded of the complexity and physiological significance of the multidimensional context within which genes, and indeed genomes in their entirety, function. This plenary session provided the perfect opportunity to do so. The first presentation was entitled 'The 3D genome organisation into topologically associating domains (TADs) and chromatin nanodomains'. It was delivered by **Frédéric Bantignies** from Giacomo Cavalli's group at the Institute of Human Genetics in Montpellier. Fredric's presentation provided an elegantly illustrated, comprehensive overview of the key principles of higher-order genome organisation and function, including work done by their research group on the elucidation of nanoscale features of chromatin folding by super-resolution microscopy and their more recent discoveries on the role of chromatin contacts in establishing and maintaining transgenerational epigenetic inheritance. The second presentation was by **Irina Solovei** from the Ludwig Maximilian University of Munich. Irina presented her paradigm-shifting research on the spatial organisation of eukaryotic gene transcription, the findings of which challenge the prevalent view of stationary transcription factories as agglomerates of RNA polymerases through which activated genes pass. Research by Irina's team has identified by light microscopy long, highly expressed genes in mouse that, during transcription, unfold and expand in the nuclear space. Irina and her team suggest a model in which highly expressed genes form open-ended loops, spanning a few micrometres, along which RNA polymerases move and carry nascent RNAs similarly to giant 'lampbrush' chromosomes. The third presentation – a selected abstract – was by **Paola Caria** from the University of Cagliari and was entitled '3D nuclear architecture distinguishes thyroid cancer histotypes'. Paola's presentation illustrated her team's efforts at accruing evidence supporting the potential applicability of three-dimensional nuclear architecture for cancer stratification in situations of diagnostic and prognostic complexity, heralding a new era for the nucleus in pathology. The beautiful work presented in this plenary session is a reminder that not all biological answers can be provided by next generation sequencing, and microscopy remains an indispensable tool in chromosome biology and single cell genetics.

Concurrent Session 5 - Animal and Plant Cytogenomics II
Chairs: Trude Schwarzacher and Brankica Mravinac

In the second session, **Tony Heitkam** (Graz and Dresden) showed the huge value of adding a chromosome perspective to genomics in her talk about retained retroviruses, moving retrotransposons and expanding satellite DNAs. Using examples from her lab, she showed use of in situ hybridizations of repetitive DNA probes to understand the chromosomal basis of emerging crops and their wild relatives. She then showed how cytogenetics strengthens genomic studies in looking at polyploids, heterochromatic and other underrepresented genomic regions, and assessing chromosomal and genomic stability. **Yi Tzu Kuo** (Gatersleben, Germany) presented remarkable work about holocentric chromosomes – starting with a revision of the ECA conference logo with holocentromeric properties rather than the monocentromeric chromosome! Clear in situ hybridization experiments with genomic data revealed that only a few (7 to 11) megabase-size centromere-specific units made up of 23bp and 28bp long tandemly-arrayed monomers form the holocentromeres of a *Chionographis* species, although there were surprising differences between species, showing the necessity of making evolutionary comparisons and the presence of novel structures. The final talk of the session was a beautiful presentation by **Alla Krasikova** (St Petersburg) of the nuclear and cytoplasmic whole transcriptome profile of chicken oocytes at the lampbrush chromosome stage. In the post-genomic era, she showed co-transcriptional splicing and intron removal: BAC FISH allowed remarkable visualisation of the process showing loops with transcriptional units and RNA processing

Concurrent Session 6 - Accreditation, Quality Control and Education
Chairs: Konstantin Miller and Martine Doco

The first speaker in this session, **Volker Spitzenberger** from Lübeck, reported on the new version of the standard "ISO 15189:2022 Medical laboratories - Requirements for quality and competence“. This new version developed by the ISO Technical Committee "Clinical laboratory testing and in vitro diagnostic test systems" was adapted to the ISO/IEC 17025 standard. The requirements for the documentation of the management system and opportunity and risk management were also adapted to ISO/IEC 9001:2015 with a specific focus on risk management in medical laboratory diagnostics. New aspects are impartiality and confidentiality. Further issues are the requirements for internal quality control of examination procedures, EQA programs, IT security and emergency preparedness. ISO 15189:2022 will become valid after a transition period on 5 December 2025.

Johan T. den Dunnen (HGVS Variant Nomenclature Committee) presented the current nomenclature standards in molecular genetics, the Human Genome Variants Society (HGVS) nomenclature and the International System for Human Cytogenomic Nomenclature (ISCN) by the ISCN Standing Committee The committees work closely together in the approach to harmonize nomenclature. It became clear, however, that not all recommendations are consistent and the historic development sometimes hampers harmonisation.

The selected abstract was presented by **Mathilde Quibeuf** from Rouen who reported on the analysis of highly complex chromosomal anomalies by Optical Genome Mapping. Based on an example of chromoanagenesis with various rearrangements, the benefit of such analysis in training users in retrieving the whole spectrum of anomalies was demonstrated.

Tuesday 4 July

Plenary session 6 - Prenatal Diagnosis and Preimplantation
Chairs: Jean-Michel Dupont and Rosário Pinto Leite

The Prenatal plenary session was the last session of the conference with three invited speakers and two selected communications.

The first talk by **Robert-Jan H. Galjaard** from Erasmus Medical Center in Rotterdam reported on the follow-up results of the TRIDENT2 study. This nationwide NIPT program was set up to offer genome wide NIPT to all pregnant women, and gives new clues on the clinical impact of the additional findings (Rare Autosomal Trisomies (RAT) and segmental anomalies (SA). These additional findings accounted for 0.36% of cases in the general obstetric population, roughly half RAT and half SA. The origin of these anomalies was assumed to be placental in 50% of cases, and proved to be of fetal or maternal origin for most of the other half. Clinical impact was demonstrated for both fetal anomalies (mostly pathogenic aberrations) and confined placental mosaicism with adverse perinatal outcome in ≈ 50% of cases. Maternal aberrations were associated with either constitutional CNV (pathogenic or VUS (Variant of Unknown Significance), the remaining CNV were acquired chromosome aberrations.

The second talk by **Joris Vermeesch** from Leuven University was also dedicated to NIPT, and more specifically to additional data that can be obtained from circulating cell free DNA (cfDNA). One of the major steps in setting up NIPT was the discovery that fetal DNA fragments were of shorter size than maternal derived fragments, allowing for an increased efficiency by focusing analysis on shorter fragments. The same observation holds true for neoplastic circulating DNA. Many other molecular features of cfDNA are now actively worked out to gather new molecular information regarding for example the tissue of origin of cfDNA or the mechanism of formation of DNA fragment through various enzymatic pathways. Main fragmentation patterns of DNA that could be used as biomarker (referred to as 'fragmentomics') include detailed analysis of end signature of DNA fragments (preferred end and end motifs), nucleosome footprint and presence of single DNA at the end of the fragments. All this information may lead to new opportunities to enhance the diagnostic tools for NIPT and cancer detection.

The last talk by **Lyn Chitty** from UCL Great Ormond Street Institute of Child Health in London was dedicated to fetal exome sequencing in a clinical setting. Previous studies had shown the clinical usefulness of whole exome sequencing in case of abnormal ultrasound with normal karyotype/chromosome microarray result, leading to around 30% of diagnostic yield. However, the main issue in the field is to set up a robust workflow allowing for a rapid turnover, compatible with pregnancy follow-up. Lyn Chitty presented the experience of the rapid fetal exome service established by the NHS, which allowed sequencing of more than 700 cases with the expected 30% diagnostic yield for monogenic diseases and a turnaround time under 15 days. Main issues faced with variant interpretation and difficult genotype-phenotype correlation were illustrated with specific cases.

Two abstracts were selected for oral presentation during the session.

First, **Armelle Duquenne** from Leuven University presented the Belgian experience with NIPT offered as a first-tier screening test for aneuploidy to all pregnant women. They compared the various technologies used in the eight laboratories running the test in Belgium during a three year period (2019 – 2022), showing slight differences in terms of false positives and Positive predicting values. Interestingly, the laboratory developed method outperformed three comercially available methods in this nationwide monitoring, which raises concern regarding strict requirements for CE-IVD marked tests for accreditation following ISO 15189.

Last presentation was by **Ludovica Picchetta** from Juno Genetics Italia in Rome who took advantage of a very large dataset of trophectoderm biopsies (96,660) analysed with targeted NGS based method for preimplantation screening for aneuploidies to unravel a maternal age effect on the incidence of triploidy. Most cases resulted from a maternal meiosis II error and 16% of cases showed no evidence of recombination during maternal meiosis. The study also shows that on the other hand, haploid embryos which are diagnosed usually result from a paternal error.

Closing keynote
Chairs: Mariano Rocchi and Thierry Lavabre-Bertrand

Michael Talkowski was the Keynote speaker and gave the last talk of the conference.
His presentation clearly illustrated the challenges of discovering the causes and consequences of genomic variation in disease. In particular, he illustrated how identification and diagnostic interpretation of variants increase significantly through short-read genome sequencing (GS) rather than through the use of the three current standard-of-care diagnostic tests: karyotype, chromosomal microarray, and exome sequencing. The superiority of GS has been well demonstrated both in autism spectrum disorders (1,612 quartet families including one individual with ASD) and in 295 prenatal families where the fetus had structural abnormalities (FSA). In general, GS has improved the diagnostic capabilities not only of each individual standard-of-care test but also of the combination of all three, leading to an increase in molecular diagnosis of 0.4% in ASD and 0.8% in FSA. The causative alterations identified by GS were sequence variants hidden at the exome sequencing, structural variants impossible to detect with the three standard-of-care tests, and structural variants of which interpretation was reconsidered after GS detection of their size. In conclusion, GS deserves consideration as a first approach diagnostic test for the evaluation of FSA and ASD.
The details of these studies are now published:
Lowther C., ... Talkowski ME: Systematic evaluation of genome sequencing for the diagnostic assessment of autism spectrum disorder and fetal structural anomalies. The American Journal of Human Genetics 110:1454-1469 (2023)

Closing ceremony

Michael Speicher (1960-2023)

Pioneer of molecular cytogenetics, comparative genome hybridization and liquid biopsy

Thomas Cremer, Jochen Geigl, Sarah Verheyen, Sabine Langer-Freitag,
Marion Cremer, Anna Jauch, Ellen Heitzer

Michael Speicher, Professor and Chairman of the Diagnostic and Research Institute of Human Genetics of the Medical University of Graz in Austria, died unexpectedly September 24, 2023 at the age of 62. He was a highly respected member of the ECA, the German Society of Human Genetics (GfH), the European Society of Human Genetics (ESHG), the American Association for Cancer Research (AACR), and a member of the German National Academy of Sciences Leopoldina since 2019. From 2012 to 2018, he was President of the Austrian Society of Human Genetics, and Vice-President since then. In the framework of these memberships, he has made outstanding contribution within numerous committees to national and international scientific cooperation, which we cannot acknowledge properly in this short retrospective.

Michael was promoted to Dr. med. with a study on the analysis and prognosis of Ph-positive CML, (Supervisor: Reinhard Becher), and received initial clinical training at the Internal Clinic and Polyclinic at the West German Tumor Center of the University of Essen. Throughout his research career, he continued to act as a physician dedicated to the well-being of patients. Michael's scientific lifetime achievement is characterized by major methodological contributions to studies of the human genome from multiple angles with the intention of diagnostic improvements, wherever possible. We illustrate his break-through achievements with a few selected examples. These examples demonstrate Speicher's innovative spirit, readiness to risk taking and perseverance with which he dealt with complicated methodological developments over many years and in different places.

Comparative genomic hybridization (CGH), single-cell CGH, single-cell array CGH (1993-2009)

In Heidelberg, Michael started pioneering contributions to the establishment of CGH, a method that allows the detection of complete and partial gains and losses of chromosomes at any stage of the cell cycle (1). In particular, he established a protocol for CGH studies, based on the generation of DNA from formalin-fixed and paraffin-embedded tumor material (DOP-PCR) (2). In Munich, he pioneered the development of CGH in single cells (3). In Graz, Michael established a protocol for this new method (4, 5). This protocol required the isolation of individual cells and efficient amplification of their genome (6).

Multicolor painting of mitotic chromosomes and interphase chromosome territories (1996-2005)

In New Haven, Michael developed combinatorial multi-color fluorescence in situ hybridization (FISH) for karyotyping human chromosomes (7, 8). In Munich, he employed multicolor chromosome painting for the first three-dimensional map of all chromosome territories in human fibroblast nuclei (9). In 2000, Michael achieved his habilitation, a post-doctoral academic qualification that demonstrates an individual's exceptional ability to conduct independent research and teaching, with his habilitation thesis "The colorful genome: New methods for high-resolution analysis of numerical and structural chromosomal changes".

Nucleic acid analysis for the detection of tumor DNA in blood ("liquid biopsy")

In Graz, Michael contributed essentially both to the development of liquid biopsies to identify circulating tumor cells and cell-free DNA (10). A paper published in 2013 "Complex tumor genomes inferred from single circulating tumor cells by array-CGH and NGS" (11) was recognized by the American Association for Cancer Research among the best four articles published in AACR Journals in 2013 and listed as a milestone in single cell sequencing (SCS) (12). Afterwards, he focused more on the clinical applicability of cfDNA and made key contributions as a pioneer of whole genome analysis (13, 14, 15). He published

numerous important papers using genome-wide genetic variation profiling at a lower sequencing depth to track down resistance mechanisms in solid tumors and monitor tumor evolution (16, 17). Moreover, he developed groundbreaking machine learning-based algorithms to analyze the expression of tumor genes or the accessibility of transcription factor binding sites (18).

Whoever has worked together with Michael, remembers his generosity and loyalty to all his coworkers. Just one example may suffice here: When Michael was offered the position as full professor in Graz, he asked Jochen Geigl to come with him, expanding his area of expertise. "Just do what you want", Michael said. As Jochen recalls: I have worked side by side for more than 20 years and we had much more in common than just work. I always knew that things couldn't get that bad at work, because not only was the CEO sitting one office away, but also a good friend." Michael Speicher was at the height of his outstanding career, when he suddenly died. Like everyone knowing his inexhaustible wealth of ideas, his skills, and kind, supportive manner, we took it for granted that he would continue his research work for many years to come. We are deeply saddened by his loss as a friend and mentor. Our thoughts are with Michael's wife Irene, his daughter Julia and son Alexander.

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Literature on Social Media

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

ANEUPLOIDIES AND CANCER

Aneuploidies are commonly observed in cancer cells and and are thought to influence tumor progression and genetic stability. Specific chromosome gains occur in a defined temporal order, suggesting that aneuploidies, such as 1q trisomy, that are consistently gained early during tumorigenesis, may enhance cancer fitness. Girish et al. (Science) wanted to validate this generally accepted opinion with a very clever experiment.
The authors developed a technique, ReDACT (Restoring Disomy in Aneuploid cells using CRISPR Targeting), which they used to get rid of the extra copy of 1q in a tumor cell line and to re-establish diploidy. The cell line lost malignancy. They conclude that trisomy 1q is required for malignant growth and that the trisomy acts on *MDM4* overexpression and suppression of p53 signaling.

[1] https://www.science.org/doi/10.1126/science.adg4521

PRIMATE EVOLUTION AND HUMAN DISEASES

The Premise is that evolution is the study of the past to understand the present. Nevertheless, more often than not, it is merely a matter of curiosity and lacks practical significance. This post shows that the study of evolution occasionally also has relevant practical implications.
Recently, Science published two papers on the analysis of 233 primate genomes (Kuderna et al.[1]; Gao et al[2]).
Evan Eichler's comment[3] stresses the importance of these two papers for the interpretation of human variants in protein-coding genes with respect to human diseases. This is because of the relatively low degree of genetic diversity within our species as compared to the diversity in primates. Indeed, Gao et al[2] created a primate population variant database of 4.3 million common missense variants that is 50 times larger than the clinical variant database (ClinVar) generated from human data. From this primate database they derived a semi-supervised 3D convolutional neural network, PrimateAI-3D, which outperforms 15 machine-learning classifiers bases on human variation only.
The last sentence by Eichler is thought provoking: "There is an irony in that the genetic information present in nonhuman primates—facing extinction due to human interference—may improve our understanding of our own species and the health of our children".

[1] https://www.science.org/doi/10.1126/science.abn7829
[2] https://www.science.org/doi/10.1126/science.abn8197
[3] https://www.sciencedirect.com/science/article/pii/S2666979X23001416?via%3Dihub

ANEUPLOIDIES AND CANCER: JUST PASSENGERS?

The Nature publication by Shih et al.[1] explores the prevalence of aneuploidies in cancer genomes and investigates whether they result from selection or ease of generation (as passengers). The authors developed a method called BISCUT, which identifies loci with fitness advantages or disadvantages related to copy-number events. These loci include cancer driver genes and provide insights into the role of aneuploidy in tumorigenesis. BISCUT identified, in particular, the helicase-encoding gene *WRN* as a haploinsufficient tumour-suppressor gene, mapping on chromosome 8p. The result is supported by several lines of evidence, and 8p aneuploidies are, indeed, a frequent encounter in tumors.

[1] https://www.nature.com/articles/s41586-023-06266-3

AN ATLAS OF VARIANT EFFECTS

Deciphering the biological implications of the very high number of human genetic variants, spanning both coding and regulatory regions, has proven to be a challenging task. Often, researchers resort to scouring previous reports for insights into variant consequences, as functional experimental data remains extremely rare. A

consortium of some universities has proposed a groundbreaking initiative[1] to tackle this challenge head-on.
Their project, aptly named Multiplexed Assays of Variant Effect (MAVE), aims to comprehensively characterize the variants present in all genes and regulatory elements within the human genome. By utilizing multiplexed assays, MAVE endeavors to create a comprehensive atlas of variant effects, shedding light on their functional implications. This ambitious endeavor has the potential to revolutionize our understanding of genetics, revolutionize precision medicine, and significantly enhance the utility of genomics for diagnosing and treating disease.

Note: The recently published post titled "PRIMATE EVOLUTION AND HUMAN DISEASES" (end of July) perfectly complements the content of this post, offering valuable additional insights into the broader context of genetic variants and human health.

[1]https://genomebiology.biomedcentral.com/articles/10.1186/s13059-023-02986-x

AGE-SPECIFIC BIOLOGICAL MECHANISMS GOVERNING HUMAN OVARIAN AGING

Age of onset and time-to-event data play a pivotal role in understanding the genetic aspects of disease development and progression; it is likely that the etiological causes are initiated well in advance of the appearance of visible symptoms. Therefore, the identification of the genetic variants influencing the variable phenotypical onset is of great relevance. The paper by Ojavee et al.[1] (AJHG) is aimed at testing the hypothesis that genetic propensity for age at onset is age specific. To this end the authors have focused on the most common time-related phenotype in humans: the age at natural menopause (ANM). The study was conducted on the UK and Estonian Biobank data.

[1] https://www.cell.com/ajhg/fulltext/S0002-9297(23)00246-X

LONG TELOMERE SYNDROME

Shortening of telomere with aging has been associated with shortening of lifespan itself. Maintenance of long telomeres, therefore, has been regarded as a cure for aging. Centenarians and their offspring have indeed been reported to maintain longer telomeres compared with controls[1]. The common notion is that critical telomere shortening, the consequent onset of telomeric DNA damage and cellular senescence are a general determinant of the life span of a species[2]. Furthermore, “Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice”[3].
Things, however, are more complex, almost paradoxical. In neuroblastomas, the reactivation of telomerase or ALT (alternative lengthening of telomeres), point to a poor prognosis for the patient[4]. In line with this, DeBoy et al. [5] recently reported a familial *POT1* mutation causing excessively long telomeres, along with an inherited capacity to lengthen telomeres. The mutation “conferred a predisposition to a familial clonal hematopoiesis syndrome that was associated with a range of benign and malignant solid neoplasms. The risk of these phenotypes was mediated by extended cellular longevity and by the capacity to maintain telomeres over time”.

[1]https://www.pnas.org/doi/10.1073/pnas.0906191106?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6660761/
[3] https://www.nature.com/articles/nature09603
[4] https://www.science.org/doi/full/10.1126/science.aat6768
[5]https://www.nejm.org/doi/10.1056/NEJMoa2300503?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

WHOLE GENOME DOUBLING AND CANCER

Unscheduled whole-genome doubling (WGD) events give rise to tetraploid cells that are prone to replication-stress-induced DNA damage, chromosome instability, and oncogenic epigenetic alterations.
Proliferating whole-genome doubled cells are tumorigenic and comprise ~37% of primary and ~56% of metastatic solid tumors.
Whole-genome doubled cancer cells must acquire specific genetic and physiological adaptations to accommodate the unique stresses imposed by their doubled DNA and cellular content.
Identifying genes that are essential for the viability of proliferating whole-genome doubled cancer cells, yet dispensable for the viability of

diploid cells (i.e., ploidy-specific lethal genes), has the potential to to uncover new cancer therapeutics.
Paper published in TIG[1].

[1] https://www.cell.com/trends/genetics/fulltext/S0168-9525(23)00187-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952523001877%3Fshowall%3Dtrue

EVOLUTION AND DISEASES. A TRADE OFF

This concept has been illustrated several times in earlier posts. This is another example.
The *apolipoprotein-ε4 (APOE-ε4)* allele increases the risk for several chronic diseases. In this case and similar cases the obvious question is: why were these variants not wiped out during evolution?
The authors (Trumble et al., Science Advances, 2023[1]) investigated a "wild" population (Tsimane, Bolivia). In this population, they discovered that women carrying at least one APOE-ε4 allele tended to have 0.3 to 0.5 additional children compared to individuals with the (ε3/ε3) homozygous genotype. Moreover, those with two APOE-ε4 alleles exhibited an even more substantial increase, with 1.4 to 2.1 more children on average. The enhanced fertility among APOE-ε4 carriers was attributed to their tendency to commence reproduction 0.8 years earlier and have a 0.23-year shorter interbirth interval.
They concluded that "alleles that are deleterious in sedentary urban environments may have been maintained by selection throughout human evolutionary history" (because they were connected to a higher fitness).

[1]https://www.science.org/doi/full/10.1126/sciadv.ade9797?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org

MORE INSIGHT INTO THE MOLECULAR MECHANISMS OF A PREMATURE OVARIAN FAILURE

A significant contributor to infertility is the natural aging process, which leads to the gradual depletion of the ovarian follicle reserve, ultimately culminating in menopause. Premature ovarian failure (POF) is diagnosed when a woman's ovaries cease functioning prematurely, typically before the age of 40. Several gene alterations have been linked with POF, with FMR1 being the most pivotal, while other gene variants, like those affecting NR5A1, are involved at a lower frequency.
NR5A1, also known as Steroidogenic Factor-1 (SF-1), is a transcription factor with multifaceted roles in reproductive and endocrine system development and function. It serves as a master regulator of steroid hormone synthesis in both the adrenal glands and gonads. Additionally, it plays a central role in gonadal development and the maintenance of ovarian function.
In a recent study published in PNAS by Hughes et al.[1], researchers delved into the intricate molecular mechanisms underlying SF-1's role in regulating ovarian follicle reserves. To explore this, they developed an experimental mouse model involving the conditional depletion of SF-1, which resulted in a remarkable reduction in ovarian reserve. The study's authors pinpointed that this reduction was primarily attributed to disruptions in critical follicular processes, including the communication between oocytes and granulosa cells. Collectively, these disruptions led to an elevated loss of oocytes and a significant decline in the ovarian reserve.
These findings emphasize SF-1's essential role in preserving lifelong fertility in mammals. This research is relevant for future studies on conditions such as premature ovarian insufficiency and menopause, paving the way for possible future treatments.

[1]https://www.pnas.org/doi/10.1073/pnas.2220849120

INDUCED ANEUPLOIDY IN CANCER

Aneuploidies play a crucial role in cancer (see post "Aneuploidies and cancer: just passengers?"). Lakhani et al., TIG[1]) review the recent advances in this field, focusing, in particular, on a new strategy: the induction of specific aneuploidies with a CRISPR-based technique. This approach allows the creation of isogenic cell lines with specific chromosomal changes. The advantage of these experiments is the generation of genetically controlled backgrounds for the identification of multiple dosage-sensitive genes encoded on aneuploid chromosomes.

[1] https://www.cell.com/trends/genetics/fulltext/S0168-9525(23)00219-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952523002196%3Fshowall%3Dtrue

THE NUMBER OF THE HUMAN GENES

The story of the number of human genes is amusing. The starting point was self-conceit and the idea that a great distance separates us from other animals. The reasoning was: if a worm (*Caenorhabditis elegans*) has about 20,000 genes, what about humans? So, we started confidently from ~100,000 (see article by Pertea and Salzberg, 2010[1]).
Now a paper in Nature takes stock[2].

[1] https://genomebiology.biomedcentral.com/articles/10.1186/gb-2010-11-5-206
[2] https://www.nature.com/articles/s41586-023-06490-x

INCREASED HOMOZYGOSITY NEGATIVELY AFFECTS FITNESS

It is not easy to measure fertility in populations where it is more cultural than natural. Swinford et al. (PNAS[1]) investigated the fertility of Namibian Himba, an endogamous agro-pastoralist population, that until very recently practiced natural fertility. The population has recently experienced a bottleneck which, in addition to consanguineous marriages, has led to a notable increase in haplotype sharing (long runs of homozygosity) in many of the 681 analyzed individuals. The study revealed that higher homozygosity is significantly associated with lower fertility.
In simpler terms: heterozygosity is better (from a different, but equally interesting point of view), as evidenced in a 2019 paper by Xu et al. (BMC Genetics[2]).
If extrapolation is permitted, the idea of a "pure race" is genetically meaningless.

[1] https://www.pnas.org/doi/10.1073/pnas.2309552120
[2] https://bmcgenomdata.biomedcentral.com/articles/10.1186/s12863-019-0758-4

KARYOTYPE EVOLUTION IN VERTEBRATES

The *Elasmobranchii* (sharks and rays) are one of the two branches of cartilaginous fish. Their usually large genomes and difficulty in preparing chromosomes have hindered studies of genome organization and comparison. Yamaguchi et al. (Genome Res[1]) focused on the sequencing of the zebra shark *Stegostoma tigrinum* (or leopard shark), which displays a smaller genome, and the whale shark, *Rhincodon typus*. The results, together with the cytogenetic preparations, allowed the authors to assemble these two genomes at the chromosomal level. Their achievements represent a starting point for studying karyotype and synteny conservation in a large set of vertebrates. An interesting observation is the differences between elasmobranchs and other vertebrates in the ancestral autosomes that are adopted as sex chromosomes.

[1] https://genome.cshlp.org/content/33/9/1527.long

ASSORTATIVE MATING, PARENTAL RELATEDNESS AND NEURODEVELOPMENTAL DISORDERS

Many neurodevelopmental disorders show a complex inheritance.
Smolen et al. (Am. J. Hum. Genet.)(1) used a cohort of 97,000 families and the UK Biobank to analyze phenotypic and genetic patterns that contribute to the risk of neurodevelopmental diseases in children. They confirmed that parental relatedness plays a crucial role in generating risk, but that assortative mating also plays an important role.

[1] https://www.cell.com/ajhg/fulltext/S0002-9297(23)00393-2

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COMMITTEE

ECC SCIENTIFIC PROGRAMME COMMITTEE

E.C.A. News

- The 2023 General Assembly of the E.C.A. with Board elections took place on 3 July 2023, at 18:30 at Montpellier, France.
- Renewal of the Board in 2023: the following members were elected or re-elected at the General Assembly: Blanco Rodriguez (E), Lindstrand (S), Miller (D), Pellestor (F), Yirmibes (TR).

E.C.A. Fellowships

- The **E.C.A.** offers two **Fellowships** for each of the following courses:
  European Advanced Postgraduate Course in Classical and Molecular Cytogenetics
  to be held in Nîmes (France) 18-24 March 2024 (see pages 33-34)
  Goldrain Course in Clinical Cytogenetics
  to be held in Goldrain Castle (South Tyrol, Italy) 20-26 August 2024 (see page 35-37)
- The fellowships **include the course fees and the accommodation** during the lectures in Nîmes or in Goldrain but **do not include travel expenses** for either of the courses or for accommodation during the practical training for the Nîmes course. Applications with CV, list of publications and a letter of support should be addressed to the appropriate course organizer. The Educational Advisory Council of the E.C.A. will select the successful candidates.

Kind reminder

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

MINUTES OF THE E.C.A. GENERAL ASSEMBLY, JULY 2023

Minutes of the General Assembly held on 3rd July 2023 in the Room Pasteur of Le Corum, Montpellier, France.

Approximately 72 members of the Association were present. All active members had been sent postal ballots and were invited to the General Assembly .

The President Mariano Rocchi opened the Assembly at 17.45 and welcomed those attending.

The President overviewed the activities of the Association. He discussed the active Facebook with 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/. He encouraged engagement and contributions. The President then reviewed the two Courses organized under the auspices of ECA in Nîmes and in Goldrain. He thanked Professor Jean Michel Dupont, who coordinates and organizes the Nîmes course (European Advanced Postgraduate Course in Classical and Molecular Cytogenetics), and Professor Albert Schinzel, director of Goldrain Course in Clinical Cytogenetics.

The General Secretary Jean-Michel Dupont thanked the previous General Secretary, Professor Konstantin Miller, for his huge efforts on behalf of the Association. He then discussed the membership of the ECA. The membership includes 1267 members among them 121 technologists), 181 overseas/associated members and 20 honorary members, patient organizations or affiliated companies. The number has remained stable but he noted that a few members were not up to date with the payment of their subscriptions. He noted the official change of the Registered Address of the Association.

The General Secretary is also the outgoing Treasurer. He noted the change of bank account following administrative problems with the bank. Income in 2022, a year not including a conference, was satisfactory including memberships and the Nimes course income. Expenses included the courses and meeting expenses. The 2021 online conference had a small surplus, and overall ECA has a satisfactory balance to enable operations to continue in line with the Financial Policy. The accounts of the Association were approved by the Assembly.

The Minutes of the General Assembly held on 25th August 2022 in the Goldrain Castle, Italy and published in Newsletter 51 from December 2022 were approved.

Three members, Sevilhan Artan, Felix Mitelman, and Ron Hochstenbach are standing down from the Board. Three candidates standing for election to the Board introduced themselves to the Assembly: Anna Lindstrand, Meral Yirmibes-Karaoguz and Franck Pellestor. The voting for board members was closed and a group, not including any candidates, was appointed to count the ballots.

Emanuela Volpi discussed the importance of Social Media for publicising the activities of the Association. Nicolas Chatron @NicoChatron offered to assist with the Twitter dissemination. There was a question about conferences as hybrid events. The availability of Fellowships to support early career researchers was discussed.

The President announced the results of the ballot for election of Board Members. A total of 89 votes were received: 86 voted ‘yes’, 2 ‘no’ and 1 abstention. The following candidates were duly elected: Blanco Rodriguez (E), Lindstrand (S), Miller (D), Pellestor (F), Yirmibes-Karaoguz (TR).

Those attending the General Assembly were thanked and the Assembly was closed at 18:23

Nîmes – France, 18-24 March 2024

EUROPEAN CYTOGENETICISTS ASSOCIATION (E.C.A.)

European Diploma
in Classical and Molecular Cytogenetics

Director: Professor Jean-Michel Dupont, Paris - France

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

Registration

You can select either

- Basic diploma : only the lectures and a final online examination
- Advanced diploma : same lectures + 2 months training in a cytogenetic laboratory, and onsite final examination in Paris

For registration, please send a letter of application with your CV to the organizers, Prof. Jean-Michel DUPONT (jean-michel.dupont@aphp.fr) or to Prof. Thierry LAVABRE-BERTRAND (thierry.lavabre-bertrand@umontpellier. fr).
The registration fee to be paid by participants was €884 in 2023. For payment by institutions and for more information, please contact the organizers.

Accommodation

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

Scholarships

E.C.A. will award two scholarships covering the registration and accommodation fees. The Education Committee of the E.C.A. will select the suitable candidate.
Scholarship will not be awarded to students whose registration is paid by a third party institution

Topics

Technical Aspects: *Classical Cytogenetics:* Cell culture techniques; Chromosome staining methods (Q-, G-, C-, R- banding and high resolution banding); *Molecular Cytogenetics:* Methods and principles of Fluorescence In Situ Hybridization (FISH) and MFISH; Array CGH; Application of Massively Parallel Sequencing to Cytogenetics; Optical Genome Mapping ; Database use 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 2020; *Clinical:* Phenotype of common autosomal and gonosomal 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 and foetal cells 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 abberations; Origin of aneuploidy; Evolution and plasticity of the human genome; Animal cytogenetics; Plant cytogenetics.

EUROPEAN CYTOGENETICISTS ASSOCIATION (E.C.A.)

European Advanced Postgraduate Course in Classical and Molecular Cytogenetics

Director: Professor Jean-Michel Dupont, Paris – France

The course is scheduled to be held in Nîmes, France 18-24 March 2024.

2024 Course provisional programme

This approximately 55-hour theoretical part of the course attempts to cover the field of cytogenetics in the broadest sense. The topics can be divided into the following categories:

Technical aspects:

Classical Cytogenetics: Cell culture techniques; Chromosome staining methods (Q-, G-, C-, R-banding and high-resolution banding);

Molecular Cytogenetics: Methods and principles of Fluorescence In Situ Hybridization (FISH) and MFISH; Array CGH; Application of Massively Parallel Sequencing to Cytogenetics; Production and use of molecular probes; Database use 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 2020.

Clinical: Phenotype of common autosomal and gonosomal 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 and foetal cells 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:

Genome architecture; Structure of chromatin; Structure of metaphase chromosomes, Mechanisms of chromosome abberations; Origin of aneuploidy; Evolution and plasticity of the human genome; Animal cytogenetics; Plant cytogenetics.

Goldrain Course in Clinical Cytogenetics 2023 Reports

In 2023, two of the Goldrain fellows have sent personal reports on the course:

It is a pleasure for me to write a short report about the 16th Goldrain Course in Clinical Cytogenetics. First of all, I want to thank Professor Schinzel, Professor Rocchi and the E.C.A. Board for awarding me a scholarship. This course gave me the great opportunity to meet such outstanding lecturers and students from different countries promoting my personal and professional growth.

This year the Course was held from 22th to the 28th of August in Goldrain Castle, in South Tyrol, Italy.

There were 39 students from several countries, including Israel, Switzerland, The Netherlands, Hong-Kong, Spain, Italy, Slovenia, Germany, Sweden, Indonesia, Finland, Pakistan, Denmark, Portugal and Hungary.

The faculty members were from prestigious universities, laboratories and clinics in Europe and USA. They gave lectures and workshop focused on classical cytogenetics and molecular cytogenetics in both laboratory and clinical settings. In details, the lectures covered the techniques such as karyotyping, FISH, MLPA, QF-PCR and array CGH as well as massive parallel sequencing. Other lectures focused on the aspects of clinical genetics, such as karyotype-phenotype correlations, chromosome aberrations in spontaneous abortions and stillborns, uniparental disomy, imprinting, microdeletion syndromes and ring chromosomes.

We had the opportunity to discuss about ethical issues concerning pre- and postnatal genetic diagnosis and about accreditation of cytogenetic laboratories. There were some practical exercises about cytogenetic nomenclature and the use of the ISCN system for describing chromosomal aberrations, the segregation of chromosomal translocations, the UCSC Genome Browser to analyse array CGH data.

In addition, many students presented their own diffucult cases.

One afternoon, we went on an excursion in Switzerland and in Malles, a beautiful city in South Tyrol. We visited historical places such as churches with fresco paintings and city buildings.

On the last day we had the opportunity to visit the Goldrain Castle, with magnificent and well preserved rooms. Such atmosphere is great for concentrating on lectures as well as for socializing with people working in the same field.

This course provides a great opportunity for learning and improving one's knowledge and getting updated on the work of other participants in the field of cytogenetics.

To conclude, I would like to express my gratitude to all the lecturers, and in particular to Professor Schinzel and Professor Rocchi for this outstanding Course.

Valentina Ferri, PhD, Medical Genetics Resident
Varese Hospital and Insubria University, Varese, Italy

The 16th Goldrain course in clinical cytogenetics was held in the last week of August 2023 in South Tyrol in Goldrain Castle, a medieval castle located in the Vinschgau valley surrounded by mountains. The directors of the course are Professor Albert Schinzel (Zurich University) and Professor Mariano Rocchi (University of Bari). It is organized by University of Zürich, and the European Cytogeneticist's Association (E.C.A.) with the support of The European Society of Human Genetics. The course is highly respected and well known and attracted 39 participants from all over the world. I am really thankful to the directors for awarding me one of the scholarships to attend this course.

The course covered a wide range of topics including basics of cytogenetics, FISH techniques, SNP array, next generation sequencing, optical genome mapping, MLPA, PCR, prenatal and postnatal testing, dysmorphology, genetic counselling, quality assurance etc. There were a number of workshops on topics such as interpretation and analysis of array results using databases, segregation of chromosomal translocations, exercises on writing laboratory reports and use of ISCN. During the workshops, participants were divided into small groups to have a discussion and practical exercises. Other topics were clinical aspects, ethical issues non-invasive prenatal testing (NIPT), pre-implan-

tation genetic diagnosis (PGD) and CRISPR/Cas9 technology.

The location of the course in South Tyrol is truly special. The region is home to a high density of medieval castles, as well as fruit orchards and vineyards. This unique setting creates a wonderful atmosphere for learning and exploring. This year's midweek excursion took us to Switzerland and on Sunday most of us took the opportunity to visit the beautiful city of Meran. The region is known for its delicious cuisine, which is a fusion of Italian and Austrian influences. I was particularly impressed by the hospitality of all the people and faculty. We enjoyed the evenings of long interesting chit-chat between participants and faculty. These informal interactions allowed participants to get to know each other and their instructors on a more personal level and added to the educational experience.

There were sessions where the participants could present their cases and scientific work and get feedback from the faculty and other participants. The course ended with an exam that covered all the topics. The Goldrain course also provided us with a cozy accommodation and of course a chance to meet so many amazing people.

It was a very comprehensive and informative event and I am glad that I had the opportunity to attend this course designed by world's renowned faculty. I highly recommend this course to anyone who is interested in learning more about clinical cytogenetics. It is a unique opportunity to learn from world class experts in a beautiful and supportive setting. It is a valuable investment in your professional development. I also express my gratitude to Prof. Schinzel, Prof. Rocchi and all the faculty members for their enthusiasm and hard work in organizing this excellent course.

Neelum Mansoor, MBBS, FCPS
Karachi, Pakistan.
Email: neelum.mansoor@tih.org.pk

1- Dennis Sulander 2- Marco Vismara 3- Robby Hertanto 4- Teresa Carrión Mera 5- Joakim Klar 6- Mar Xunclà L. 7- Erik Kjell 8- Salla Rusanen 9- Hilda Polyánka 10- Madan Kamlesh 11- Johanna Lotsari-Salomaa 12- Anahita Hamidi 13- Mariano Rocchi 14- Giorgia Catino 15- Konstantin Miller 16- Albeert Schinzel 17- Neelum Mansoor 18- Griet Van Buggenhout 19- Maria Luce Genovesi 20- Jean-Michel Dupont 21- Valentina Ferri 22- Joanna Lubieniecka 23- Stine Ramsing Brunebjerg 24- Peter Ben 25- Tina Maarslet 26- Alessandra Baumer 27- Krzysztof Lubieniecki 28- Noa Garibian Giveon 29- Sophie Ottema 30- Ina Geurts-Giele 31- Adriana Isabel Iglesias Gonzalez 32- Ho-Ming Luk 33- Candice Au 34- Maritta Löytömäki 35- Bella Weisman 36- Marwa Abo Helal 37- Angelika Humbel 38- Gitte A. Nielsen 39- Fabian Rietmann 40- Marco Graf 41- Sabrina Schreiber 42- Mohammad Alsady 43- Josefin Åhman 44- Cláudia Oliveira 45- Martina Russo 46- Katarina B. Fras 47- Cilla Söderhäll 48- Kati Pulkkinen *49- Rolph Pfundt 50- Josef Wisser 50- Josef Wisser 51- Orsetta Zuffardi 52- Deborah Bartholdi 53- Edoardo Errichiello 54- Eva Kaplocki 55- Tanja Krones (Italics: lecturers not present in the picture).*

Participants of the2023 Goldrain Course

17th Goldrain Course in Clinical Cytogenetics

August 20-27, 2024

DIRECTORS

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

PROGRAMME COMMITTEE

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

FACULTY

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

LOCATION

Goldrain Castle, Goldrain, South Tyrol, Italy

Website of the course: **www.biologia.uniba.it/SEC/**

COURSE DESCRIPTION

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

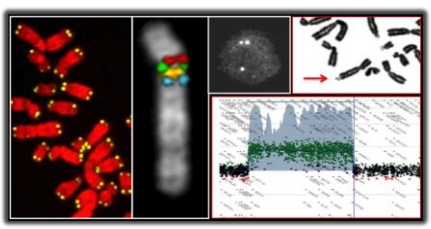
TOPICS

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

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

Scholarships, in the form of reduced fee, will be granted to students who make payments from their personal accounts (not through the institution).

For further questions please write directly to Albert Schinzel at schinzel@medgen.uzh.ch or to Mariano Rocchi at mariano.rocchi@uniba.it



Full fee is Euro 1.400-1600, depending on the accommodation. It includes tuition, course material, free access to internet, accommodation for 8 nights, all meals, coffee breaks and a ½ day excursion.