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E.C.A. on Facebook

As mentioned in the earlier Newsletters, E.C.A. is on Facebook.
Each week 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/Cytogenetic/ 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 5.
Please contact us (mariano.rocchi@uniba.it) if you wish to share an interesting news item or a pertinent article.

Web-based External Quality Assessment (EQA) for genetic diagnostics provided by the German Association of Professionals for Human Genetics (BVDH)

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External quality assessment (EQA) has become an integral part of quality control assurance in diagnostic genetic laboratories. The Association of German Professionals in Human Genetics (BVDH) established an EQA scheme for laboratories in Germany, Austria and Switzerland, as early as in 1993 (1), thus being one of the first European EQA providers in the field.

In 2011 a web-based platform for EQA (EQA-BVDH) was established, which enables a pure online based approach covering all aspects of external quality assessment in prenatal, postnatal, and tumour cytogenetics (2). This includes, besides banding cytogenetics also molecular cytogenetics and molecular karyotyping, as well as the evaluation of next-generation sequencing (NGS) bioinformatics pipelines and genetic counselor's reports to patients in clinical genetics.

The platform is certified by the German Medical Association as the competent regulatory body (RILI-BAEK)(3) and was accredited by the DAkkS (Deutsche Akkreditierungsstelle) as provider of proficiency testing schemes (DIN EN ISO 17043:2010).

Platform description

The EQA-BVDH online platform includes registration of individual laboratories, provision of forms and data for each individual scheme (see below), up- and/or downloading of images and/or reports and, eventually, provision of evaluation results and certificates.

All evaluation criteria of the reports are available online before each scheme is started. Assessors and reviewers examine lab reports and data, e.g. metaphase images. Evaluation by reviewers is also done online, speeding up the assessment and saving costs. Reviewers basically evaluate by "check boxes"; however, they also may add individual comments and suggestions for any individual aspect. All data submitted by the participants are evaluated independently by two reviewers and the scheme's chairpersons. If reviewers diverge in their evaluation, the case can be discussed among all assessors engaged in the scheme (e.g.

within the entire group of the reviewers via a telephone conference).

EQA Schemes provided by the BVDH

- EQA "Laboratory-focused cytogenetics"
  The objective of EQA "Laboratory-focused cytogenetics" (chromosome analyses of lymphocytes from peripheral blood, amniotic fluid or chorionic villi culture) is a retrospective rating of chromosome quality in karyograms, which were generated for routine diagnostic cases.
  Assessment of chromosome quality abides by the compulsory criteria set up in the RILI-BAEK specifications (Tab. 5b). Six karyograms and their corresponding meta-phase images selected from three different months have to be uploaded by the participants and are then examined by the reviewers for quality and correctness.

- EQA "Postnatal constitutional CNV detection"
  The EQA "Postnatal constitutional CNV detection" aims to assess the technical performance of molecular karyotyping (array-comparative genomic hybridization- or NGS-based), analysing the data obtained and interpretation of the results on the basis of the existing literature with regard to the clinical phenotype. The resulting report with the technical data must be uploaded by the participant on the platform. Further-more, a current knowledge of karyotype, data analysis, literature and general handling is required.

- EQA "Structural chromosome aberrations"
  The basic skill being tested in this EQA is the identification of a structurally abnormal G-banded chromosome from routine pre- or postnatal cases. It is not the detection of a tiny deletion in the lower range of microscopic resolution. For morphological evaluation, images of at least three karyograms and 10 metaphase spreads will be provided by the organizers. Participants should also be able to assess such cases according to international guidelines based on the relevant literature with regard to the clinical phenotype. The uploaded reports will be assessed for both quality and correctness.

- EQA "Rapid prenatal aneuploidy testing"
  There are two different approaches to quickly check prenatal samples (e.g. amniotic fluid) for the most relevant trisomies 13, 18 and 21 and for gonosomal aneuploidies of second trimester. Wet-specimens are sent out to participating laboratories and may be analysed either by interphase-FISH (= fluorescence in situ hybridization) or quantitative fluorescence polymerase chain reaction (QF-PCR) technique. In both settings, correct and timely analysis of the sample, reporting and appropriate interpretation of the results are assessed. For a second case provided only virtually in the platform theoretical and formal knowledge is examined (e.g. ISCN nomenclature, correct interpretation of rarer variants).

- EQA "Molecular cytogenetics"
  The quality of laboratories offering the technique of metaphase FISH (fluorescence in situ hybridization) is assessed by the EQA molecular cytogenetics. Either a wet-specimen is provided for analyses by the participants or FISH images of a virtual case are provided. Reports uploaded by the laboratories are assessed for quality and correctness.

- EQA "Tumour cytogenetics"
  The EQA "Tumour cytogenetics" covers the entire process of culturing, metaphase preparation, chromosome staining and banding in haematological neoplasia. A sample is provided by this scheme and a report including interpretation of results needs to be uploaded by the participating laboratory.

- EQA "Tumour FISH"
  The objective of EQA "Tumour FISH" is to evaluate the technical performance of interphase FISH, microscopic evaluation, reporting and interpretation of FISH results in order to simulate a real diagnostic setting. Here a report including interpretation of results has to be uploaded after a fixed cell suspension together with a clinical indication has been provided by the organizers.

- EQA "NGS data analysis"
  The EQA "NGS data analysis" focuses on bioinformatic pipelines of the participating laboratories. Here a report selected from routine diagnostics performed by the participating laboratory has to be uploaded.

- EQA "Genetic Counselling"
  The aim of the quality assessment (QA) scheme is to evaluate the quality of the written record for the patients/counselees and their referring doctors. This EQA started as a preliminary pilot study; participation is only possible in German language.

Our EQA programme offers the entire repertoire of cytogenetic analyses and ensures the competencies of laboratory personnel as an important part of quality assurance. EQA programme should also be seen as guidance for certification and/or accreditation of cytogenetic laboratories.
As the BVDH, certified by the German Medical Association, endorse the proficiency testing topics, national laboratories working in this field should participate annually. However, it is also open to laboratories in other countries if no national programme exists on the website http://www.genetic-eqa.eu/.

Literature:

1. Held KR, Brandt S, Eiben B: 20 Jahre externe Qualitätssicherung in der Zytogenetik. Langzeitauswirkungen auf die Untersuchungsqualität der teilnehmenden Labors aus Deutschland, Österreich und der Schweiz. medgen 20, 353-360, 2008

2. Rieder H, Kunz J, Siebert R, Haferlach C: Quality assurance in leukemia cytogenetics by web-based processing of inter-laboratory tests. E.C.A. Newsletter 34, 29-30, 2014

3. Revision of the "Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations - RiLi-BAEK" (unauthorized translation). J Lab Med, 39: 26-69, 2015

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.

WHY ARE HUMANS SO THIRSTY FOR WATER?

Man is one of the most water-dependent animals. The reason lies in our evolutionary history and can be summarized in a series of steps: development of a large brain greedy for energy, compensation by a reduction in muscle strength, evolution of endurance running as an alternative hunting strategy, loss of hair to achieve effective dissipation of heat by sweating – all leading to an increased need for water. How we acquired efficient sweating was reported in an earlier post, 'Evolution of sweating in humans'.
This well-told story can be found in a Scientific American article: "Human Evolution Led to an Extreme Thirst for Water" (https://www.scientific american.com/article/human-evolution-led-to-an-extreme-thirst-for-water/?utm_ source=Nature+Briefing&utm_campaign=d62593c184-briefing-dy-20210617&utm_medium=email&utm_ term=0_c9dfd39373-d62593c184-44083589).

GENES THAT DETERMINE THE ONSET OF MENOPAUSE

An international consortium found an association of 290 genomic loci and the age of natural menopause. The results are published in Nature, August 4, 2021 (K.S. Ruth et al. 2021).

About 7 million oocytes are present in a 24 weeks-old fetus, of which about 5 million will have been lost at birth. At the beginning of puberty, this non-renewable ovarian reserve is less than half a million and some 1000 oocytes are lost during every menstrual cycle. The cycles stop at an average age of 50-52 but in women with POF (Premature Ovarian Failure) this happens in their-mid-thirties. Oocyte loss is determined by environmental factors such as diet, alcohol, smoking and exposure to radiation, but there are also genetic determinants. A well-known genetic determinant is the *FMR1* pre-mutation.

The genome-wide association study involved ~200,000 women of European descent. A total of 290 statistically significant signals were identified. A high number of genes at or around these loci have a life-long function in DNA damage response (DDR) with functions in relieving replication stress, DNA-protein crosslink repair, and meiotic recombination. Also 58 genes that function in the regulation of apoptosis were found. Experimental manipulation in mice of two genes, *Chek1* and *Chek2*, each extended female reproductive lifespan. Specifically, an extra copy of *Chek1* increased ovarian reserve during life and caused a higher number of ovulated meiosis II oocytes after gonadotropin stimulation. The resulting embryos were normally healthy and fertile.

This study greatly increases the number of genes that affect female fertility, and the authors expect that their findings will instigate further work to develop therapies for preserving female fertility.

LONG-READ SEQUENCING AND MISSING DISEASE-CAUSING VARIATION

Short-read sequencing in cases of suspected genetic disease has proved to be crucial in about half of the cases studied. This approach, however, is not very efficient in detecting pathogenic structural variants such as repeated expansions, insertions, deletions or rearrangements. Long-read sequencing is much more efficient in this respect, but whole genome sequencing is currently too expensive. The authors of an article that appeared in Am J Hum Genet (Miller et al, 2021) found a way to use one of these technologies (Oxford Nanopore Technologies) for appropriate targeted sequencing (up to 151 Mb in this case). The results suggest that this approach can be used efficiently in cases where whole genome sequencing based on short reads has failed to reveal the etiology of the clinical condition.

SPERM MOSAICISM

It is well known that in humans new mutations arise more frequently in the father than in the mother (Goldman et al. Nat Genet 2016). A recent article in Trends in Genetics (Breuss et al., 2021) analyzes the different types of mutations found in spermatozoa (sperm mosaicism) and their mechanism of origin. The authors distinguish three types of mutations:
Type I: those that arise during meiosis (not age dependent)
Type II: those that arise in spermatogonia (age-dependent)
Type III: those that arise during paternal embryogenesis, and therefore contribute stably to sperm throughout life.
These mutations can contribute to disease but are also the main source of genetic variation in the population. Furthermore, their identification also has consequences for clinical practice.

EVOLUTIONARY ADVANTAGES OF SEXUAL REPRODUCTION EXPLAINED IN PLAIN WORDS

Sexual reproduction appeared about 1.2 billion years ago and spread rapidly in eukaryotes because it provided a great advantage in evolution. The paper by Hickey and Golding (BMC Ecol Evo, 21:119, 2021) masterfully illustrates this concept. In summary:
- the number of possible genotype combinations is much greater than the population size, that is, any given population contains only a small fraction of potential genotype combinations.
- Sexual reproduction produces genotypes with combinations that did not exist before, on which the selection for greater fitness operates.

In other words, the authors say, it's a game of chance, a lottery.

BIRTH WEIGHT AND GENETICS

In 2002, the group of Icelander Kari Stefansson published a very large human recombination map using 5,136 microsatellites (Nature Genetics, 2002). To do this, the authors took advantage of the cooperative attitude of the Iceland population. Since then, they have published several articles based on this cooperation. In the latest, which appeared in Nature Genetics 53, 1135–1142, 2021, they performed genome-wide association studies of 142,447 Icelandic trios (baby and parents) looking for genes that affect birth weight and length. The main conclusions are that "the maternal genome contributes to increased birth weight through blood-glucose-raising alleles while blood-pressure-raising alleles reduce birth weight largely through the fetal genome".

DNA DAMAGE AS A UNIFYING CAUSE OF AGING

Aging is a complex process involving a variety of features at the molecular, cellular and physiological level, such as genomic and epigenomic alterations, loss of proteostasis, declining overall cellular and subcellular function and deregulation of signalling systems. The old question is: has ageing a unifying causal mechanism or is it grounded in multiple sources? Schumacher et al. (Nature 592:695-703, 2021) propose that "DNA damage affects most, if not all, aspects of the ageing phenotype, making it a potentially unifying cause of ageing".

TREATABOLOME DATABASES FOR ACCELERATED DISCOVERY, TESTING AND IMPLEMENTATION OF VARIANT-SPECIFIC THERAPIES FOR RARE GENETIC NEURODEVELOPMENTAL DISEASES

Several recent publications draw attention to two databases for the treatment of rare, Mendelian metabolic diseases that cause developmental delay. These initiatives show that a precise genetic diagnosis can result in an equally precise clinical intervention by nutritional, pharmacological or vitamin/trace element supplementation therapies. These are simple and surprisingly effective in the majority of cases, much more so than the much more expensive enzyme replacement therapies.
The first is from the Treatabolome and International Rare Diseases Research Consortium (www.treatable-id.org), see the article by Hoytema van Konijnenburg in the Orphanet Journal of Rare Diseases. The database exists since 2012 and has now been updated. It provides therapeutic information on 116 disorders (with 139 genes involved).
A second is from the International Rare Diseases Research Consortium (Solve-RD, www.solve-rd.eu), founded in 2011. The database and its history are described in several papers in the Journal of Neuromuscular diseases issue of May 13, 2021, see the introductory paper by Bonne. The database covers gene variants causing Parkinson's disease, skeletal muscle ion channelopathies, peripheral neuropathies, metabolic myopathies related to glycogen storage and lipid metabolism, and laminopathies, all with the aim to have 1000 new treatment options of proven effectiveness by 2027.

Using these databases, clinicians have easy access to trustable, up-to-date, evidence-based information for the timely treatment of patients with such rare diseases.

Links:
https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01727-2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8203244/pdf/jnd-8-jnd219003.pdf

Lorenzo's oil:
https://en.wikipedia.org/wiki/Lorenzo%27s_Oil

BASIC RESEARCH AND COVID-19

Nature (Sept. 10, 2021) reports that COVID advances win $3 million Breakthrough prizes. One of the winners is Katalin Karikó, Hungarian, who now works in the United States and Germany.
Injected RNA is broken down very quickly. She discovered a few years ago that replacing the uridine with a similar molecule called pseudouridine bypassed the immune reaction. This discovery has been crucial for RNA vaccines.

In her speech during the awards ceremony, she recalled the skepticism that surrounded her work in the 1990s, which led to numerous rejections of grant proposals and papers (including the 2005 paper for which she is now being recognized), and forced her to suffer a demotion and a salary reduction.

https://www.nature.com/articles/d41586-021-02449-y

See Wikipedia
https://en.wikipedia.org/wiki/Katalin_Karikó

NHS TRIAL OF THE GALLERI BLOOD TEST FOR PRESYMPTOMATIC DETECTION OF CANCER

Cancer is one of the major causes of mortality. On September 13th, the National Health Service in the United Kingdom launched a clinical trial of a novel blood test for the presymptomatic detection of more than 50 types of cancer. The trial will include 140,000 volunteers between 50 and 77 years of age. This so-called Galleri test is based on detection of tumour-specific epigenetic changes by whole-genome bisulphite sequencing of cell-free DNA fragments that leak from tumours into the blood circulation, in combination with machine learning.
A clinical validation of the test was published by Klein et al. in the September 2021 issue of Annals of Oncology. The test had a high specificity and was accurate for predicting the cancer signal of origin for a wide variety of cancer types.
Health implications may be huge because most cancers would be detectable at a very early stage when therapeutic interventions can be less aggressive and have a higher chance of being successful. Initial results are expected in 2023.

https://www.england.nhs.uk/2021/09/nhs-launches-world-first-trial-for-new-cancer-test/
https://www.annalsofoncology.org/article/S0923-7534(21)02046-9/fulltext

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SOCIAL EVOLUTION IN MAMMALS

Tim Clutton-Brock's article in Science is a review of recent studies that have explored the causes and consequences of variation in social organization and breeding systems in mammals. Most readers will probably be scrolling through the article trying to figure out where we stand in this framework. Certainly, there are clues to understanding human sexual dimorphism, pair stability, male aggressiveness, paternal care, etc.

https://www.science.org/doi/10.1126/science.abc9699?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

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PROGRAMMED GENETIC MATERIAL ELIMINATION IN EUKARYOTES

In most organisms, the somatic cells and pre-meiotic germ cells share an identical genome. Nevertheless, some organisms can selectively eliminate parts of their genomes, during specific stages of ontogenesis, in germ cells, during meiosis and in somatic cells. Despite years of research into selective DNA elimination, some important questions still remain unresolved: (i) How are sequences that are destined for elimination recognized in different organisms? (ii) Are mechanisms of genetic material elimination similar among model organisms or are they unique to each species? (iii) Why do only some organisms eliminate their DNA, while the vast majority of them do not? (iv) Could these mechanisms be used for manipulating the genome or the karyotype?
A beautifully illustrated review, which recently appeared in Biological Reviews, looks at the phenomenon in different organisms, ranging from ciliate protozoa to mammals. The authors summarize recent developments in programmed genetic material elimination, which includes chromatin diminution (together with programmed genome rearrangement or DNA rearrangements), B and sex chromosome elimination, paternal genome elimination, parasitically induced genome elimination, and genome elimination in animal and plant hybrids.

https://onlinelibrary.wiley.com/doi/10.1111/brv.12796

HUGO GENE NOMENCLATURE COMMITTEE (HGNC) RECOMMENDATIONS FOR THE DESIGNATION OF GENE FUSIONS

There has never been a generally recommended, standardized way to denote gene fusions. In the early 80s when fusion genes were first found in cancer cells, the fusions were generally described in words but soon two nomenclature systems developed: the use of a hyphen (-) or a forward slash (/) to separate the two genes involved, e.g., *BCR-ABL1* and *BCR/ABL1*. Both types of designation suffer from important shortcomings. The HUGO Gene Nomenclature Committee (HGNC) has now published a document that for the first time proposes a unique and easily recognizable way to symbolize gene fusions (https://www.nature.com/articles/s41375-021-01436-6). HGNC recommends the use of a double colon (::) between approved gene symbols to separate the genes involved in gene fusions, e.g., *BCR*::*ABL1* or *IGH*::*MYC*. The double colon (::) has several important advantages: First, it follows the long-standing recommendation of the internationally accepted ISCN cytogenetic nomenclature in which a single colon (:) is used to indicate a chromosome break and a double colon (::) to denote break and reunion. The :: separator thus nicely reflects the principal mode of origin of most fusion genes. Secondly, it is instantly recognizable and creates a unique

symbol in the existing gene nomenclature, and hence is easily searchable in databases and in the literature.

TARGETED LONG-READ SEQUENCING AND GENETIC DISEASES

Short-read sequencing technology may occasionally fail to resolve suspected genetic diseases. The authors of a paper which appeared in Am J Hum Genet employed targeted (151 Mb) long-read sequencing (T-LRS) in 40 of these cases using the Oxford Nanopore platform. In 8/8 individuals with complex structural rearrangements, T-LRS allowed more precise mutation resolution, leading to changes in clinical management in one case. In ten individuals with suspected Mendelian conditions, T-LRS identified pathogenic or probably pathogenic variants in six, and variants of uncertain significance in two others.

https://www.sciencedirect.com/science/article/abs/pii/S0002929721002305?via%3Dihub

OPTICAL GENOME MAPPING

Optical Genome Mapping (OGM) is a powerful technique capable of resolving almost all genomic aberrations. Two papers, both of which appeared in the Am. J. Hum. Genet., explore this technology in constitutional cases[1] and in hematological malignancies[2]. Their conclusion is that OGM is very efficient and accurate. The only exceptions are rearrangements in which one of the breakpoints is in the (peri) centromeric region; OGM is unable to handle the repetitive nature of centromeres. A further limitation was that the authors, at least under their experimental design, could not detect mosaic aberrations below ~ 10%.

[1] https://www.sciencedirect.com/science/article/abs/pii/S0002929721002172?via%3Dihub
[2] https://www.sciencedirect.com/science/article/abs/pii/S0002929721002238?via%3Dihub

CRIMINAL "DOMESTICATION" OF ELEPHANTS

The domestication of animals and plants is a selection, sometimes made unconsciously, of specific, usually favorable, traits.
Context: (i) Some female elephants, and only females, lack tusks; (ii) Warfare in Africa, especially in Mozambique, has reduced populations of large herbivores in the Gorongosa National Park by >90%; poaching for ivory has exacerbated this trend in elephants.
Female elephants without tusks were obviously not targeted by poachers and consequently had higher fitness than females with tusks. The authors of a paper in Science[1] calculated that tuskless females increased from 18.5% to 50.9% in war years in Monzambique (1977-1992). They also identified two candidate genes involved in the tuskless trait (*AMELX* and *MEP1a*). The absence of tuskless males is explained by assuming X-linked, male-lethal, dominant inheritance of the mutation, which is exactly what is observed for a mutant *AMELX*[2] in humans. This gene is involved in the growth of the maxillary lateral incisors, corresponding to the tusks in elephants.
There are also side effects of this unnatural selection. Male mortality, for example, will affect population recovery in the long term. Furthermore, animals with and without tusks eat different plants, thus causing changes in the entire landscape of the region.
The "unnatural" selection made "unconsciously" (with doubts about this unawareness) by man in populations of wild animals is the subject of another interesting work, which appeared in PNAS[3]. The best example they report is the selection of the size trait in fishing. Selection caused by fisherman's preference for large fish will obviously produce smaller sized fish with early sexual maturity and problematic fishing yields in the long run.

[1] https://www.science.org/doi/10.1126/science.abe7389
[2] By the way: *AMEX* and *AMELY* are specific for X and Y, respectively. Their sequence slightly differs in length and are used in forensic genetics to distinguish female from male DNA.
[3] https://pubmed.ncbi.nlm.nih.gov/19528656/

EPIGENETIC INHERITANCE OF TRAINED IMMUNITY IN MALE MICE

It is known that gametes pass on more than the DNA to the offspring, as environmental effects can cause epigenetic changes in the germline that influence the phenotype of the progeny. Now, an international team of researchers led by Mihai Netea (Center for Infectious Diseases of the Radboud University Medical Center in Nijmegen, the Netherlands) has shown that also effects on the innate immune system are passed on to next generations via the sperm cell. The team also involved researchers from Bonn, Lausanne and Athens (Katzmarski et al. Nature Immunology[1], published Oct. 18th, 2021).

The researchers infected male mice with *Candida albicans* before mating to healthy females. When infected after birth with *Escherichia coli* and *Listeria monocytogenes*, the progeny of these males had a significantly better resistance compared to progeny of uninfected males. This was due to the enhanced expression of the MHC class II complex and of genes involved in inflammation response in the myeloid effector and progenitor cell compartments in the bone marrow. Also, in sperm cells of males that were infected before mating, there were CpG methylation differences at transcription factor genes known to be

important for myeloid cell regulation. How the epigenetic changes in the sperm get to the bone marrow is not understood, however.

[1] https://www.nature.com/articles/s41590-021-01052-7

STRUCTURAL VARIATIONS (SVs) AND GENE EXPRESSION

In 2012 a Science comment[1] on the results of the ENCODE project was paradigmatic. It reads "ENCODE Project Writes Eulogy For Junk DNA ". The project had found that 80% of the human genome has a purpose. The term "junk DNA" was no longer used. Since then, more articles have highlighted the importance of DNA once considered junk, such as the contribution of transposable elements to gene regulation (for example, Diehl et al. 2020[2], in Nature Communications).
An article in press in Genome Research by Scott et al.[3] has analyzed the impact on gene expression of 61,668 Structural Variations in 613 individuals. They found that duplications and deletions were the variant types with the most impact, while the contribution of transposable element insertions was small. They also found that the effect often extends to more than one gene and, occasionally, it can reach genes up to 1 Mb apart.

[1]https://www.science.org/doi/10.1126/science.337.6099.1159?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[2]https://www.nature.com/articles/s41467-020-15520-5
[3]https://genome.cshlp.org/content/early/2021/09/20/gr.275488.121.long

MUTANT CLONES IN NORMAL EPITHELIUM OUTCOMPETE AND ELIMINATE EMERGING TUMOURS

In 2018 the group led by P.H. Jones reported in Science[1] that somatic mutant clones colonize the human esophagus with age. This result was not entirely unexpected. What was unprecedented was the presence of tumor-causing mutations in the *NOTCH1* and *TP53* genes in 12 to 80% and 2 to 37% of cells, respectively. In particular, the prevalence of *NOTCH1* mutations in the normal esophagus was several times higher than in esophageal cancers.
How could one explain these data? Jones himself found the explanation, which appeared recently in Nature[2]. Most epithelial mutant clones are not cancerous and their growth outcompetes and eliminates emerging tumours.

[1]https://www.science.org/doi/10.1126/science.aau3879?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[2]https://www.nature.com/articles/s41586-021-03965-7

PATHOGENICITY PREDICTION OF RARE VARIANTS

Predicting the pathogenic consequences of rare disease variants is a very difficult task. Computational models are of little help at the moment. American guidelines[1] suggest treating them as "weak evidence". Researchers are therefore looking for better computational methods. An article, which appeared in Am J Hum Genet[2], proposes a software, VARITY, which, according to the authors, identifies at least 10% more pathogenic variants at thresholds achieving high (90% precision) stringency. This approach, like the previous ones, is based on the data available for the human population.
A second, almost simultaneous, article published in Nature[3] uses a different and very interesting approach. The authors present a software, EVE, which investigates the consequences of the variant(s) under study in the evolutionary landscape. EVE is trained exclusively on evolutionary sequences (140,000 organisms!), thus avoiding biases present in other computational approaches. According to the authors, EVE outperforms current state-of-the-art computational methods in predicting the pathogenicity of variants.
The paper concludes with thought provoking comments, particularly relevant during the ongoing COP26: “Our analysis is one small but unusually direct demonstration of how the diversity of life on Earth benefits human health.” ... “The progressive disappearance of species is a threat to the diversity on which this work is built”.

[1] https://www.nature.com/articles/gim201530
[2] https://doi.org/10.1016/j.ajhg.2021.08.012
[3] https://www.nature.com/articles/s41586-021-04043-8

AGING AND DNA REPAIR

DNA damage has recently been proposed as a unifying cause of aging (see October 7 post). An article in Science[1] substantially reinforces this theory. The Pacific Ocean is home to several species of rockfish. Some have very long lifespans (up to 150 years), others much shorter (~20 years). The authors have compared their genomes in search of genes involved in providing a long lifespan. They found several longevity-associated genes that influence lifespan through insulin signaling and with pleiotropic effects through size and environmental adaptations. But the most interesting and relevant finding is the identification of repeated signatures of positive selection in DNA repair pathways in long-lived taxa, strengthening the hypothesis that accumulation of DNA damage is the primary and unifying cause of aging.

https://www.science.org/doi/10.1126/science.abg5332

A NEW ERA IN ANTIBIOTICS?

In the last decades, the search for new antibiotics has relied heavily on the chemical modification of natural products (semisynthesis). This method is now showing considerable limitations, especially due to the generalized appearance of resistance.
A paper, in Nature[1], reports the engineering of a new antibiotic, iboxamycin, which is fully synthetic.
Iboxamycin is orally bioavailable, safe and effective in treating both Gram-positive and Gram-negative bacterial infections in mice.
Is a new era of antibiotics on the horizon for humans?

[1] https://www.nature.com/articles/s41586-021-04045-6

PARENT-of-ORIGIN EFFECTS (imprinting)

Imprinted genes can affect the phenotype depending on the parent from whom the alleles are inherited. That is, identical genetic variations can have different phenotypic effects as a consequence of their parent-of-origin (PofO). Prader-Willi syndrome is probably the best known example in humans. In the clinic, the identification of the phenomenon requires knowledge of the patient's genealogy. The authors of a paper in BioRxiv used a new probabilistic approach to deduce the PofO of individual alleles, in the British biobank, that does not require parental genomes or prior knowledge of genealogy. They examined 59 biomarkers and 38 anthropomorphic phenotypes for PofO effects and found 101 significant associations that contribute to the genetics of complex traits. This study (and similar studies underway with other biobanks) substantially expands the catalogue of imprinting genes in the human population.

https://www.biorxiv.org/content/10.1101/2021.11.03.467079v1

MOSAICISM IN PREIMPLANTATION EMBRYOS

Dwindling fertility is one of the major health concerns of our (Western) societies. Not surprisingly, approaches to increase fertility rates are long sought for. With the development of techniques to map aneuploidies in single blastomeres and blastocysts of human preimplantation embryos came the discovery of high numbers of chromosomal mosaic aneuploidy. It was hypothesized that the selection against aneuploid embryos could increase the in vitro fertilization (IVF) success rate. Hence, preimplantation genetic testing for aneuploidy (PGT-A) was swiftly evaluated and implemented in IVF centres.

The high rate of mosaicism in blastocyst biopsies puzzled the IVF field. Most IVF centres offering PGT-A do not transfer mosaic embryos. While different lines of evidence suggested that some mosaic embryos could develop into healthy fetuses and babies, convincing evidence was lacking. In a study led by Capalbo et al. (in press in Am J Hum Genet[1]), this evidence is convincingly provided. By dissecting blastocysts and analyzing five different samples of each embryo, the authors provide a glimpse of the incidence of mosaicism in embryos and also demonstrate that for low grade mosaicism the aneuploidies are often confined to a single biopsy. When mosaicism impacts fewer than 50% of cells in one Trophectoderm (TE) biopsy (low-medium mosaicism), only 1% of aneuploidies affect other portions of the embryo. More importantly, the study presents the results of a double blinded prospective randomized trial demonstrating that the transfer of low and medium grade mosaic embryos does not affect the IVF outcomes at all. The pregnancy rate, miscarriage rate and baby-take-home rates are equal to those for euploid embryos. This study is a landmark paper for the IVF field as it demonstrates that the main-stream practice in IVF centres performing PGT-A destroys embryos and has the potential to reduce rather than enhance pregnancy rates.

Interestingly, another landmark study suggests that PGT-A does not improve cumulative baby-take-home rate. Whereas embryo selection with PGT-A has been shown to improve pregnancy outcome per embryo transferred, it has remained uncertain whether PGT-A improves the cumulative live-birth rate as compared with conventional in vitro fertilization. Yan et al. (New England Journal of Medicine2 (N Engl J Med[2]) addressed this question by performing a multicenter, randomized, controlled trial which randomly assigned subfertile women to undergo either PGT-A or conventional IVF. Interestingly, the cumulative live-birth rate after up to three embryo-transfers within 1 year following randomization did not show any significant difference. This study undermines the clinical rationale for PGT-A.

One gets a feeling of déja vu: The hypothesis that selection against aneuploid embryos could increase the IVF success rate was first launched at the beginning of this century and led to a first wave of FISH based PGT-A screening of cleavage stage embryos. However, several randomized trials showed no benefit. This was probably because the chromosome constitution of a single blastomere is, as was later shown, not representative for the rest of the embryo, due to the chromosomal instability at the cleavage stage. Since the degree of chromosomal instability is much lower at the blastocyst stage, aneuploidy screening of blastocyst biopsies was shown to be more reliable. Randomized control trials did show an increased IVF success rate per embryo transferred. But now, the question remains whether this also benefits the (subfertile) women. Clearly, both studies, which will require follow-up studies, raise new questions. Is too strong a selection against

mosaic embryos resulting in a reduced baby-take-home rate and does it jeopardize overall fertility rates? Would transferring low grade mosaic embryos result in an improved baby-take-home rate? Can we develop better approaches to select viable embryos? Hopefully we can provide the answers… and increase the IVF success rates. That is what society expects.

[1] https://linkinghub.elsevier.com/retrieve/pii/S0002-9297(21)00412-2

[2] https://www.nejm.org/doi/full/10.1056/NEJMoa2103613

MOBILE ELEMENTS AND THE HUMAN GENOME

In recent years, data on human genome variability for SNPs and copy number variations have accumulated. Data on variations due to Mobile Elements Insertion (MEI) lagged slightly behind. An article in press in Genome Research[1] reports improved software to unveil MEIs (CloudMELT). The authors used this new tool to study 57,919 human genomes. They found 104,350 insertions and analyzed their mutagenic impact, such as disruption of genes, but also the potential consequences on gene expression. They also identified the active L1 elements that drive MEI mutagenesis.
Some insertions are very rare and probably arose relatively recently.

[1] https://genome.cshlp.org/content/31/12/2225.long

MAMMALIAN X-INACTIVATION: SURPRISE FINDINGS IN MACAQUE

Our knowledge of the phenomenon of the X-chromosome inactivation (XCI) in mammals comes mainly from mice. Okamoto et al. (Science[1]) report a detailed investigation of the phenomenon in a non-human primate, the cynomolgus monkey (*Macaca fascicularis*). The study comes with surprises. The most relevant are:
- In females, *XIST* expresses in both Xs, but the inactivation starts around day 9. Then, XIST accumulation continues only on the inactive X. That is, XIST accumulation and X-inactivation are transiently uncoupled.
- The XIST coating initially occurs also in males.
- The timing of the XCI reversion in female germline and X chromosome upregulation in males have been determined in detail.
- In females, X-chromosome dampening may begin earlier than both XCI and active-X up-regulation.

The study, in summary, further uncovers the remarkable differences in the biology of the X chromosome between mammalian species and highlights the critical divergences between macaques and mice. It can be assumed that the biology of the X chromosome in humans resembles that of the macaques much more than that of mice.

[1] https://www.science.org/doi/10.1126/science.abd8887?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

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COMMITTEE

ECC SCIENTIFIC PROGRAMME COMMITTEE

E.C.A. News

- The 2021 General Assembly of the E.C.A. with Board elections took take place in Milan on 1 September 2021.
- Renewal of the Board in 2021. The following members were re-elected in 2021: J-M. Dupont (France), J. Garcia-Sagredo (Spain), M. Rocchi (Italy), E. Syk Lundberg (Sweden), and R. Vanni (Italy).

E.C.A. Fellowships

- The **E.C.A.** offers two **Fellowships** for the following course:

  Goldrain Course in Clinical Cytogenetics
  to be held in Goldrain Castle (South Tyrol, Italy) 20-28 August 2022.
- The fellowships **include the course fees and the accommodation** during the lectures in Goldrain but **do not include travel expenses**.
- Applications with CV, list of publications and a letter of recommendation should be addressed to the course organizer (see page 25).

MINUTES OF THE E.C.A. GENERAL ASSEMBLY, MILAN, SEPTEMBER 2021

Minutes of the E.C.A. General Assembly held on Wednesday 1st September 2021 in the Grand Rosa Hotel, Milan, Italy.

Seven members of the Association were present.

The President Mariano Rocchi opened the Assembly at 10.30 and welcomed those attending. The voting for board members was closed and a group, not including any candidates, was appointed to count the ballots.

The Minutes of the General Assembly held 8 July 2019 in the Congress Center in Salzburg, Austria, and published in the Newsletter NL45 page 34 were approved.

The President and the General Secretary reported on the scientifically and technically very successful 2021 European Cytogenomics Conference, which was held online for the first time due to the Covid-19 pandemic.

The General Secretary overviewed the membership of the E.C.A., with 43 new members joining since the last General Assembly. Currently, there are 945 members, 117 technologists, 111 associated members and 20 honorary members.

The President announced the results of the ballot for election of Board Members. A total of 54 votes (including those received by mail) were received; 54 voted 'yes' and the list comprising J-M. Dupont (France), J. Garcia-Sagredo (Spain), M. Rocchi (Italy), E. Syk Lundberg (Sweden), and R. Vanni (Italy) was duly elected.

In view of the submitted abstracts at the conference, changes in the designation of some Permanent Working Groups were discussed. A task force of several members will be asked to work on proposals.

The Treasurer reviewed the finances of the E.C.A. for 2019 and 2020. The reserves of the Association were sufficient to ensure the stability of the Association and in line with the financial policy. The General Assembly approved the accounts.

There being no other business, the President closed the General Assembly at 11.25.

MINUTES OF THE E.C.A. BOARD MEETING, MILAN, SEPTEMBER 2021

Minutes of the E.C.A. Board meeting held on Wednesday 1st September 2021 in the Grand Rosa Hotel, Milan, Italy.

The Board Members present were: Jean-Michel Dupont (Treasurer), José M. Garcia-Sagredo, Konstantin Miller (General Secretary), Mariano Rocchi (President), and Roberta Vanni.

Apologies were received from Sevilhan Artan, Juan Blanco, Pat Heslop Harrison (delegation to J. Garcia-Sagredo), Ron Hochstenbach, Thierry Lavabre-Bertrand, Kamlesh Madan (delegation to K. Miller), Felix Mitelman (delegation to M. Rocchi), Rosário Pinto Leite, Harald Rieder (delegation to JM. Dupont), Elisabeth Syk Lundberg (delegation to R. Vanni).

The President Mariano Rocchi opened the meeting at 12:10 and welcomed those attending.

The Minutes of the Board meeting held 8 July 2019 in the Congress Center in Salzburg, Austria, and published in the Newsletter NL45 page 34 were approved.

The Secretary General reported on membership. The list of new members was approved.

The Board was informed about the result of the 2021 13th European Cytogenomic Online Conference which was satisfactory in every respect.

Possible venues for future conferences were discussed.

The Board discussed a change in the domiciliation of the E.C.A. in France due to the increased cost at the present address. The President asked the General Secretary and the Treasurer to evaluate a possible change. The decision will be taken at the next Board meeting in 2022.

It was decided that the 2022 Goldrain Course will receive two E-C.A. fellowships with full costs.

The Nimes course 2022 will again be organised online; the E-C.A. will grant two fellowships.

The General Secretary, who has now served for 21 years, announced his intention not to stand for re-election as a committee member at the committee election next year.

The next General Assembly and Board meeting are planned in Vienna on 11 June 2022 in connection with the conference of the ESHG.

The President closed the Board meeting at 13.30.

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

PWG: PRENATAL DIAGNOSIS.

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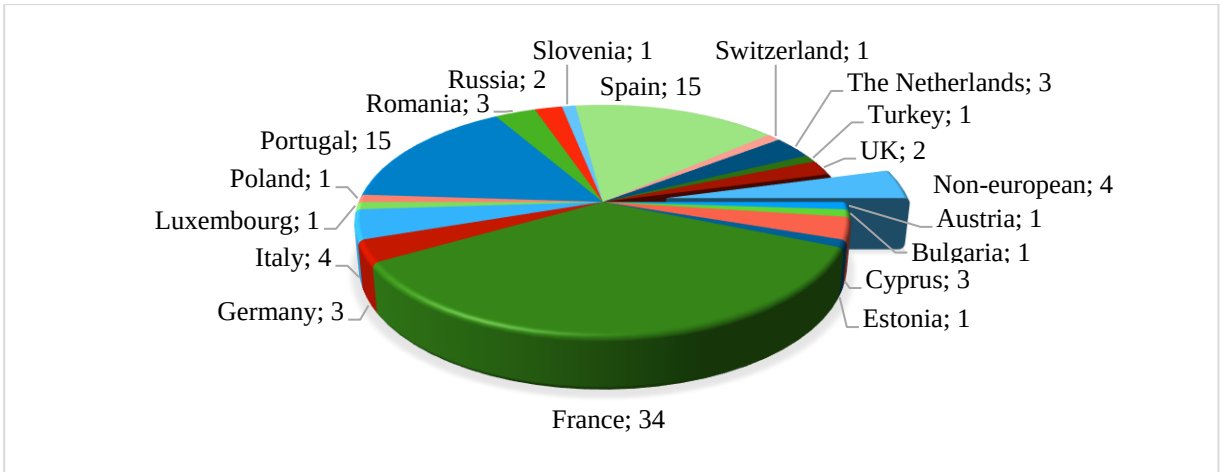
A meeting of the PWG on Prenatal Diagnosis was held during the 13th European Cytogenomics Conference in July 2021. There were two presentations, one on segregation errors generated during the process of parental genome fusion, and the other on the results of the extended NIPT in clinical use in a French laboratory.

Tommaso CAVAZZA from Max Planck Institute in Göttingen (GERMANY) presented the results of his research on the process of fertilization. The two parental genomes are clustered in each pronucleus and are polarized towards each other. This specific organization is thought to help capture kinetochores by microtubules during the following mitosis, by reducing the cell volume in which chromosomes are spread.
The clustering and the polarization occur during the migration of pronuclei, a process driven by dynein and nuclear pore complexes (NPCs). The clustering is the result of the interaction between the NPCs and the chromosome arms. In this way the maternal and the paternal chromosomes are in close proximity ensuring rapid unification of the parental genomes when the nuclear envelope breaks down.
Embryos with incomplete clustering of the parental genomes show an increased rate of segregation errors, leading to mitotic aneuploidies. Visualization of clusters could thus constitute a biological marker to help in selecting embryos based on morphological criteria.
(Cavazza, T. et al. Parental genome unification is highly error-prone in mammalian embryos. Cell 184, 2860-2877.e22 (2021)).

In the second talk, Laurence LOHMANN from CERBA Laboratory in Pontoise (FRANCE) presented the results of using extended NIPT in a clinical setting. More than 1500 samples have been analyzed since the test was first offered to patients in early 2020, after obtaining their specific consent. Only 7 Rare Autosomal Trisomies were reported, according to the recommendations of the French National Cytogeneticists society, as well as segmental unbalanced rearrangements over 7 Mb.
With these criteria, authors report a rate of 0.7% abnormal results, compared to 0.97% positive results for common trisomies (13, 18 and 21) in a medium risk population (main indication is a Trisomy risk ≥1/1000 after maternal serum screening). The positive predictive value of the test is reported to be around 40%, which confirms the usefulness of the extended NIPT for the follow-up of pregnancies.

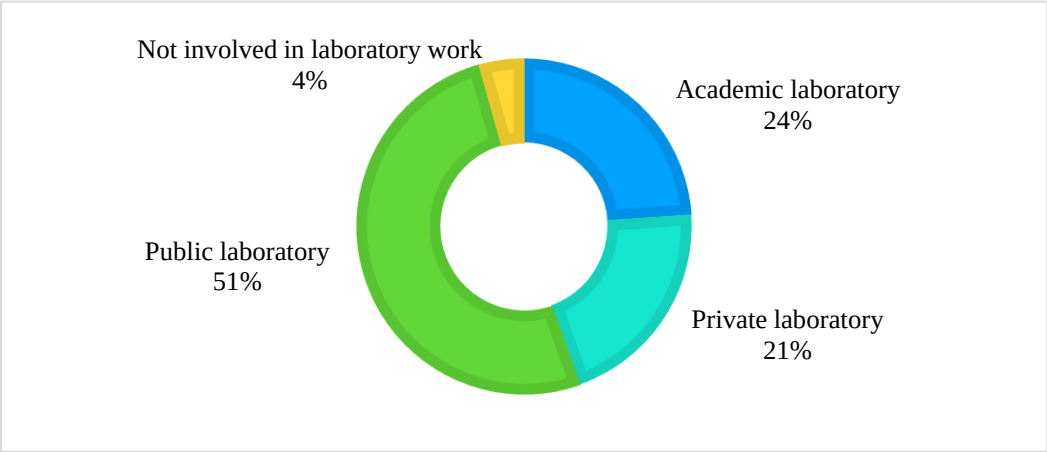
During the session, a survey was launched on how clinical laboratories use chromosome microarray (CMA) in a prenatal setting. A 20-item questionnaire was made available online https://app.wooclap.com/KSRZRE) and was answered by 102 colleagues, from 96 different laboratories from 18 European and 4 non-European (Bahrain, Iran, South Africa and USA) countries.

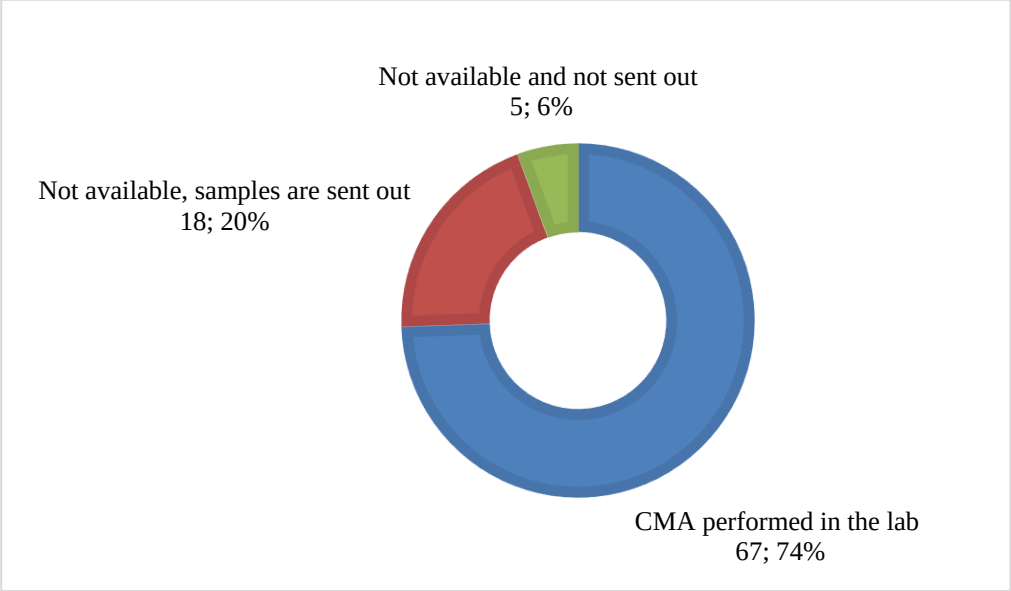
Participants to the survey



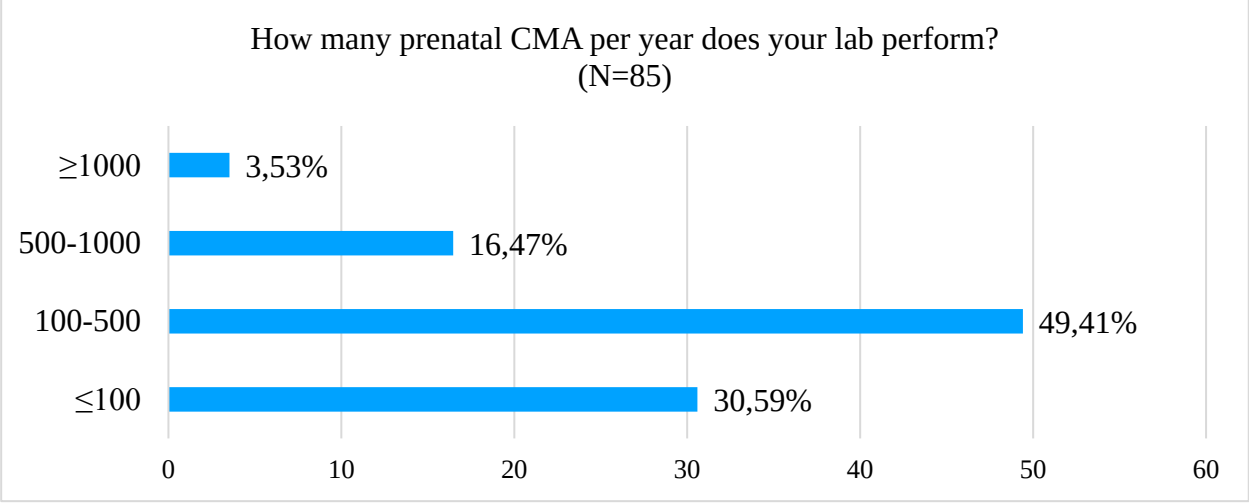
2/3 of the respondents were from public laboratories, academic and non-academic.

Most of the participating laboratories claim to use CMA in a prenatal setting (74%), almost 20% send the samples to another laboratory whereas in 6%, the test is not available for prenatal diagnosis.





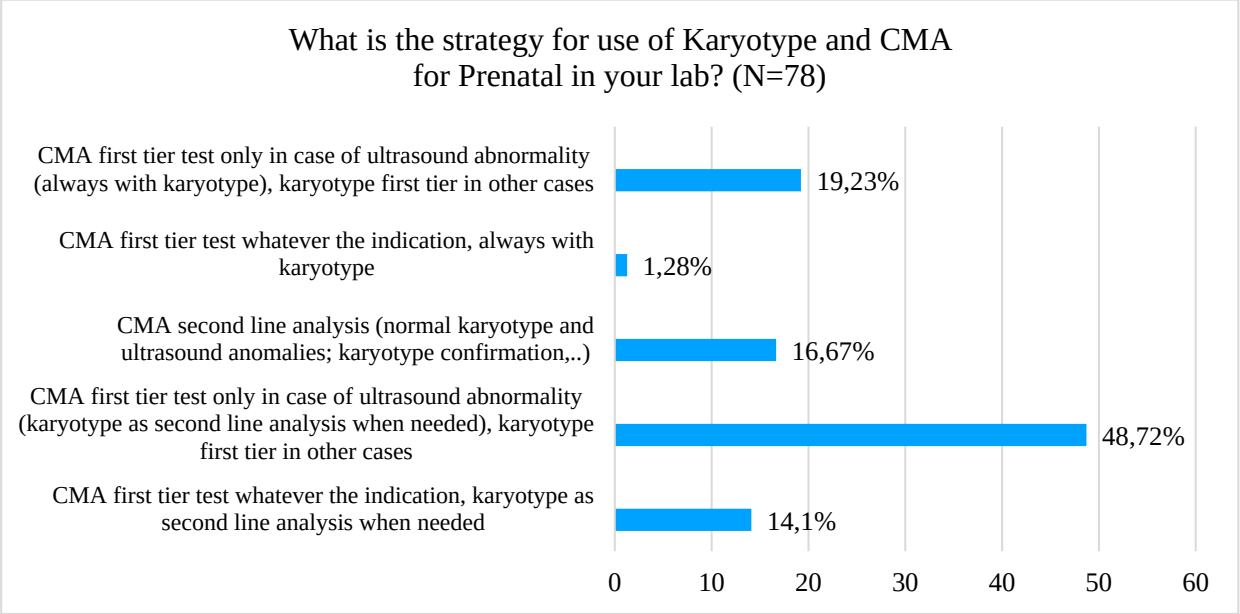
Whereas most laboratories have a small to medium workflow, 17 labs have a workflow of over 500 samples/year.

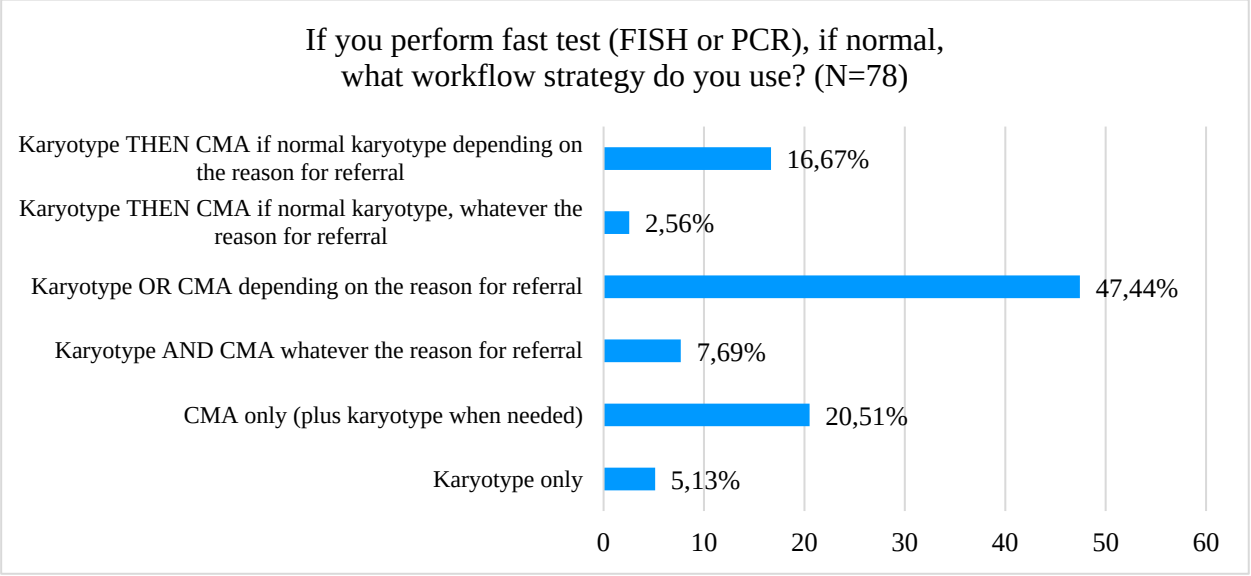


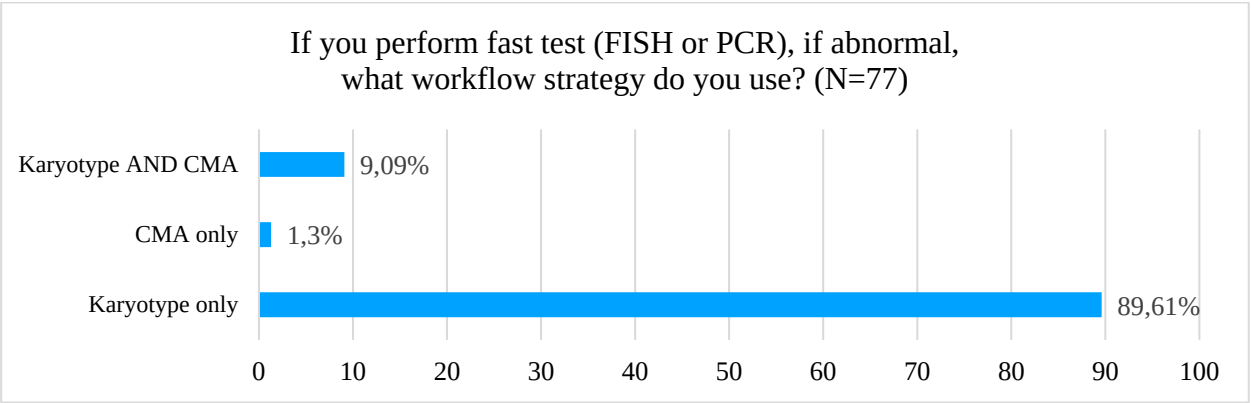
Strategy for using CMA

The second part of the questionnaire addressed the strategies used by ~~the~~ laboratories for prenatal CMA.

CMA as first tier test: at least in case of abnormal ultrasound, CMA is now the first-tier test for most of the participating laboratories. Only 1 – 2 % of the labs use CMA as first-tier test, regardless of the reason for referral, while for 16% of participants, CMA is always performed after karyotyping.

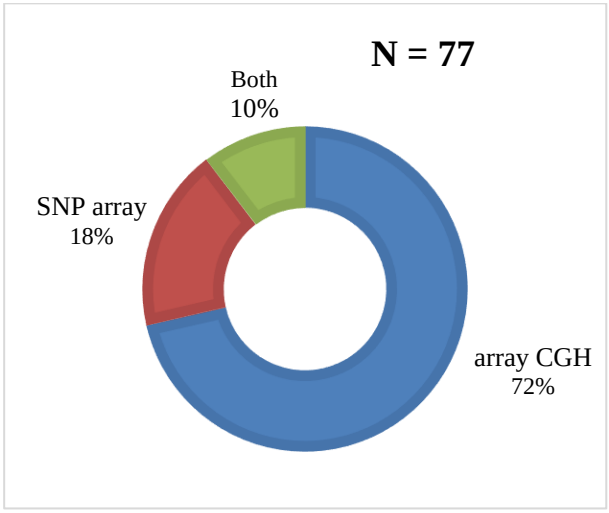


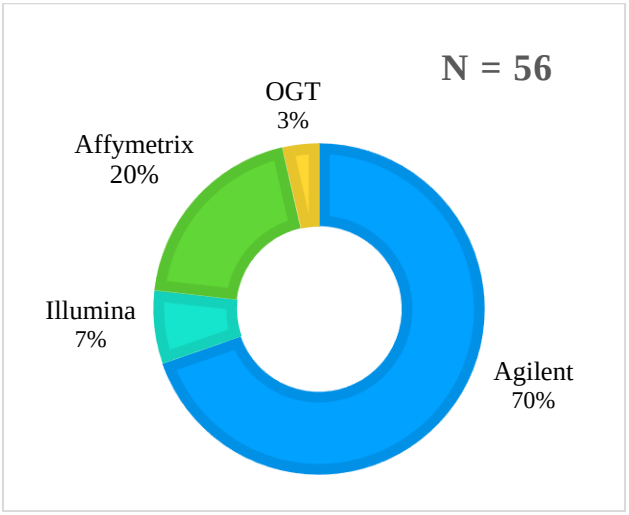




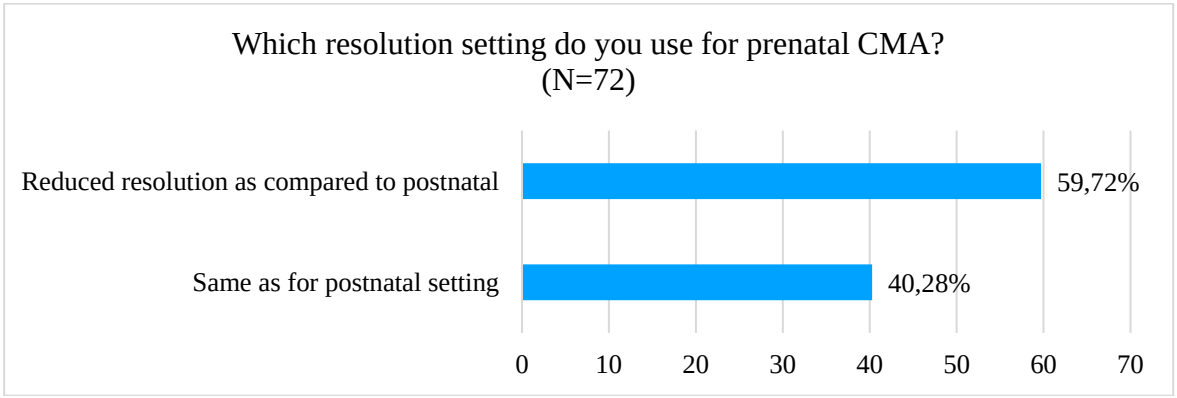
Experiment designs

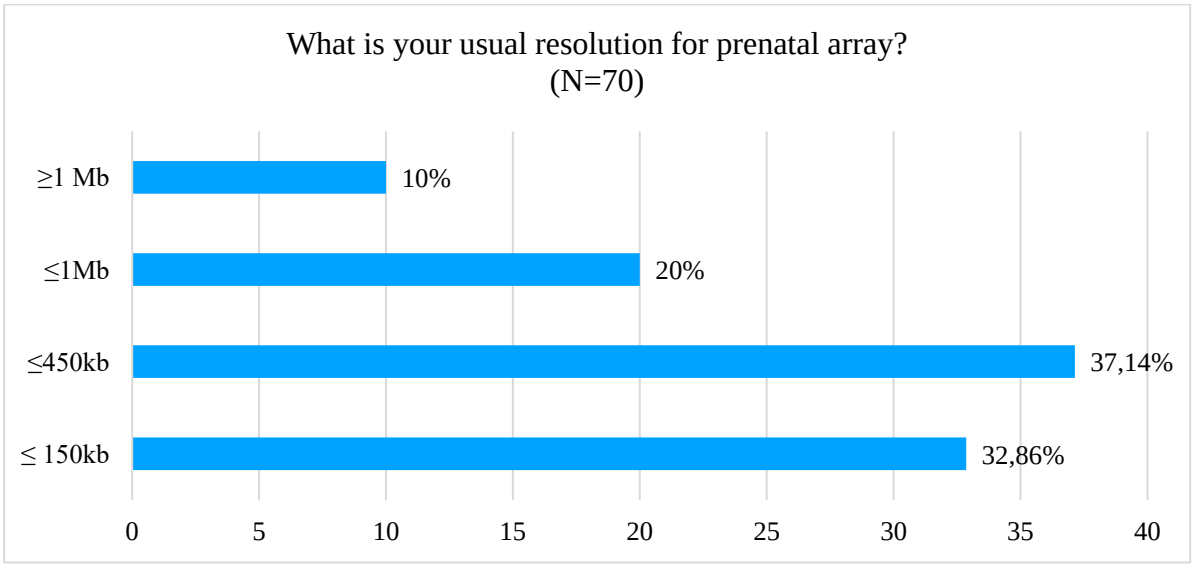
From a technical point of view, array CGH is the most commonly used technique for CMA, with Agilent as the major provider. It should be noted, however, that these figures are merely indicative and may be quite far from the real commercial landscape since the survey is not extensive.



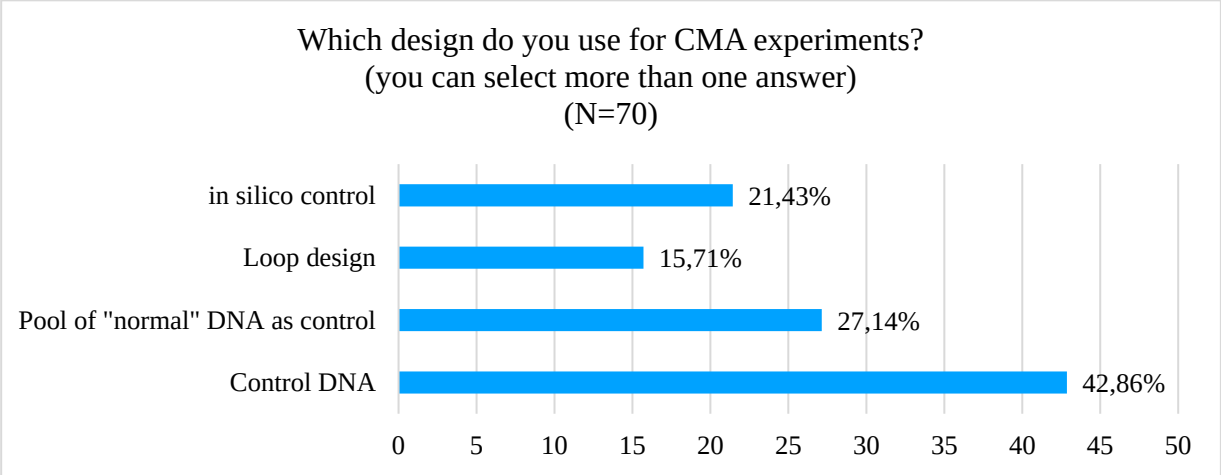


60% of the participants use a reduced resolution compared to postnatal setting but nevertheless more than two third use a resolution under 450kb (which is almost the lowest resolution recommended by the ACMG for postnatal setting). Only 30% of respondents claim a resolution greater than or equal to 1 Mb.



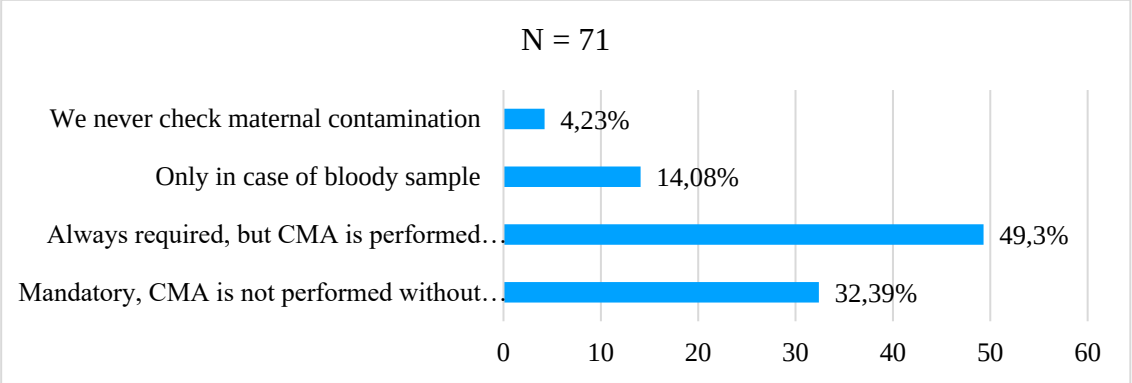


Various experiment designs are used, the single control DNA being the most widely used for CGH array.

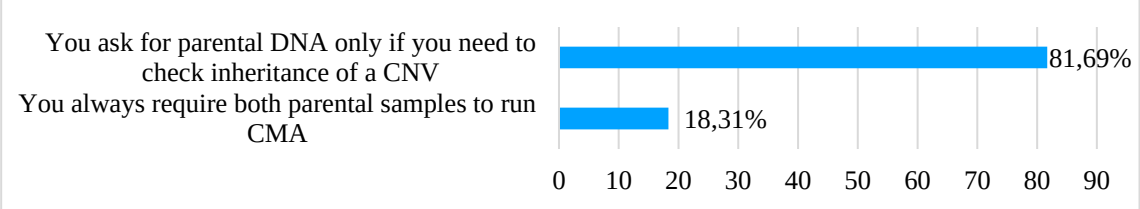


N.B. some labs are already switching from CMA to Exome sequencing for CNV detection in prenatal in cases where Exome is performed because of abnormal ultrasound.

To be able to check for maternal contamination, most laboratories require parents DNA in order to run CMA in prenatal setting. However, only one third will not perform the test without these DNAs.

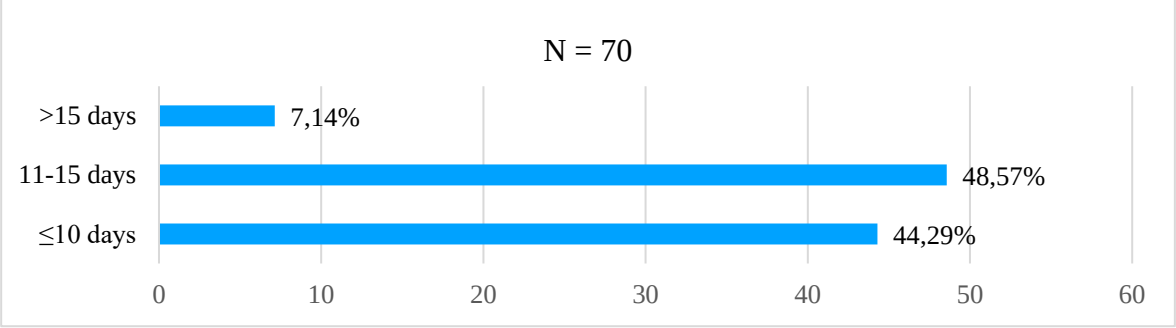


Those parental DNAs are also used to control inheritance of detected CNVs to help classification of the variants.

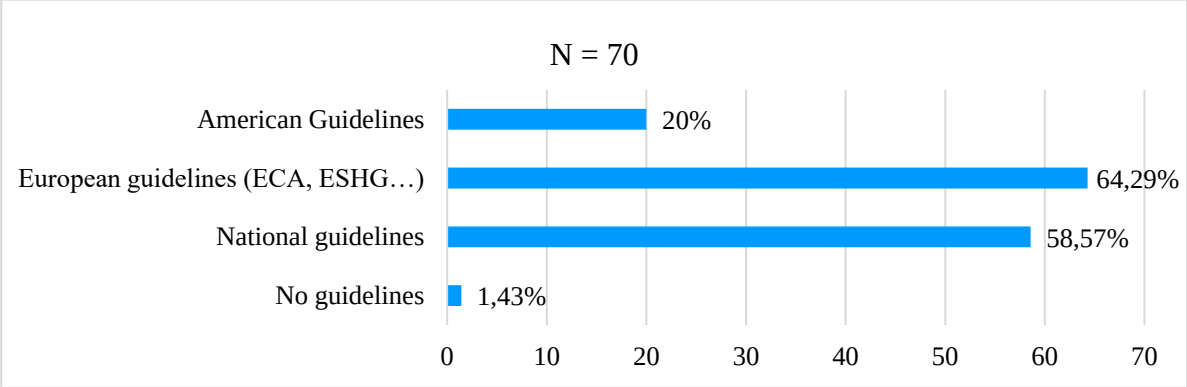


Reports and Quality control

More than 90% of the labs issue a report in less than 15 days for CMA, with more than 40% claiming an impressive average reporting time of less than 10 days.

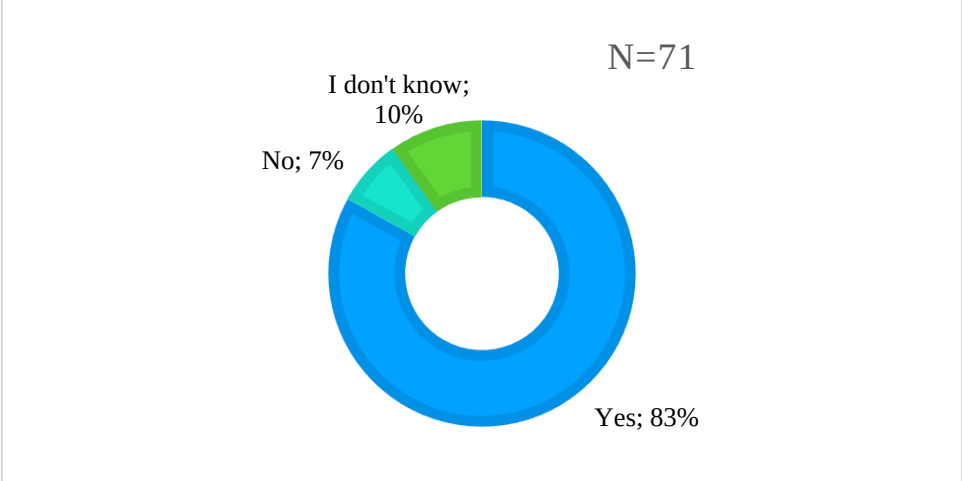


Interpretation and reports follow international Guidelines, or National rules when they do exist.

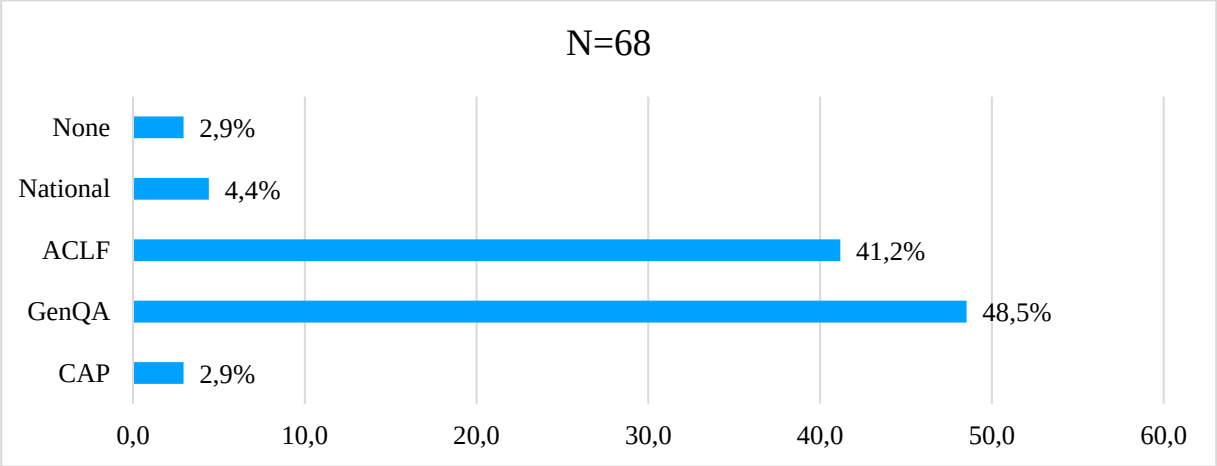


All participants include a sentence warning on the limitation of the technique in the final report.

At least 80% of the labs in the panel participate in an External Quality Control scheme for CMA; however, this could be a minimal figure since it does not include information from colleagues who send CMA to a referral laboratory.



Among the participant of the survey, the two most popular Quality Control schemes are GenQA and ACLF, with 7% of the labs registered to two different schemes for CMA.



Conclusion

This survey was relevant in order to assess how laboratories spread amongst several European and some non-European countries have been dealing with CMA. The high rate of participations by colleagues, which is much appreciated by the authors, allowed the authors to draw the main conclusions given above, which consistently show that CMA is being widely used in Prenatal setting and in a very successful manner.

The PWG co-ordinators present a report on the Sesson on Prenatal and Preimplantation diagnosis at the European Cytogenomics Conference 2021

The first session of the conference was devoted to the major advances brought by NGS technologies to prenatal and preimplantation diagnosis. Three invited speakers dealt with different aspects of the topic.

Lyn CHITTY, from the Institute of Child Health, University College London, presented the prenatal diagnosis of monogenic diseases, either after noninvasive or invasive sampling.
She emphasized that in contrast to NIPT for aneuploidies, NIPT for monogenic diseases was indeed a diagnostic tool mainly because of the absence of concerns about confined placental mosaicism. She presented the various methodologies for dominant diseases (bespoke diagnosis methods and NGS based panels) and then for recessives diseases which need to be able to detect either absence of the paternal pathogenic allele or a variation in the ratio of normal to pathogenic alleles when it is shared by the mother. Rather than focusing only on the pathogenic allele, another strategy could be to use haplotype analysis, which has the advantage that it avoids developing a new test for every family.
The second part of the talk was devoted to fetal exome sequencing after invasive sampling. This whole genome analysis allows for a dramatic increase in diagnostic yield but at the expense of increased incidental findings. The Institute of Child Health worked out a prenatal panel of 1200 clinically significant genes that simplifies the interpretation of the results and reduces the rate of incidental findings. They now offer an optimized workflow for exome sequencing, with a mean turnaround time for results of only 13 days.

The second talk was by Erik SISTERMANS, from the Amsterdam University Medical Center, who presented the results of The Netherlands policy for NIPT for aneuploidies. Since 2017, NIPT is offered as a first tier screening test to all pregnant women, with an uptake of around 50%, roughly identical to previous serum marker screening.
Dr. Sistermans presented the results of the Trident2 study, based on the follow-up of more than 150.000 pregnancies that were screened (van der Meij, K. R. M. et al. TRIDENT-2: National Implementation of Genome-wide Non-invasive Prenatal Testing as a First-Tier Screening Test in the Netherlands. Am J Hum Genet 105, 1091-1101 (2019).
He more specifically addressed the question of twin pregnancies, for which the results are almost as good as for singletons, and the matter of incidental findings (rare autosomal trisomies, segmental anomalies and complex profiles suggestive of a cancer process in the mother). Rare autosomal trisomies are of importance for pregnancy follow-up because they are associated with adverse outcomes even if the aneuploid lineage is confined to the placenta and the fetus is not affected.
The last part of the talk was devoted to extra findings that could be obtained from the sequencing data, with ongoing work on the deciphering of viral sequences from DNA viral infections (mainly herpes viruses, among which CMV infections). First results were presented but the research is ongoing.

The last invited lecture was by Carmen RUBIO, from Igenomix and University of Valencia in Spain, who addressed the question of aneuploidy testing in preimplantation embryos.
Aneuploidy is associated with high rates of implantation failure and miscarriages, which reduces the pregnancy rate. Preimplantation aneuploidy testing from trophectoderm biopsies has been available for many years and has been validated by numerous randomized studies. The main concern nowadays is the attitude towards mosaic embryos and the development of non-invasive preimplantation genetic testing (niPGT) based on analysis of spent culture medium. Mosaics embryos have been shown to have a lower implantation rate than euploid embryos, mainly for those with a high level of mosaicism (>50%), but with an overall good prognosis for ongoing pregnancies. Further studies are ongoing to strengthen the recommendation regarding the selection criteria for these mosaic embryos.
The other hot topic in the field is the use of cell free DNA available in the culture medium in which the embryo is grown, allowing for niPGT. From the available studies, an overall rate of 85% of concordance with trophectoderm biopsy is obtained but larger studies are needed to assess clinical utility of the test.

Three abstracts were selected for presentation
Stanislav Vasilyev (Tomsk, RUSSIA): Aneuploidy is associated with increased methylation of different LINE 1 retrotransposon families in placenta of first trimester miscarriages

Kris Van Den Bogaert (Leuven, Belgium): Outcome of publicly funded nationwide first tier noninvasive prenatal screening

Radhia M'Kacher (Evry, France): Direct inheritance of telomere shortening and aberrations detected during prenatal period

PWG: MARKER CHROMOSOMES.

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The activities of this PWG concerning meetings or conferences have been reduced due to the corona pandemic. Nevertheless new achievements have been published; these are summarized and are freely available on http://cs-tl.de/DB/CA/sSMC/0-Start.html. Here are some recent papers which could be of interest for those dealing with small supernumerary marker chromosomes (sSMCs) in diagnostics.

- Several papers have pointed out that (molecular) cytogenetics is the best for characterizing sSMCs; chromosomal microarray alone misses 30-90% of the sSMCs and/or is unable to determine their chromosomal origin (Reddy et al., Genet Med 2013, 15:3-13; Liehr et al., Sex Dev 2018, 12:281-287; Huang et al., Taiwan J Obstet Gynecol 2019, 58:139-144; Sun et al., Medicine (Baltimore) 2020, 99:e22532.)
- Next-generation phenotyping is now available not only for Pallister-Killian-syndrome and Emanuel-syndrome, but also for cat-eye syndrome (Liehr et al. Mol Genet Genomic Med 2021, 9:e1785).
- A comprehensive study on sSMCs derived from chromosomes 14 or 22 using the probe D22Z4 located in 22p11.2 was able to show that ~40% of the sSMCs were derived from #14 and the remainder from #22 (Liehr et al., Mol Cytogenet 2021, 14:13).

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

PWG: CYTOGENOMIC TOXICOLOGY AND MUTAGENESIS.

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We welcome Palma Finelli as a new co-ordinator of this PWG. A new titele has been proposed for the PWG:
INTEGRITY, STABILITY AND DYNAMICS OF CHROMOSOMES. The Board of the ECA will discuss this proposal at the next meeting.

PWG: ANIMAL, PLANT, AND COMPARATIVE CYTOGENOMICS.

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PWG: CYTOGENOMICS OF HAEMATOLOGICAL MALIGNANCIES.

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PWG: CANCER CYTOGENOMICS, SOLID TUMOR STUDIES.

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PWG: CYTOGENOMICS AND SOCIETY

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The activities were limited to a workshop session at the 13th European Cytogenomics Conference, which was a virtual event at 3, 4 and 5 July 2021. The session was organized by Ron Hochstenbach (Amsterdam) and Martine Doco-Fenzy (Reims). There were two presentations. Rosalind Hastings (GenQA, Oxford) gave an overview about the major changes in cytogenomic nomenclature in ISCN 2020. Thomas Liehr (Jena) described an international collaboration for human ring chromosomes (ICHRC), with the aim to develop standards and guidelines for best practice in laboratory diagnosis, clinical management and collaborative research.

PWG: CYTOGENOMICS.

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PWG: CLINICAL AND MOLECULAR APPROACHES TO CYTOGENETIC SYNDROMES.

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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 as an online version 14-26 March 2022.

2022 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.

15th Goldrain Course in
Clinical Cytogenetics
August 20 to 28, 2022

LOCATION

Goldrain Castle, Goldrain, South Tyrol, Italy
Website of the venue: **www.schloss-goldrain.it**

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 – 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.
- The students will have the opportunity to perform a test at the end of the course.

DIRECTOR

A. Schinzel (Zurich, Switzerland)

FACULTY

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For further questions please write directly to Albert Schinzel at **schinzel@medgen.uzh.ch**

Full fee is Euro 1600 for a single room or Euro 1450 (VAT included) in a 2-bed-room. It includes tuition, course material, free access to internet during the course, accommodation for 7 nights, all meals, beverages during the breaks and a ½ day excursion.