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Please contact us (mariano.rocchi@uniba.it) if you wish to share an interesting news item or a pertinent article.

Sex-bias in COVID-19 disease: when one more X chromosome makes the difference

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Abstract

Epidemiologic data indicate that males are more likely than females to be target of COVID-19 infection and to manifest a more severe disease evolution. This commentary explains why X-linked genes are likely to be implicated in modulating COVID-19 disease progression conferring females an advantage over males. It focuses on the functional mosaicism of females heterozygous for X-linked variants resulting from the random inactivation of one X chromosome in early embryogenesis. It goes on to describe how many X-linked genes escape from silencing, resulting in higher expression levels in females. Given that the X chromosome is highly enriched in immune-related genes, the great phenotypic diversity provided by their heterozygous condition may disproportionally benefit females in the immune response to COVID-19 infection.

Keywords

COVID-19; Male Bias; Chromosome X; immune-related genes; X chromosome inactivation; escaping genes; phenotypic diversity; female advantage

One peculiarity of COVID-19 disease is its wide spectrum of clinical severity, which can range from asymptomatic to mildly symptomatic, to severe, to requiring hospitalization, and to fatal. In patients hospitalized with COVID-19, many individual conditions have been outlined as predictors of successful or unsuccessful clinical care, including sex, age and underlying diseases.

In the first cluster of 41 hospitalized COVID-19 molecularly confirmed patients in Wuhan, China (median age 49 years), 30 (73%) were men and 30% had underlying diseases, such as diabetes, hypertension and cardiovascular disease [1]. In a wider cohort of 161 Chinese patients who died from COVID-19, 75% were men (median age 64 years) and 74,4% had chronic comorbidities, namely hypertension (50%), diabetes (25%) and ischemic heart disease (18,5%) [2]. Out of the 1591 patients included in the COVID-19 Lombardy, Italy, ICU Network (median age 63 years), 1304 (82%) were males; out of the 1403 patients with available data 709 (68%) had at least 1 comorbidity and 509 (49%) had hypertension [3].The study on the characteristics and early outcomes of 5700 subsequentially hospitalized patients with COVID-19 in the New York City area (median age 63 years) confirms the male prevalence (61% males) and the most common comorbidities: hypertension (56,6%), obesity (41,7%), diabetes (33,8%) [4].

Men are 1.5 times more likely to die from COVID-19 and underlying chronic diseases have been found in all cases who died from COVID-19 with less than 1% exceptions [5], making these features integrated in advanced machine learning predictive models increasingly used to estimate the risk of people being infected or experiencing a poor outcome [6].

I will herein comment on the sex bias of COVID-19 infection and highlight why X-linked genes are likely to be implicated in modulating COVID-19 disease progression. I will not address the contribution of genes on the X chromosome or autosomes to susceptibility to multifactorial diseases, which themselves are predictors of unfavorable COVID-19 outcome. Such indirect effects will occur increasingly with age, but are exerted on both males and females, and their occurrence will depend on age and on the individual genetic make-up.

The unique biology of human X chromosome

Females have two homologous X chromosomes one contributed by each parent, while men have one X chromosome from the mother and the sex-determining Y chromosome from the father. The X and the Y chromosome, derived from an ancestral autosomal pair approximately 300 million years ago, are dramatically different. The X chromosome spanning about 156 million DNA basepairs (156 Mb) represents approximately 5 percent of the total DNA in cells and contains 852 genes which provide instructions for making proteins and 665 non coding genes. A high number of immunity-related genes are located in the X chromosome as well as a high number of genes for long non coding RNA (lnc RNA) and small non coding micro RNA (miRNA), with the latter acting as negative regulators of protein synthesis in different processes, including immune response. By contrast, the Y chromosome is about 59 Mb, represents about 2 percent of the total DNA in cells and contains 50 to 60 coding genes, many unique to the Y chromosome such as SRY, the male determining gene, and genes related to male fertility, whereas functionality is retained only for 17 of the over than 600 genes once shared with the X chromosome.

During early female embryogenesis one of the X chromosomes is inactivated in order to have an equal dosage in the expression of proteins encoded by X-linked genes in males and females. The X Chromosome Inactivation (XCI) process is achieved by a multistep epigenetic mechanism initiated by the long noncoding (lnc) RNA X-inactive specific transcript (XIST) resulting in packaging into transcriptional inactive heterochromatin of the X chromosome [for review see7]. The XCI occurs at random across alleles irrespective of parental origin and is clonally maintained once established, resulting in functional mosaicism of females who have mixed cell populations for the inactive X: about half of cells with inactive Xp, expressing the maternal X-inherited genes, and half of cells with inactive Xm, expressing the paternal inherited X-linked genes [8]. Availability in heterozygous females of two sets of X-linked variants may be a favorable condition, should a deleterious or disadvantageous variant of an X-linked gene be present, as the effect would be manifest in only half of the cells of a female instead than in all cells, as it occurs in males. And such availability confers a first advantage to females relative to males.

Inactivation is however neither uniform nor complete and some genes on X chromosome escape inactivation [9]. Many of these genes are located at the ends of each arm of the X chromosome in areas known as PAR1 and PAR2 (pseudo autosomal regions) and are present on both sex chromosomes (Fig.1). Thanks to an XCI escape mechanism allowing gene transcription on both X chromosomes, men and women have each two functional copies of these genes. Yet there is evidence of differences between the Y and the X allele in the expression and tissue distribution of most of these genes: Xi expression remains below Xa expression that means is higher in men [10].

Beside the genes in the PAR regions, other genes escape XCI. XCI escaping genes are

defined as showing >10% expression from the inactive X allele compared to the active X allele [9]. There is evidence that at least 23% of X-linked genes continue to be expressed by the otherwise inactive X chromosome, leading to a female bias less than twofold in the expression levels [10]. Although the chance of escaping XCI can vary between individuals (enhancing phenotypic diversity) and across cells within tissues and also over development and aging [10,11], there is increasing recognition that incomplete XCI contributes to sex biases in susceptibility to disease, including infections by different pathogens which trigger immuno-logical reaction by host related factors.

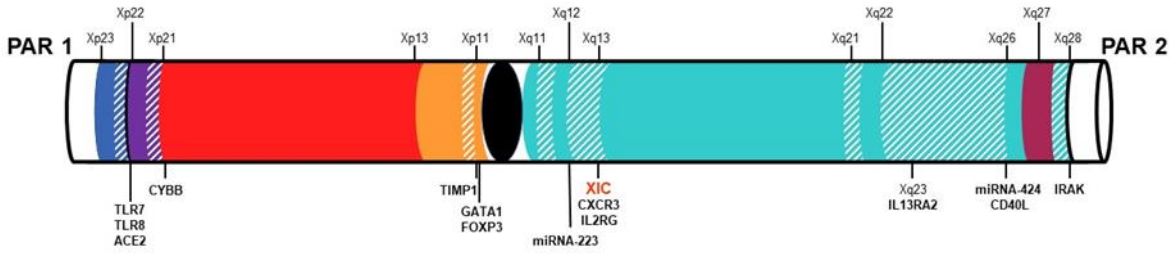

Figure 1. Schematic representation of the "inactive" X chromosome and clustering of immunity-related genes. Regions with clusters of immune-related genes are indicated by diagonal white lines. The black oval indicates the centromere. XIC: X chromosome Inactivation Center. PAR1 and PAR2: Pseudo Autosomal Regions 1 and 2 located at the ends of p and q arms, respectively. Different colors distinguish the regions with different chance of escaping X chromosome Inactivation (XCI). From pter to qter: blue: very low chance; violet: high chance; red: moderate chance; orange: low chance; turquoise: subject to inactivation; purple: low chance. *TLR7*, *TLR8*: Toll-like receptor 7 and 8 ; *ACE2*: Angiotensinogen converting enzyme; *CYBB*: Cytochrome b-245 beta polypeptide; *TIMP1*: Tissue inhibitor of metalloproteinase 1; *GATA1*: GATA binding protein 1; *FOXP3*: Forkhead box P3; *CXCR3*: Chemokine (C-X-C motif) receptor 3 ; *IL2RG*: Interleukin 2 receptor gamma; *ILE13RA2*: Interleukin 13 receptor alpha 2; *CD40L*: CD40 ligand; *IRAK1*: Interleukin receptor-associated kinase 1. Genes for microRNAs are indicated by miRNA followed by the miRNA number. Modified from Schurz, 2019 [12].

The chances for escaping X inactivation vary between genes, ranging from high to moderate to low in different X chromosome regions, as depicted in Figure 1. For example, the toll-receptor gene *TLR7*, an important element of antiviral immunity and the *ACE2* (Angiotensin Converting Enzyme) gene are biallelically expressed in females in keeping with their location to Xp22 within a chromosome region prone to escape XCI. The *TIMP1* (tissue inhibitor of metalloproteinase 1) gene encoding a member of a family of proteins involved in response to infections and septic shock, maps to Xp11, within a region enriched in dosage sensitive genes with a low chance of escaping XCI and is characterized by a variable expression from the inactive X chromosome. This pattern of expression also applies to the nearby immune-related genes, *GATA1* encoding for GATA binding protein 1 involved in differentiation of erythrocytes and megakaryo-cytes, and *FOXP3* (Fork head Box P3) for a transcription factor which promotes differenti-ation of regulatory T cells. The long arm of

chromosome X is the evolutionarily most conserved portion of the X chromosome, containing dosage sensitive genes strictly subject to XCI. There are however regions with immune-related genes escaping silencing in female lymphocytes: *CXCR3* at Xq13, encoding a chemokine receptor and *CD40L* at Xq16 encoding CD40 ligand, a B cell costimulatory molecule member of the tumor necrosis factor (TNF) family, for which biallelic expression is restricted to some mature B and T cells. Due to a functional advantage these cells become overrepresented in tissues involved in the immune response. Location at Xq12 of miRNA-223, a fine tuner of granulocyte production and the inflammatory response and at Xq26 of miRNA-424 regulating monocyte/macrophage differentiation, are also indicated in Figure 1.

Additional diversity in the expression of X linked genes may occur in females by "skewed or non-random" X inactivation. This is the process by which one X chromosome is preferentially silenced in over 75% of the cells. As a result, different females may have different levels of mosaicism according to the percentage of the cell population with the parental X chromosome preferentially inactivated. Skewed XCI may occur by chance alone or by selection against the cell population with a pathogenic variant on the active X. There is a trend for this process to increase with age so that 10% of healthy females over 50 years have haploinsufficiency for X-linked genes in immune-related cells with reduction of diversity in their expression, losing their advantage compared to males. Skewed XCI is considered a mechanism contributing to disturbances of self-recognition and to the onset of autoimmune diseases which present a female sex bias [13, 14].

Recent studies also revealed that the inactive state of the Xi is predisposed to be locally "reactivated" in mammalian lymphocytes as shown by the lack of the typical heterochromatic modifications of the inactive X and biallelic expression of the immunity-related genes *CD40L* and *CXC33* (both located in the X long arm subject to XCI) in single B and T cells [11]. These studies provide mechanistic evidence for enhanced female immunity to infectious diseases. On the other hand, the increased expression of immune-related genes can also explain the proneness of females to develop autoimmune diseases [13, 14].

All together XCI, escaping genes, non-random X inactivation and localized reversion of inactive X epigenetic silencing confer a physiological diversity to females that may impact sex differential expression of X-linked genes in disease.

The human X chromosome and immune-related genes

The X chromosome is known to contain the largest number of immune-related genes of the whole human genome and about 10% of the total genome regulatory RNA, long non coding RNA (lncRNAs) and microRNA (miRNA) which play a role in sex differences in immune responses [12]. The X chromosome is partly responsible for the enhanced response of the female immune system. Indeed, immunological sex differences manifesting during the reproductive life are hormone-dependent, while those present throughout life are gene-dependent. Many X-linked genes have a direct or indirect role in the innate and adaptive immune system, such as *TLR7*, *TLR8* encoding the pattern recognition receptors of the Toll-like family, *IRAK1* (interleukin 1 receptor associated kinase 1) acting in the TLR-dependent signaling pathway, *CYBB* (cytochrome b-245 beta polypeptide) that affects immune-related cells, several chemokine and interleukin receptor genes (*CXCR3*, *IL2RG*, *IL13RA2*) and the above

mentioned *CD40L*, *GATA1*, *TIMP1* and *FOXP3* genes (Figure 1). Also non coding miRNA, overrepresented in the X chromosome, may influence the sex differences in susceptibility to certain diseases as females may have a higher expression due to XCI and related mechanisms.

Naturally occurring variations in one gene copy of X-linked genes may produce two distinct alleles with different regulatory and response activity, providing diversity precluded to males. The X-linked mosaic make up of females resulting from X chromosome inactivation, escape of a consistent number of genes to XCI, variable expression from the inactive X of some "escapees", and overexpression in some mature naïve B and T cells upon local Xi reactivation [11] can account for different immunological response between sexes and between individual females and influence the sex bias of susceptibility to infections.

It has been extensively reviewed [5, 13 ,14] that females live longer than males and have higher survival from infectious disease, sepsis, trauma. A female-related immunological advantage has been documented by studies showing their capability to mount stronger and adaptive immune response than males, to respond to seasonal influenza vaccines twice as strong as men, to have a faster clearance of pathogens (40% less viral RNA in the blood of HIV infected women than men). It has also been proposed that the female robust immunological system has been acquired through evolution to face the immunological challenges of pregnancy. The immunological advantage of females to infections caused by selected bacteria (Mycobacterium tubercolosis), parasites (leishmania) and viruses (HIV, influenza A, Hepatitis C) has been subject of dedicated investigations and has been ascribed to the sex-specific host response against the invading pathogen [12]. In the case of tuberculosis (TB) associations with genetic variants in the *TLR8* gene were found significantly associated with TB susceptibility in males, though further studies are needed to fully understand the sex-bias. The X-linked *ACE2* gene escaping XCI, has been proposed to modulate susceptibility to SARS-COVID as it mediates viral attachment to target cells [15] and is a good candidate to mediate sex –related effects. No significant differences in the burden of *ACE2* rare deleterious variants were observed comparing genetic data of the Italian population with Europeans and East Asian populations [16]. A higher *ACE2* burden could have helped explain the sex bias in the Italian population. In addition, the authors, by retrieving *ACE2* expression levels in the lung from the largest available database in the literature, did not evidence differences between males and females nor between younger and older women [16]. However, no data on *ACE2* expression levels has so far been collected on COVID-19 patients stratified according to sex, age and related comorbidities.

Conclusion

Data on Wuhan [1, 2], Lombardy (Italy) [3] and New York [4] case series show a preponderance of males affected by COVID-19 and with severe outcome of the disease. Sex hormones may contribute to the recognized sexual dimorphism, but do not fully account for it. Genetically determined sex is a biological variable that affects immune response to foreign antigens of different pathogens. Genes on the X chromosome may contribute to physiological distinctions between males and females (and across females) that influence the exposure, recognition and clearance of COVID-19. It is not known which innate immune receptors, transmembrane or cytosolic, recognize Sars-Covid [5]. Transmembrane Toll-like receptors can sense both live and dead virus particles and play an important role in antiviral immunity as TLR signaling induces the expression of pro-

inflammatory cytokines, type I interferons (IFNs) and IFN–stimulated genes (ISGs). Males are more likely to be the target of COVID-19 as they have a relatively reduced antiviral immunity. They produce a lesser amount of IFNs and inflammatory cytokines and possess a lower number of circulating T cells [5,13,14]. Elderly individuals presenting with one or more comorbidities appear to have the highest rate of infection and death by COVID-19. Evidence links aging to cytokine dysregulation and reduction of T-cell repertoire and COVID-19 related comorbidities to hyperinflammation [5]. Patients with severe COVID-19 infection show dysregulated innate immune response as subsets of T-cells develop an exaggerated release of cytokines and chemokines, the so called "cytokine storm", which correlates with acute respiratory distress (ARSD) syndrome and multi-organ failure.

As aged individuals affected by chronic disease have an altered immune profile and the virus genome and its structural proteins impair immunological surveillance [5] we expect the female advantage to diminish with age: thus it would be important to match patients on age and chronic disease to investigate the differential effect of X-chromosome genes in immunological response to COVID-19.

No studies are yet available on the role of X-linked immunity genes, differentially expressed in females and males and across female patients in eliciting and maintaining the immune reaction to COVID-19. A challenge for a research translatable in patient care would be to search by Next Generation Sequencing targeted to the X chromosome single nucleotide variants (SNVs) in genes with a direct or indirect role in immune response and explore their effect on the disease course in COVID-19 patients stratified according to sex and age as well as their mosaic level in affected women. Studies on the expression of X-linked gene variants candidate to modulate the risk of severe disease evolution could add knowledge on the immunological response to COVID-19 infection and provide the basis for medication tailored to a specific sex, improving treatment outcome.

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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.

BUT WHAT DOES SCIENCE SAY?

Many people, disoriented by the coronavirus pandemic, are asking themselves this very question. This article is intended to help you navigate a world in which the news is suddenly full of science, or at least information sold as 'science'.
You can find the full text of this informative and delightful address given on 15 May 2020 at the University "Aldo Moro" of Bari by Mariano Rocchi, Emeritus Professor of Genetics (https://www.uniba.it/ricerca/dipartimenti/biologia/la-scienza-ai-tempi-del-coronavirus-riflessioni-del-professore-emerito-mariano-rocchi)

CRISPR-Cas9 ON DEMAND

Conditional gene knockout in mice is a technique in which a specific gene is knocked out at will by the administration of an appropriate substance to an adult knockout mouse. A paper in Science describes a CRISPR-Cas9 system, which the authors call very fast CRISPR (vfCRISPR) that can be activated by light. The system is described as "a caged RNA strategy that allows Cas9 to bind DNA but not cleave until light-induced activation". In this paper the technology is used to induce double strand brakes in order to study DNA repair mechanisms. This may be a beginning of a new direction of CRISPR-Cas9 applications.

THE INTROGRESSED NEANDERTHAL PROGESTERONE RECEPTOR (*PGR*) GENE ENHANCES FECUNDITY OF PRESENT-DAY *HOMO SAPIENS*

In the May Issue of Molecular Biology and Evolution (https://academic.oup.com/mbe/advance-article/doi/10.1093/molbev/msaa119/5841671), Seberg. Kelso and Pääbo from the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, show that a *PGR* gene variant of Neanderthal origin promotes human fertility. It is well known that pieces of the Neanderthal nuclear genome are carried around by present-day, non-African humans. In total, these pieces represent about 20% of the Neanderthal genome, and in an average non-African individual of *Homo sapiens*, they account for about 2% of the nuclear DNA. Now, Seberg et al. show that the V660L variant of *PGR*, which is homozygous in Neanderthals, is present as a heterozygous variant in up to 22% of individuals in European and Native American populations. Data from the UK Biobank show that female carriers of V660L experience significantly less bleeding in early pregnancy, have fewer miscarriages, and have more sisters. In addition, the variant is associated with higher mRNA production, possibly mimicking the effect of orally administered progesterone, which increases fertility in women who had multiple miscarriages. Thus, this introgressed Neanderthal gene variant is associated with an increased fitness, explaining why it rose to high frequency in modern human populations.

MALE/FEMALE RATIO AMONG COVID-19 DEATHS

Statistics on COVID-19 show a substantial higher number of deaths among males than females in all age groups from 50 years and above.

To better understand these data, it is worth noting that in many species there is a significant longer lifespan of females compared to males. *Lemaître et al.* (PNAS) recently analyzed 101 mammalian species and found that the median lifespan of females is on average, 18.6% longer than that of males (7.8% in humans). The evolutionary reason is well summarized in another paper which recently appeared in BMC Evolutionary Biology: " ... while males may maximize fitness by increasing mating success at the expense of longevity, females may maximize fitness through longevity because offspring production, although resource intensive, requires time too". It is also worth noting, in this context, that while menopause is rare in mammals (females are fertile also at older ages), humans and killer wales are a big exception. The title of one paper on this subject, which appeared last year in PNAS, is self-explanatory: "Postreproductive killer whale grandmothers improve the survival of their grandoffspring". In general, selection does not care about what happens after the reproductive period. However, if a trait (grandchild care by females in this case) is related to fitness, then evolution makes an exception.

Future genomic and functional studies will better clarify the male/female ratio among COVID-19 deaths, but its full understanding requires an evolutionary frame. As Dobzhansky said, nothing in biology makes sense except in the light of evolution.

A CHROMOSOMAL INVERSION THAT HAS LASTED FOR 8 MILLION YEARS

Chromosomes evolve. Translocations, fusions (e.g. human chromosome 2) and, above all, inversions differentiate the chromosomes of even closely-related species. Consider the donkey and the horse: the genes in the two are more or less the same but are arranged differently so that there is a difference in the structure of chromosomes. The two species have no problem with crossbreeding and producing offspring. The problem, however, is that in the germ line of the hybrid offspring (the mule or the hinny) the chromosomes cannot pair leading to the breakdown of meiosis and to sterility. In populations, therefore, heterozygosity of chromosomes is not frequent and often results in the fixation of one of the two forms.

There are however exceptions. The first one was described in *Drosophila pseudoobscura* by Dobzhansky (1944). He reported inversions that persisted in the population of *Drosophila*. It is known that sexual reproduction, by crossovers, can create favorable combination of gene variants in the same chromosome, but a meiotic crossover could disrupt the combination. If, however, the chromosomal segment with the two genes is inverted, then the combination persists. This is because if a meiotic crossover disrupting the combination occurs, the resulting recombinant chromosomes which have deletion/duplication are lost. In this way inversion heterozygotes have a selective advantage because the favorable combination of genes is passed on while the embryos with the disrupted combination are lost. This is the most plausible explanation of the very long persistence (~ 8 million years) of a chromosomal inversion present in the heterozygous state in two species of *Cercopithecus* (Old World Monkey). This work has appeared in the latest issue of Chromosoma.

EVOLUTION OF TUMORS

The study of the evolution of a population goes through the analysis of changes in allele frequency over time. The term "evolution" has always been widely used in the context of tumors, but it often referred only to the successive stages and not to evolution in the Darwinian sense. Then, the possibility of analyzing the genome of a single cell opened the way for an evolutionary study of the tumor population in the strict Darwinian sense. The first work based on these new technologies was published 2011. The following year, a review specifically dedicated to Darwinian concepts in the evolution of tumors appeared. In fact, the famous sketch of the tree of life designed by Darwin in 1837 appears in this paper.

The variability of a population allows it to cope with a changing environment (adaptation through the selection of the fittest). From the tumor point of view, the changing environment can be chemotherapy. The authors say: "The inherently Darwinian character of cancer is the primary reason for this therapeutic failure" (i.e. of the evolutionary success of the cancer).

In a recent issue of Nature several articles from a collaborative study involving 2658 tumors, of 38 different types, have appeared. The title of one of these papers reads "*The evolutionary history of 2,658 cancers*". One of the most interesting observations concerns the fact that "driver" mutations (ones responsible for the tumor) can arise years, sometimes many years, before the tumor manifests itself clinically. Mutations in cancer-related genes, however, are not rare in normal people. The Nature paper elucidates that "*Early oncogenesis is characterized by mutations in a constrained set of driver genes, and specific copy number gains, such as trisomy 7 in glioblastoma and isochromosome 17q in medulloblastoma. The mutational spectrum changes significantly throughout tumour evolution in 40% of samples. A nearly fourfold diversification of driver genes and increased genomic instability are features of later stages*".

DISRUPTION OF GENES SPANNING THE BREAKPOINTS IN BALANCED RECIPROCAL TRANSLOCATION CARRIERS CAUSES INFERTILITY

Carriers of some reciprocal translocations are infertile. The infertility is caused by two main mechanisms. The first is synaptic alterations at prophase I which lead to meiotic arrest. The second is the production of chromosomally unbalanced gametes by different modes of segregation at anaphase I which leads to reproductive failure. For a long time, some authors have claimed an additional source of infertility associated with the loss of functionality of the genes situated around the breakpoints.

In this new paper from the Journal of Assisted Reproduction and Genetics
https://link.springer.com/article/10.1007/s10815-020-01702-z
the authors have performed a breakpoint analysis in nine reciprocal translocation carriers with subfertility (without any other apparent phenotypic effect) using single-molecule optical mapping (SMOM; also known as next-generation mapping). This genome mapping technique allows the construction of high-resolution karyotypes, and hence, is very useful in establishing genotype - phenotype correlations.

SMOM analysis on the nine translocation carriers was able to map the breakpoint regions allowing the identification of some genes spanning the breakpoint intervals. In four carriers, disrupted gene sequences were identified. Interestingly, some of the disrupted

genes had been associated with infertility in previous studies: FNDC3A, NUP155, DPY19 L1, and BAI3.

The authors suggest that the possibility of identifying disrupted genes in apparently balanced reciprocal translocations opens up a new scenario in the field of reproductive genetics. In these carriers, preimplantation genetic diagnosis techniques could be used not only to identify embryos with unbalanced segments of the reorganized chromosomes, but also to identify embryos with disrupted genes causing infertility; this would be embryos with a balanced chromosome constitution.

CHROMOSOMAL SEGREGATION FIDELITY

The spindle assembly checkpoint (SAC) is a signaling pathway that prevents cells from exiting mitosis until all chromosomes are correctly attached to spindle microtubules. This ensures that daughter nuclei receive one copy of each chromosome, thus maintaining the appropriate karyotype. The SAC relies on the localization of the Mad1-C-Mad2 complex at unattached kinetochores but also on its binding to Megator/Tpr at nuclear pores (NPs) during interphase. However, the molecular mechanism controlling the spatiotemporal redistribution of Mad1-C-Mad2 as cells progress into mitosis remain elusive. A very recent paper in the Journal of Cell Biology (https://rupress.org/jcb/article-abstract/doi/10.1083/jcb.201906039/133569/Mps1-mediated-release-of-Mad1-from-nuclear-pores)

shows that activation and nuclear import of Mps1 kinase during prophase triggers Mad1-C-Mad2 release from NPs and that this is required for kinetochore recruitment of Mad1-C-Mad2 and robust SAC signaling. The authors provide evidence that Mps1 phosphorylates Megator/Tpr to reduce its interaction with Mad1 in vitro and in cells. Furthermore, artificially preventing Mad1 from binding to Megator/Tpr was sufficient to restore Mad1 accumulation at unattached kinetochores, the fidelity of chromosome segregation, and genome stability in *mps1*-null mutant cells. These findings demonstrate that the subcellular localization of Mad1 is tightly coordinated with cell cycle progression by kinetochore extrinsic activity of Mps1. This strategy ensures that both NPs in interphase and kinetochores in mitosis contribute to generate an efficient SAC response to preserve genomic stability.

MITOTIC SEGREGATION ERRORS IN OOGENESIS AS A SOURCE OF HUMAN ANEUPLOIDY

In humans, aneuploidy in offspring is mainly associated with chromosome segregation errors during the first meiotic division of the oogenesis. Nevertheless, other mechanisms have been also described. One of them is the occurrence of errors during the mitotic division of oogonia (premeiotic germ cells). This phenomenon gives rise to germinal mosaicism, that is, the coexistence of euploid and aneuploid germ cells in the ovary.

Although the contribution of this phenomenon to human aneuploidy is well recognized, their characteristics and incidence have been poorly explored. In this review authors show several pieces of evidence that allow them to conclude that premeiotic aneuploidy is one of the age-independent mechanisms that predispose women to produce aneuploid oocytes. The authors estimate that this phenomenon could explain up to 40% of oocyte aneuploidy.

KARYOTYPING HELPS TO FIND A NOVEL GENE FOR MALE FERTILITY

Several hundred genes are mutable to cause male infertility, and many novel genes remain to be identified. Karyotyping can help to find these, as shown in the January 2, 2020 issue of the American Journal of Human Genetics by a group of researchers from Boston, Manchester, Münster and Stanford (Schilit et al.). They studied a male patient with unexplained severe oligospermia who had a balanced translocation t(20;22)(q13.3;q11.2). By analysing the expression of all genes in the TADs that were disrupted by this translocation, they found a 20-fold overexpression of the *SYCP2* gene on the chromosome 20 segment in the der(20)t(20;22). 4C-Seq analysis indicated that this was caused by adoption of an enhancer in the segment derived from chromosome 22. *SYCP2* encodes synaptonemal complex protein 2, and its overexpression in a budding yeast model caused meiotic arrest by disruption of the synaptonemal complex. Together with the identification of exonic deletions in *SYCP2* in three other infertile males, one of which also caused meiotic arrest, this study adds *SYCP2* to the growing list of male fertility genes. In this case, karyotyping was essential to find the causative gene.

FERTILITY IMPAIRMENT, A MATTER OF TIME

In humans, oocytes are stored in the ovary prior to ovulation. Long-term oocyte storage is associated with functional impairment, including chromosome segregation errors leading to aneuploidy. The loss of chromosomal cohesion with time in mature aging oocytes increases the risk of fetal aneuploidy and miscarriage.
This paper from *elife* (https://elifesciences.org/articles/49455) demonstrates that other factors, besides the loss of cohesion, contribute to the functional impairment of mature aging oocytes. Using a very elegant experimental design based on Drosophila oocytes, the authors show that the storage of oocytes itself increases the risk of aberrant spindle formations and non-disjunction. These impairments are related to a decline in the translation of meiotic metaphase proteins and spindle-related proteins. This means that the storage itself is enough to destabilize chromosome segregation through a significant decay in translation efficiency.
Since all human oocytes are naturally stored to some extent, some of them for long periods, the proposed mechanisms could be relevant also for our species and could be crucial for the decline of fertility in older women.

GENE EDITING OF EMBRYOS

In 2019, the first known application of CRISPR/Cas9 in human embryos was presented at the Second International Summit on Human Genome Edition in Hong Kong. The principal scientist involved, Dr. He Jiankui, announced the birth of twins that carried CRISPR/Cas9 corrective mutations produced in one-cell embryos before the transfer to the uterus. Dr. Jiankui's work was widely condemned for the premature use of this new technology.
CRISPR/Cas9 technology allows gene editing of specific genomic target sequences with high efficiency. Prior to Dr. Jiankui's study, there had been several published reports of successful results in one-cell human embryos (which were not implanted), suggesting the possibility of permanently correcting some genetic disorders.
These successful results, however, went together with some disadvantageous consequences: 1) Off-target mutagenesis; 2) Mosaicism; 3) Large

deletions and chromosome rearrangements; 4) On-site damage and biallelic modifications.
In an article in Human Reproduction (https://academic.oup.com/humrep/article/34/11/2104/5613882), the author has extensively reviewed the origin and the frequency of the harmful events that appear as a consequence of the application of the CRISPR/Cas9 technology. In agreement with the scientific community, the author highlights the need for more research to optimize the method before therapeutic editing can be considered. In this respect, the implementation of new editing methods, such as prime editing (https://www.nature.com/articles/s41586-019-1711-4) has already begun to open some promising alternatives.

COHESIN AND CHROMATIN 3D STRUCTURE

Importance of 3D architecture of chromatin for genome function is now widely recognized. Chromatin organization relies on small loop domains, either active or inactive, and is delimited by the zinc finger CTCF anchor and cohesins. However, the way by which cohesins generate DNA loops has remained elusive up to now. Cohesins are multiprotein complexes which belong to the family of Structural Maintenance of Chromosomes (SMC), as do Condensins. Condensins have been shown to form DNA loops by extrusion during mitosis, through their motor activity: the authors of this paper (appeared in Science) sought to investigate whether cohesins could act in a similar way using an assay designed to visualize looping on DNA molecules tethered to a glass slide.
The authors show that cohesins do have an extrusion activity which depends on ATP hydrolysis and needs the presence of two partner proteins, NIPBL and MAU2. Furthermore, the authors shed a first light on a long-debated issue regarding the topology of DNA – cohesin interaction during the extrusion process. According to the results obtained with engineered cohesins, in which all the proteins of the complex are cross-linked together avoiding opening of the cohesion ring, the authors suggest a model where cohesins extrude DNA without entrapping chromatin inside the ring.

A NEW HOPE FOR DOWN SYNDROME PATIENTS?

A paper which appeared in Science few months ago attributed the phenotype of the Down syndrome not to specific chromosome-21 genes but to dysregulation of several genes scattered in the genome. A very recent paper in Cell Rep is, in a way, in line with the Science paper. This paper reports that in yeast the abnormal phenotype of trisomies (in general) is due to the disruption of the morphology of the nucleus. Mutations that increase the levels of long-chain bases, involved in the nuclear membrane integrity, suppress the nuclear abnormalities and restore fitness. Similar results are reported for cells from Down syndrome patients and also patients with Patau (trisomy 13) and Edwards (trisomy 18) syndromes.
Suppressing Aneuploidy-Associated Phenotypes Improves the Fitness of Trisomy 21 Cells
Sunyoung Hwang, Jessica F.Williams, Maja Kneissig, Maria Lioudyno, Isabel Rivera, Pablo Helguera, Jorge Busciglio, Zuzana Storchova, Megan C.King, Eduardo M.Torres.
Cell Rep. 2019 Nov 19; 29(8): 2473–2488.e5. doi: 10.1016/j.celrep.2019.10.059
Activation of the ISR mediates the behavioral and neurophysiological abnormalities in Down syndrome
Ping Jun Zhu, Sanjeev Khatiwada, Ya Cui, Lucas C. Reineke, Sean W. Dooling, Jean J.

Kim, Wei Li,, Peter Walter, Mauro Costa-Mattioli
https://science.sciencemag.org/content/366/6467/843.editor-summary

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PIGS AND TRANSPLANTS

The pig is known to be, potentially, a good organ donor for man. However, there are problems. For example, the 62 retroviruses present in the pig genome are potentially dangerous to humans. The various problems have not come to terms with the CRISPR-Cas9, and, one by one, are falling under its cleaver.
Short history:
- 2015: the 62 retroviruses are inactivated in a pig cell culture.
- 2017: the first piglets with all 62 inactivated retroviruses are born in China.
- 2019: Some specialized firms operate a whole series of modifications (always with CRISPR-Cas9) that have solved, or almost solved, all the problems.
The work on these latest results is available on bioRXiv. bioRXiv is a public archive of works not yet published in journals (the publication involves an evaluation by experts in the field). However, Science has already dedicated a comment to it.

THE TAMING OF THE (male) SHREW

One of the most obvious features in domestic-cated animals is that, as the word says, they have become domesticated. They lost the original aggression. And what about man? An article in Science Advances highlights the involvement of the *BAZ1B* gene in the "self-domestication" process. See a comment in Science.
The concept of self-domestication is not new; a 2018 paper underlines how women have played an important role in this process, through the selection of less aggressive partners.

LENGTH OF LIFE AFTER MENOPAUSE

Homo sapiens is the only primate where females have a much longer life span after menopause; this can even exceed the length of the fertile period. The most convincing explanation is that grandmothers help their grandchildren survive. The phenomenon was thought to be the consequence of an effective selective pressure. A similar situation exists in female killer whales, who have the longest life after the last calving. Now, we have experimental evidence of this selection, reported in a paper which appeared in PNAS and deserved a comment in Science.

PATERNAL AGE AND EMBRYO ANEUPLODY IN HUMANS

Advanced age has become a major concern in western societies as men and women delay starting families. There are many publications about the negative impact of advanced maternal age on the fertility of couples. However, less attention has been paid to the possible impact of advanced paternal age (APA). Some studies have shown an increase in de novo mutations associated with APA (doi:10.1038/ng.3597) as a result of an accumulation of errors during the fertile lifespan of men (mutations related to the process of DNA replication). This new paper from The Journal of Assisted Reproduction and Genetics (doi.org/10.1007/s10815-019-01549-z) explores whether there is an association between APA and aneuploidy in embryos. To exclude the contribution of advanced maternal age, authors have compiled data from IVF cycles using egg donors (fertile women under 35 years old). Results support previous findings that indicate a

negligible effect of APA on the genesis human aneuploidy.

LOSS of CHROMOSOME Y

It is known that, in males, aging is associated with the loss of the Y chromosome in a proportion of blood cells. A very recent paper in Nature (https://www.nature.com/articles/s41586-019-1765-3) estimates that 45,X/46,XY mosaicism is present in 20% of the male population represented in the British biobank (n = 205,011). In the same study, the authors show that the loss of the Y chromosome is genetically determined by a series of variants located in 156 autosomal loci, an observation that was replicated in 757,114 men of European and Japanese origin.

HEMOGLOBINOPATHIES AND CRISPR-Cas9: FIRST RESULT IN ADULTS

Hemoglobinopathies lend themselves to genetic manipulations because hematopoietic cells can be withdrawn, treated and reintroduced. And there is also a shortcut. Instead of manipulating the specific mutation of the patient, one could reactivate the fetal hemoglobin. There are cases in which the pathology is attenuated, even completely, because of the casual presence of a mutation that causes the persistence of fetal hemoglobin (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6292363/).
This 2018 publication was about the strategy of reactivating fetal hemoglobin using CRISPR-Cas9 (https://www.sciencedirect.com/science/article/pii/S0168952518301562?via%3Dihub).
Now there are results obtained by CRISPR Therapeutics (Zurich) https://investors.vrtx.com/news-releases/news-release-details/crispr-therapeutics-and-vertex-announce-positive-safety-and) and there is a short paragraph in Science titled "CRISPR's first clinical success?" (https://science.sciencemag.org/content/366/6468/930).

CRISPR AGAIN

This Nature paper (https://www.nature.com/articles/s41586-019-1711-4) about a new CRISPR system able to "search & replace" a single base is still in press, but its echo is enormous. However, there are limitations and problems. For now, for example, you can only replace a G with a C or an A with a T. Furthermore, the system needs PAM sequences downstream of the site under consideration. This new comment by Nature (https://www.nature.com/articles/d41586-019-03536-x) points out these issues and for many of these provides a glimpse of possible solutions at hand.

GENOMIC CODE

For decades non-coding DNA in our genome has been viewed as "junk" DNA, of which the role, if any, was elusive, even though increasing evidence in recent years has supported its role in gene regulation. Also the biological significance of the base composition of the genome, with unevenly distributed, GC-rich "gene-rich" regions versus AT-rich "gene-poor" regions, named isochores, is still under debate.
This review in BioEssays (https://onlinelibrary.wiley.com/doi/full/10.1002/bies.201900106) sheds light on the most recent advances in our understanding of the "genomic code" and shows how base composition is the

precursor of genome 3D architecture (A and B compartments, TADs, LADs…), restoring the reputation of the 98% of our once called "selfish" DNA. This is further evidence that Nature does not waste resources; the burden of such a large genome for "only" 20,000 genes has turned out to be an evolutionary resource for better tuning of the genome organization and functioning.

ETHICS IN BIOLOGY

In the Star Treck series Captain Kirk used a "Communicator". We smiled. Now we smile if we compare it to our mobile phones. The cloning of mammals was considered almost impossible, then Dolly arrived.
The debate on the CRISPR experiment in a pair of Chinese twins is not yet over, and now a similar experiment is planned in Russia, to treat prenatally a mutated gene that causes deafness (https://www.sciencemag.org/news/2019/10/deaf-couple-may-edit-embryo-s-dna-correct-hearing-mutation).
Many concerns are about potential uncontrolled side effects. But the specificity of CRISPR is continuously improving (https://www.nature.com/articles/s41586-019-1711-4).
Finally, Nature reports that a monkey embryo was grown in the laboratory up to 20 days (https://www.nature.com/articles/d41586-019-03326-5)
Much to think about.

DOWN SYNDROME: NEW PERSEPCTIVES FOR THE CARE?

Comparative studies in Down syndrome (DS) patients have shown that the expression of several genes, not just those mapping on chromosome 21, are dysregulated. Proteostasis, that is the balance between protein synthesis and degradation, is essential for cellular health. The non-specific dysregulation of this balance has been found to be crucial in neuropathological syndromes, like fragile X, Alzheimer, and Parkinson; it may also play a role in DS. This very recent Science paper shows that in mouse models for Down syndrome treatments aimed at restoring this balance results in the rescue of the synaptic plasticity and long-term memory deficits. This finding opens up new perspectives for the cure of DS.

CHROMATIN ACCESSIBILITY AND GENE EXPRESSION

Chromatin accessibility to transcription factors is considered a proxy for gene activation. Thousands of papers are based on this equation. A recent paper in Genome Research questions the full validity of this equation.

RESULTS OF FIRST YEAR NIPT FOR ALL PREGNANT WOMEN IN THE NETHERLANDS

Non-invasive prenatal testing (NIPT) is being offered as a first-tier test to all pregnant women in The Netherlands since April 2017. Now, Karuna van der Meij et al. have published the results of the first year of NIPT (TRIDENT-2 study, licensed by the Ministry of Health), based on 73,329 pregnancies (The American Journal of Human Genetics (2019). Of all pregnant women, 42% participated and of these, 78% opted for genome-wide NIPT. Because of intensive cytogenetic follow-up studies in case of abnormal findings, this study provides an accurate perspective on the findings that can be expected in a low-risk population in addition to

the common trisomies (13, 18, 21). The percentage of additional findings (0.36%) was in the same order of magnitude as trisomy 21 (0.33%) and included cases with confined placental mosaicism, other trisomies in the fetus, chromosomal rearrangements in the mother and – in rare cases - complex profiles suggestive of a maternal malignancy. This study provides an input for the debate on whether NIPT should be performed genome-wide or should be restricted to the trisomies. There is a trade-off between the benefits of finding other chromosomal anomalies in the fetus on the one hand and, on the other, increased parental anxiety and unnecessary invasive procedures.

GENES FROM THE JUNKYARD

Pasteur showed us that spontaneous generation does not occur. But can (Mendelian) genes generate spontaneously? Many genes arise from duplications where one copy of the duplicated gene can acquire new functions. However, new genes do not always evolve from existing ones. This article in Nature https://www.nature.com/articles/d41586-019-03061-x gives a review, with many examples, of how new genes are born from desolate stretches of non-coding 'plebeian' DNA. True democracy at play!

WE EURASIANS AND THE NEANDERTHALS

For millennia man has considered himself as something completely / intrinsically / absolutely ... different from the rest of the creatures on Earth. Then, evolutionary genetics, especially with the advent of sequencing, showed us how much of our genome has in common with other organisms, even very distant ones. A total change in the way of thinking! Saying, for example, that we diverged from yeast about a billion years ago is correct, but perhaps it is even more correct and effective to say that we were the same living organism for ~ 2.5 billion years (considering the origin of life was ~ 3.5 billion years ago). The last blow to our self-image of "exceptionality", for us Eurasians, came with the discovery that our ancestors had interbred with the Neanderthals. Part of our genome, although small, came to us from the Neanderthals, especially those genes that represent adaptation to new conditions, pathogens in particular, to which the Neanderthals had had more time to adapt. The Neanderthals, indeed, came to Eurasia much earlier than *Homo sapiens*. This movement of genes between species by backcrossing is called introgression. Now, a new publication in Science https://science.sciencemag.org/content/366/6463/eaax2083 adds new data and shows that not only single genes or mutations, but entire duplicate blocks of DNA (segmental duplications) have introgressed into the genome of some modern human populations.

BLOOD TRANSFUSIONS

There is often a shortage of blood for transfusions. This is further complicated by the fact that only group 0 individuals are universal donors. Researchers have long tried to make up for the shortage by using other blood groups after eliminating the specific sugars that determine the group. The cost problem has so far been insurmountable. However, a Canadian group is now using an enzyme of a microbiome bacterium to eliminate the sugar that determines group A (the most common one after 0). This method, still in the research phase, looks very promising.

From Science: Type A blood converted to universal donor blood with help from bacterial enzymes
https://www.sciencemag.org/news/2019/06/type-blood-converted-universal-donor-blood-help-bacterial-enzymes.

DANCE

Many of you may have seen the rhythmic dance of the Snowball parrot on Youtube (there are several versions). In all these cases one always wonders about the scientific validity of what the images suggest. Now Snowball has appeared in the journal Current Biology. So the existence of an animal other than man that has a sense of rhythm in dance is a reality. (See also Not a human, but a dancer). Humans have already lost the exclusivity of various prerogatives (see the use of tools ... finally the "Theory of mind"), what will be the next prerogative to be lost?

MITELMAN DATABASE OF CHROMOSOME ABERRATIONS AND GENE FUSIONS IN CANCER

The database has been transferred to the Institute for Systems Biology (ISB)
https://mitelmandatabase.isb-cgc.org/
The updated web site offers some major advances:
1) **Fast Search**. Powered by Google BigQuery, a cloud-enabled parallel query engine, each search can be executed faster than most web applications with conventional database engines.
2) **User Interface Enhancements**. The user interface for the new web site has been simplified with a more responsive front-end, and is easier to use. Major changes added to the web site include the autocomplete drop-down list for Gene, Topography, and Morphology inputs.
3) **Capability to Download Search Results**. Users can now download query results into a TSV text file.
4) **Easier Online Navigation**. Search results are simpler to navigate, through use of text filtering, paginations on the search result pages, and user-defined sorting of columns in the search results.
The last update on October 15, 2019, contains information on cytogenetic abnormalities in 69,551 cases and 22,091 unique gene fusions involving 12,044 genes.

CANCER DRUGS

Many drugs are identified while looking for those that are specifically toxic to cancer cells. However, very few of these drugs go beyond clinical trials; why is that so has been a mystery. A group of researchers has investigated this mystery. The first experiment involved the MELK protein, considered essential for the growth of various tumors against which specific drugs had presumably been identified. To test whether the target of these drugs was actually the *MELK* gene, they specifically inactivated it with CRISPR-Cas9. Surprise! The cells did not respond at all. The researchers then inactivated, again with CRISPR-Cas9, the presumed target genes of other anticancer drugs with mostly the same result. Conclusion: the target gene, often identified with iRNA (RNA-interference), is not the presumed one. New pharmacological strategies need to be thought of.
From Science Translational Medicine

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COMMITTEE

ECC SCIENTIFIC PROGRAMME COMMITTEE

E.C.A. News

- A physical General Assembly in 2020 will be difficult, if not impossible, due to the Covid – 19 situation in most European countries, though the restrictions in some countries may be relaxed later this year. However, members from countries where Covid –19 is still a threat will not be able to participate. For this reason we are exploring the legal feasibility, due to "force majeure", of postponing the assembly and extending the mandate of the present Board of Directors by one year, just as some other societies have done.

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 March 2021 (see pages 24/25).
  - **Goldrain Course in Clinical Cytogenetics** to be held in Goldrain Castle (South Tyrol, Italy) 28 August – 5 September 2021 (see page 26).
- 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.

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

PWG: CLINICAL AND MOLECULAR APPROACHES TO CYTOGENETIC SYNDROMES.

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Please remember that the sSMC homepage can now be reached under
http://cs-tl.de/DB/CA/sSMC/0-Start.html
and UPD/ heteromorphisms and M-FISH pages under http://cs-tl.de/ and http://cs-tl.de/DB.html

PWG: CYTOGENETICS OF HAEMATOLOGICAL MALIGNANCIES.

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PWG: CANCER CYTOGENETICS, SOLID TUMOR STUDIES.

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PWG: CYTOGENETIC TOXICOLOGY AND MUTAGENESIS.

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PWG: ANIMAL, PLANT, AND COMPARATIVE CYTOGENOMICS.

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PWG: PRENATAL DIAGNOSIS.

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PWG: QUALITY ISSUES AND TRAINING IN CYTOGENETICS.

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PWG: CYTOGENOMICS.

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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

Objectives

This course was started by Professor Jean Paul Bureau 24 years ago 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, either as ***a Diploma (Basic = only the lectures or Advanced = lectures + practical training)*** or as a stand-alone course (lectures only)

Practical information

Lectures: A ten-day course held in February/March of each year.
Venue: Faculty of Medicine, Nîmes, France.
Official language: English.

Practical training (**only for students registered for the advanced Diploma**): A training of maximum 2 months in a cytogenetic laboratory. A list of laboratories is provided during the theoretical course.

Assessment **:** The assessment for the **basic diploma** will be on the basis of a one-hour examination held at the end of the lecture course**.** The knowledge of the students for the **advanced diploma** will be assessed in September by a written test (three questions) and an oral examination including a presentation (10-15 min) related to the practical training. The University will award a diploma to only those students who have passed.

All participants (including those for the stand-alone course) will receive a certificate of attendance by the E.C.A.

Topics (see opposite page).

Accommodation

A special price is available for participants in the 4* Vatel hotel close to the course venue. 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.
Accommodation is included in the stand-alone course fee

Registration

Registration opens in September and closes on January 30th.
To register please send a letter of application together with your CV by e-mail to one of the organizers mentioned below. If you are accepted you will receive a registration form.

Prof. Jean-Michel DUPONT
Laboratoire de Cytogénétique
Hôpital Cochin
27 rue du Fbg St Jacques
75014 Paris, France
jean-michel.dupont@aphp.fr
sylvie.mendez@aphp.fr

Prof. Thierry LAVABRE-BERTRAND
Laboratoire de Biologie Cellulaire et Cytogénétique Moléculaire
Faculté de Médecine Montpellier-Nîmes
Avenue Kennedy
30900 Nîmes, France
tlavabre@univ-montp1.fr
marie.martinez-lucon@umontpellier.fr

Registration fees

Diploma: From €360 to €1734 for the University, depending on the status of the student. Accommodation **NOT included.**
Indicative accomodation price in Vatel hotel (2020): €730 to be added to the University fee
Stand-alone course: €1300 (E.C.A. members) or €1400 (Non E.C.A. members); accommodation **included** on a shared double room basis. Extra fee for a single room on request.

2021 Course provisional program

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 2013.

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.

The students will have the opportunity to evaluate the course.

The **European Cytogeneticists Association** offers **two scholarships** for **the European Advanced Postgraduate Course in Classical and Molecular Cytogenetics** to candidates of excellence. The Education Committee of the E.C.A. will select the suitable candidates.

The scholarship includes registration to the course and accommodation in Vatel Hotel in a shared double room but **does not include travel costs.**

Scholarships will not be allocated to students whose registration is paid by a third party institution.

15th Goldrain Course in
Clinical Cytogenetics
August 28 to September 5, 2021

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

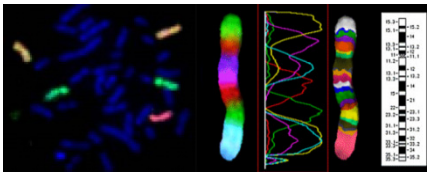
A. Schinzel (Zurich, Switzerland)

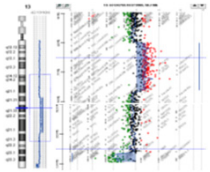
FACULTY

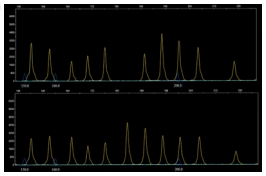
D. Bartholdi (Berne, Switzerland), A. Baumer (Zurich, Switzerland), P. Benn (Farmington CT, U.S.A.), J.M. Dupont (Paris, France), N. Kurtas (Florence, Italy), E. Klopocki (Würzburg, Germany), K. Madan (Leiden, The Netherlands), K. Miller (Hannover, Germany), R. Pfundt (Nijmegen, The Netherlands), G.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

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.







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