



RESEARCH HIGHLIGHT

Symposium summary: Epigenetic inheritance—impact for biology and society 26–28 August 2019, Zurich, Switzerland

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Abstract

The concept of epigenetic inheritance proposes a new and unconventional way to think about heredity in health and disease, at the interface between genetics and the environment. Epigenetic inheritance is a form of biological inheritance not encoded in the DNA sequence itself but mediated by epigenetic factors. Because epigenetic factors can be modulated by the environment, they can relay this information to the genome and modify its activity consequentially. If epigenetic changes induced by environmental exposure are present in the germline and persist in germ cells during development until conception, they have the potential to transfer the traces of ancestral exposure to the progeny.

This form of heredity relates to the extremely important question of nature versus nurture and how much of our own make-up is genetically or epigenetically determined, a question that remains largely unresolved. Because it questions the dominant dogma of genetics and brings a paradigm shift in sciences, it has to creating strong bridges between disciplines and provide solid causal evidence to be firmly established.

The second edition of a conference fully dedicated to epigenetic inheritance was held in August 2019 in Zurich, Switzerland. This symposium titled 'Epigenetic inheritance: impact for biology and society' (<http://www.epigenetic-inheritance-zurich.ethz.ch>), gathered experts in the field of epigenetic inheritance to discuss the concept and pertinent findings, exchange views and expertise about models and methods, and address challenges raised by this new discipline. The symposium offered a mix of invited lectures and short talks selected from abstracts, poster sessions and a workshop 'Meet the experts: Q&A'. A tour of a local omics facility the Functional Genomics Center Zurich was also offered to interested participants. Additional comments and impressions were shared by attendees on Twitter #eisz19 during and after the symposium. This summary provides an overview of the different sessions and talks and describes the main findings presented.

Key words: symposium report; epigenetic inheritance; posters; workshop; speakers

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Epidemiological Evidence and Animal Models

The first two sessions of the symposium focused on epidemiological evidence and animal models used in epigenetic inheritance studies. In the first talk, Romain Barrès (University of Copenhagen, Denmark) discussed the effects of high-fat diet (HFD) in animal models and humans. After a short description of the main effects of HFD on physiology and metabolism in rat models of obesity, Dr Barrès presented data from several human studies in which sperm of men exposed to diet-induced obesity, gastric bypass or exercise were analyzed. Differences in DNA methylation (DNAm) and alterations in small non-coding RNA content, including piRNA and tRNA could be detected. Interestingly, the most altered pathways were related to nervous system development, neurogenesis and axon guidance. These alterations linked to obesity had a 79% overlap with alterations reported in autism. Single-cell DNAm analyses by whole-genome bisulfite sequencing (WGBS) in sperm from obese and lean individuals also identified differences in Alu sequences, which are evolutionary young transposable elements. These data suggest the existence of genomic regions with high sensitivity for epigenetic variation or 'gametic hotspots' in humans. Prof. Barrès is currently leading a Gametic Epigenetics Consortium against Obesity to study the mechanisms of epigenetic variation and transmission of metabolic risk.

Michael Skinner (Washington State University, USA) continued this session with an overview of transgenerational effects of endocrine disruptors and toxicants, work that his lab pioneered and contributed the most to in the past 20 years. He described how systematic analyses of the physiological and epigenetic effects of compounds like vinclozolin and glyphosate showed that multiple generations are affected by obesity, infertility, parturition anomalies, ovary diseases, etc. In most cases, there is a dynamic cascade of epigenetic changes including differentially methylated regions (DMRs) and altered histone retention across generations that parallel symptoms transmission. These changes affect germ cells across successive stages of development including primordial germ cells (PGCs), spermatogonia, round spermatids and sperm. His latest work tested male and female grand-offspring of dichlorodiphenyltrichloroethane (DDT) and vinclozolin-exposed males that were outcrossed to F3 to generate hybrids and test for the transmission of pathological traits associated with parent-of-origin alleles. Initial results showed that some exposure-induced traits are maternally driven, while others are paternally driven in sperm, suggesting imprinting-like features. Somatic cells in gonads, such as Sertoli cells, are also affected in exposed F3 animals and have many DMRs but also altered small and long non-coding RNA and mRNA. These alterations may interfere with pyruvate production by Sertoli cells which ultimately compromises spermatogenesis and increases apoptosis. Michael Skinner concluded his talk by highlighting the necessity to identify tissue-dependent epigenetic markers of disease susceptibility and risk in humans to better understand the consequences of environmental exposure.

Expanding on the importance of studying epigenetic regulation in the human germline, Azim Surani (University of Cambridge, UK) presented an *in vitro* model based on human embryonic stem cells and induced pluripotent stem cells to assess specification of human PGCs (hPGCs) and conduct comparisons with the mouse. The *in vitro* model shares key characteristics with hPGCs from human fetuses and allowed to reveal molecular divergence with mouse PGCs. While in

humans, SOX17 and BLIMP1 are sufficient and necessary for hPGC specification and likely contribute to the initiation of epigenome programming, PRDM14 and BLIMP1 are required in mice. BLIMP1 carries SOX motifs in enhancer and promoter regions, and some of the targets of these factors involve DNAm regulators. In both species, hPGCs specification requires imprints resetting and X-reactivation which implicates mechanisms of DNA demethylation through TET1/TET2 enzymes. Bisulfite sequencing showed that some young hominoid-specific loci, primarily young transposable elements, such as LTR12C, associated with neuronal and metabolic genes, evade reprogramming, suggesting that these loci may play a role in the transmission of epigenetic information. Such resistant loci have not been found in the mouse, suggesting a human-specific feature. A key approach in this research is the use of organoids and germinoids from *in vitro* cultured gonadal soma precursors and nascent PGC-like cells to better recapitulate tissue environment.

To expand on the significance of transgenerational inheritance across the animal kingdom, Patrick Allard (University of California, Los Angeles, CA, USA) presented how germ cells in *Caenorhabditis elegans* are affected by environmental exposure to bisphenol A (BPA). Ancestral BPA exposure in *C.elegans* causes reproductive dysfunctions in the 3rd generation, resulting in embryonic lethality and germline apoptosis. Molecular analyses by immunofluorescence imaging and ChIP-Seq showed a decrease and redistribution of the repressive histone marks H3K9me3 and H3K27me3 in the germline. Subsequent RNAi experiments targeting the histone demethylases *jmjd-2* and *jmjd-3/utx-1* rescued reproductive dysfunctions, implicating their role in sustaining germline toxicity by BPA across five generations. In a heterozygous or homozygous knockout model of Spo-11, an initiator of meiotic double-strand breaks with impaired sensing of chromatin dynamics, specimens showed increased germline apoptosis. Thus, BPA can trigger chromosome dynamics and recombination in F3, potentially altering chromosome interactions contributing to transgenerational inheritance.

This first session was concluded with a talk by Jill Escher (San Jose, CA, USA), founder of the philanthropic Escher Fund for Autism and mother of two children with non-verbal autism. Ms Escher presented her own touching experience with this neurodevelopmental disorder and described personal accounts of other affected families. By investigating her family's medical history, she discovered repeated exposure of her mother to high doses of synthetic steroids during pregnancy. Other families with autistic children similarly reported parental exposure to high doses of volatile general anesthesia (GA) gases during medical procedures at a young age. GA gases are known to be powerful neurotoxic modulators of chromatin remodeling in somatic cells, and gestational exposure impairs learning in mice. So far, only a few studies have explored the potential inter- and transgenerational effects of these compounds, despite the possibility that they also diffuse into the germline. Jill Escher presented the activities of her foundation to educate the public on germline vulnerabilities, advocating for policy changes in health agencies, and once more emphasizing her support for research on germline perturbations.

The second session of the symposium was opened by Larry A. Feig (Tufts University, USA) who presented evidence for a link between exposure and miRNAs in the germline in mice and men. Using a mouse model of social instability induced by rearranging objects in the cage, he showed altered LTP and anxious behaviors in male mice, symptoms that could be rescued by

exposure to environmental enrichment later in life. This rescue seems to be mediated by a specific miRNA, miR-49-3p. When analyzing early embryos and adult offspring generated from the stressed fathers, alterations in the expression of several members of the miR-34/449 family could be detected. Interestingly, the same family of miRNAs was found to be altered in sperm samples collected from adult men with a history of childhood trauma evaluated with the Adverse Childhood Experiences questionnaire. This research shows that, although there are important differences in germline development and morphology between mice and men, common factors such as specific miRNAs appear to be similarly affected and represent, therefore, conserved markers of childhood trauma, possibly linked to an increased risk for psychological disorders.

In the second talk of the session, Anne Ferguson-Smith (University of Cambridge, UK) discussed the importance of genome repeats, such as endogenous retroviruses (ERVs), in modulating inheritance. She presented data on two classical mouse models of epigenetic inheritance, Agouti viable yellow (A^{vy}) and axin fused ($Axin^{Fu}$). In these mice, an intracisternal A particle (IAP), a class of murine ERVs, is inserted in the vicinity of the *agouti* or *axin* gene, respectively, leading to different levels of DNAm, gene expression and phenotypic variation between individuals that is transmitted across generations. Building on this work, her team conducted a genome-wide screen for metastable epialleles at ERVs using mouse strain-specific datasets as part of the BLUEPRINT reference epigenome project. This identified an enrichment of the methylation-sensitive CCCTC-binding factor CTCF at variably methylated IAPs, suggesting its contribution to the establishment and maintenance of metastable epialleles across generations. Her team also explored the sensitivity of metastable epialleles to different factors and found that, while defects in folate metabolism modulate methylation level in these regions, other exposures like BPA and aging do not.

The last speaker of the second session was Ali Jawaid from Isabelle Mansuy's lab (University and ETH Zurich, Switzerland). He showed that physiological and epigenetic alterations observed in a mouse model of postnatal trauma (unpredictable maternal separation combined with unpredictable maternal stress, MSUS) could be comparably observed in children exposed to paternal loss and maternal separation (PLMS). PLMS children had depressive symptoms and reduced level of serum high-density lipoproteins (HDL), similarly to MSUS mice. Further, a comparable alteration in HDL-associated miRNAs (miR-16, miR-29a, and miR-375) was also observed in serum and saliva from PLMS children and MSUS serum. To assess the relevance of these miRNAs for epigenetic inheritance, spermatogonial-like cells (GC-1) in culture were treated with serum from MSUS mice. This treatment led to an increase in the expression of miR-375, an effect that was reversed by siRNA-mediated knockdown of the HDL receptor, SCARB1. Together, these results suggest that circulating miRNAs are potential markers of trauma exposure in mice and humans, and that serum carries signals of exposure that can perturb miRNA expression in germ cells.

The session was followed by a video talk by Andrew Pospisilik (Van Andel Institute, Grand Rapids, USA) in which he discussed the importance of the epigenome in shaping phenotypes in humans and animals by comparing genetically identical twins. Phenotypic variability also viewed as phenotypic bi-potential or polyphenism, is largely due to the epigenome and its action on the genome. Using RELACS (restriction enzyme-based labeling of chromatin *in situ*), a method for

high-throughput chromatin immunoprecipitation based on bar-coding, the epigenetic landscape of obese (Nnat+ giant) or lean mice could be examined. Changes in enhancer landscape were detected, which may be associated with metabolism-mediated polyphenism.

Gerlinde Metz (University of Lethbridge, Australia) then presented data on a mouse model of stress during gestation with exposure of either, every generation or only the initial generation to assess the effects of cumulative versus single exposure. Fifty percent of the males from the 4th generation suffered from renal failure and 20% developed tumors and respiratory disorders. In aged mice exposed at each generation, miR-21 expression was decreased when compared with young mice and their metabolic profiles differed from those of mice exposed only at the initial generation. Some of these effects could be reversed by environmental enrichment. In humans, alleviation of symptoms can be similarly achieved by providing social support. In women, support is determinant for behavior and is reflected in their physiology, with telomere length being higher in individuals living in a socially supportive environment.

The last talk of the day was a short presentation by Rose Schrott from the lab of Susan Murphy (Duke University, USA) who showed data on the effects of drugs of abuse on the epigenome. DNAm analyses by reduced representation bisulfite sequencing conducted in semen and urine from 12 cannabis users and 12 non-users identified DMRs, 78% of which were hypomethylated. The imprinted gene, DLG-associated protein 2 was one of the loci affected. Tetrahydrocannabinol (THC) injection in rats followed by DNAm analyses in sperm could confirm hypomethylation of DGLA2 locus.

Mechanisms of Epigenetic Inheritance

The second day of the symposium discussed potential mechanisms of epigenetic inheritance. Qi Chen (University of California, USA) highlighted the importance of a particular class of small non-coding RNAs enriched in sperm, tRNA-derived small RNAs (tsRNAs), in sperm-mediated intergenerational inheritance. He suggested the existence of an RNA 'code' in sperm, in which the combination of RNA sequences and RNA modifications are essential determinants of the transmission of phenotypes. He presented new data on HeLa cells, showing that a specific tsRNA can hijack the ribosome machinery and disturb mRNA loading, particularly onto polysomes, with little effect on the actual mRNA landscape of the cells.

Victor Corces (Emory University, USA) then showed how a 'single hit' BPA exposure *in utero* at E13.5 in mice, a time when the genome goes through demethylation, is enough to cause obesity in the offspring up to the 5th generation. He highlighted the importance of transcription factors in the initiation of an epigenetic inheritance cascade and showed evidence from ATAC-Seq and ChIP-Seq data that such factors are important. Contrary to the general belief, the sperm epigenome is equipped with all components of the transcriptional machinery, at regions which escape histone-to-protamine exchange. Nucleosomes are still present in enhancers and are enriched in known transcription factors that recruit the widely expressed transcriptional regulator CTCF, which in turn leads to long-range interactions. These findings were validated by chromosome conformation capture (HiC). Additionally, by using HiC and WGBS, new CTCF sites could be identified in the sperm of F1-F3 obese mice compared to control animals, which correlated with changes in DNAm at these sites. Dr Corces concluded by hypothesizing that these new BPA-induced CTCF-

binding sites may represent enhancers that are active in early embryonic development or in target tissues to alter gene expression and pass on the acquired phenotypes.

Building on previous findings on the role of RNAs in epigenetic inheritance, Upasna Sharma (University of California, Santa Cruz, CA, USA) presented evidence for intergenerational transmission by sperm small RNAs in mice. Paternal protein restriction diet results in offspring with altered cholesterol and lipid biosynthesis. To study the mechanisms of transmission, she focused on the role of non-coding RNAs, specifically tRNA fragments (tRFs), after not observing any change in the methylome or chromatin states in sperm. tRFs are abundant in somatic caput and cauda epididymis epithelium, and their proximodistal distribution in the epididymis is recapitulated in sperm. A transit of tRFs from somatic tissues to sperm by epididymis-derived extracellular vesicles (epididymosomes) was shown through chemo-genetic tracking of small RNAs and comparison of sperm and epididymosome transcriptomes. Sperm small RNAs responded to low protein diet with an increased amount of 5' fragments of glycine transfer RNAs (tRF-GlyGCC). Further, injection of antisense tRF-GlyGCC repressed genes associated with the endogenous retroelement MERVL both in pre-implantation embryos and embryonic stem cells. MERVL regulates totipotent states during early embryonic development, making it a potential candidate to study RNA-mediated soma-germline communication and its consequences for offspring development.

In the following short talk, Tracie Baker (Wayne State University, USA) showcased Zebrafish as a model to study the heritable effects of endocrine-disrupting chemicals. Exposure to dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) in early life induces reproductive abnormalities in adult animals that persist for multiple generations and are primarily transmitted via the male germline. Delayed spermiation in both exposed father and non-exposed offspring and altered testicular transcriptome, steroidogenesis, lipid and xenobiotic metabolism were observed in all generations. WGBS in dioxin-exposed paternal testis found DMRs associated with altered gene expression in subsequent generations. Many of the identified genes are involved in epigenetic modifications and reproductive functions. WGBS on F1/F2 testis also overlapped with observed gene expression changes, suggesting that DNAm is an important mediator of epigenetic inheritance in zebrafish.

Ramji K. Bhandari (University of North Carolina at Greensboro, USA) concluding the fourth session of the day with a short talk on DNA de- and re-methylation in PGCs of Medaka fish (*Oryzias latipes*). PGCs undergo a two-step global demethylation during early embryonic development, except at CpG island promoters which remain hypomethylated. Similar to human and mouse, DNAm is reinstated by *de novo* methyltransferases at 25 days post-fertilization. Exposure to BPA induces reproductive defects in subsequent generations and epimutations that are not erased by PGCs reprogramming. Additional *de novo* epimutations were even observed during gametogenesis. Only a few of the epimutations were transmitted to sperm in adulthood.

The 5th session was opened by Alexander Meissner (Max Planck Institute for Molecular Genetics, Germany), whose talk focused on the role of epigenetic regulators in early development. He introduced Polycomb repressive complex as a classical example of epigenetic regulators of early embryogenesis, highlighting how perturbation of this complex leads to a loss of spatiotemporal control of gene expression due to alterations in DNAm. He then introduced the zygotic sgRNA/Cas9-based system developed in his lab, with which many embryos can be

assayed simultaneously at a single-cell resolution. By assaying over 84 200 cells from 50 embryos with 712 markers genes and at embryonic day 6.5 and 8.5, a lineage tree could be reconstituted, in which rare populations of cells, such as PGCs, could be detected. Using this experimental pipeline, the role of specific members of the Polycomb complex family, such as EED, in lineage development was assessed. EED knock-out embryos have delayed development and strong overproduction of PGCs in a lineage-specific manner. This experimental pipeline provides an efficient high-throughput and unbiased way to study how cellular diversity emerges from a single-genome *in vivo*.

The second speaker of the session was Antoine Peters (Friedrich Miescher Institute, Basel, Switzerland) who talked about nucleosome-dependent epigenetic information in father-to-embryo transmission. To understand how chromatin states contribute to offspring fitness, his team used a micromanipulation assay in which nuclei of immature spermatids that did not undergo histone-to-protamine transition are injected into oocytes (ROSI). ROSI embryos have impaired development, altered gene expression and an overall higher level of DNAm. They also have aberrant histone marks deposition with impaired establishment of H3K4me3 but not H3K36me3. Compared to intracytoplasmic sperm injection, ROSI alters RNA profiles more and leads to a loss of bi-allelic expression of many genes which are then expressed only from the maternal allele. A series of RNA-Seq and ChIP-Seq experiments in hybrid animals revealed the parental-specific allelic role of H3K27me3 and Polycomb protein PRC2 in the transfer of marks to the embryo and in embryogenesis. Overall, the results underline the importance of histone-to-protamine exchange in the developing sperm for embryo fitness and development.

Following up on the mechanisms of genome regulation, Lucia Daxinger (Leiden University Medical Center, NL, USA) presented a model of N-ethyl-N-nitrosourea treatment in mice that identified variegation genes called MommeD (Modifiers of murine metastable epiallele Dominant) involved in transposon repression. MommeD has several components including Setdb1 alleles (Su(var) and E(var)) required for heterochromatin formation and gene silencing. They are important for silencing of the young IAP element ERVK. Together with Trim28, Setdb1 silences repeat elements and regulates the agouti gene. Setdb1 haploinsufficiency is associated with paternal effects and induces over 1200 DMRs specifically in sperm. The relevance of such hypomethylation in the paternal genome is, however, still unclear.

In a short talk, Valérie Grandjean (University Sophia Antipolis, Nice, FR, USA) then showed how HFD affects the progeny, by comparing metabolic phenotypes in animals treated for 1 or 5 generations (HFD1 vs HFD5). In both, there is increased fat and body weight, cholesterol and leptin. However, when HFD1 or HFD5 animals are crossed with control animals, the metabolic phenotypes persist beyond F3 in the progeny of HFD5 but disappear after two generations in HFD1. Sperm RNA microinjection in fertilized oocytes recapitulates metabolic phenotypes however not persistently but for not more than two generations, suggesting that RNA is involved in the initiation but likely not the stability over generations of phenotypes.

The afternoon ended with six flash talks selected from abstracts that covered various subjects ranging from the role of low-grade chronic inflammation in epigenetic inheritance of paternal obesity by Stine Thorhauge Bak, (Aarhus University, Denmark), long-term and transgenerational neurobehavioral effects of the insecticide permethrin in zebrafish by Mélanie Blanc (Örebro University, Sweden), ethical aspects of the vulnerability of the germline by Anne Le Goff (University of California

Los Angeles, USA), molecular characterization of transgenerational epigenetic phenomena after genistein exposure in quail by Frédérique Pitel (Université de Toulouse, France), effects of adolescent THC exposure on sperm microRNA by Gregory Rompala (Icahn School of Medicine at Mount Sinai, USA), and epigenetic inheritance of cardiac regenerative capacity in zebrafish by Andres Sanz-Morejon (University of Bern, Switzerland).

Conceptual Challenges and Computational Aspects

The last day of the symposium discussed conceptual challenges and computational aspects in epigenetic inheritance. Corrado Spadafora (National Research Council, Rome, Italy) opened the session with findings on the role of LINE-1 expression in the genesis and assimilation of epigenetic variation. Based on findings that exogenous DNA and human exosomes are taken up and internalized by murine spermatozoa, he investigated them as a tool for the production of genetically modified animals. Retrotranscribed, spliced eGFP cDNA was sexually transferred to the offspring and had mosaic expression in several somatic tissues. Based on the observation that tumor cells release vesicles containing DNA and RNA fragments, eGFP-RNA containing human melanoma cells were xenografted in athymic mice and resulted in eGFP-RNA in circulating vesicles and spermatozoa. eGFP-RNA was partially transmitted to the progeny and expressed sporadically in various tissues due to non-integrated episomes. For DNA, exogenous DNA binding to sperm, usually prevented by seminal fluid, was shown to repress nuclear functions and involve LINE-1-encoded ORF2p, an endogenous reverse transcriptase and endonuclease, which is scaffold-associated to spermatozoa and expressed in sperm and early embryos. These findings suggest that LINE-1 ORF2p can modulate chromatin organization upon stimuli, and affect cell fate determination leading to the emergence of novel traits.

Switching from conceptual to computational challenges in epigenomic studies, Mark Robinson (University of Zurich, Switzerland) discussed challenges and solutions arising from genome-wide and allele-specific methylation analysis of bisulfite sequencing data. He described available technologies to assess DNAm with their advantages and disadvantages, highlighting current issues, specifically for single-cell analysis. This was followed by a conceptual introduction to 'bump-hunting' in bisulfite sequencing data to identify DMRs. This widely used type of analysis lacks allele-specific methylation (ASM) information which is a limitation. His group developed an effective approach to screen for altered ASM using existing computational methods and clustering positions with persistent changes into regions (differential AMEs). The tool, DAMEfinder, is available as an R package from GitHub. Using DAMEfinder, numerous DAMEs were identified in a colorectal cancer dataset, highlighting its potential utility for investigating the role of AME in epigenetic inheritance.

Impact on Society and Evolution

The last session of the symposium discussed epigenetic inheritance in a broader context in relation to its societal role. Michael Penkler (Technical University of Munich, Germany) highlighted the importance of life sciences for shaping the society and for understanding health, happiness and life itself. He framed the importance of epigenetics in creating a 'biosocial model of health' which can avoid misbeliefs leading to racism and

sexism as those raised by genetic determinism. He drew attention to the creation of forms of epigenetic determinism that could be brought by incorrect framing and reporting of epigenetic findings. A relevant example refers to studies showing that certain populations are predisposed to obesity due to poor social context that is perpetuated. To avoid such deviations, researchers need to communicate their findings clearly without over-interpretating their implications and by emphasizing the plasticity of epigenetic marks to avoid the notion of epigenetic fate. The higher complexity of social environments in humans compared to experimental animals should always be considered when bringing such findings to the lay public.

The symposium was concluded by a talk on nature versus nurture generously given by Marcus Pembrey (University College London, UK) on short notice to replace an absent speaker. Dr Pembrey reviewed the seminal work he did with Lars Olov Bygren on the impact of food availability on health and mortality of across generations in the Överkalix study. This was one of the first studies to introduce the idea of a critical period in germline development, during which germ cells are particularly sensitive to environmental insults. These stunning results were recently replicated by an Uppsala Multigeneration Study, a three-generation cohort 40 times larger than the Överkalix cohort. This study confirmed that paternal grandfather's food access in pre-puberty predicts mortality in male but not female grandchildren. Further to these studies, epidemiological evidence for the importance of environmental factors in increasing the risk for disease is also now established. Large cohorts, such as the Avon Longitudinal Study of Parents and Children (ALSPAC), showed that granddaughters have an increased risk for autism if the maternal grandmother smoked during pregnancy. Such extensive work is solid evidence that early life experiences of past generations contribute to developmental variation, independent of social transmission.

Additional Symposium Activities

Poster Sessions

In addition to oral presentations, over 50 posters were presented during two sessions. A poster prize was awarded at the end of the symposium. The winning poster 'Effect of maternal obesity and pre-conceptional weight loss on fetoplacental growth and offspring health in mice: expression of epigenetic modifiers at the interface with metabolism' was presented by Anne Gabory (French National Institute for Agricultural Research, Paris, France).

Workshop 'Meet the Experts: Questions and Answers'

The last afternoon of the symposium, a Q&A workshop for registered participants was organized at the University of Zurich for an interactive discussion with four of the speakers: Victor Corces, Anne Ferguson-Smith, Upasna Sharma and Michael Skinner. Topics on the questions of study design in epigenetic inheritance, the importance of animal models and timing of exposure, data analysis and their complications, animal welfare issues, ethical challenges, etc. were discussed. The workshop was lively and constructive, with open and collegial exchanges.

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job preparing the symposium and who took care of every detail during the event, and to Fabio Sias who helped with organization, fund raising, accounting and for the design of the web page, brochure and conference poster. We thank Anina Eglin for help with the website. This summary is a short account of the symposium aimed to reflect major topics discussed. It does not include references associated with topics or speakers. Readers interested in the bibliography are referred to PubMed or the speakers home pages.

Conflict of interest statement. None declared.