

CORRESPONDENCE

Open Access

Relationship between genome and epigenome - challenges and requirements for future research

Geneviève Almouzni¹, Lucia Altucci², Bruno Amati^{3,4}, Neil Ashley⁵, David Baulcombe⁶, Nathalie Beaujean⁷, Christoph Bock⁸, Erik Bongcam-Rudloff⁹, Jean Bousquet¹⁰, Sigurd Braun¹¹, Brigitte Bressac-de Paillerets¹², Marion Bussemakers¹³, Laura Clarke¹⁴, Ana Conesa¹⁵, Xavier Estivill¹⁶, Alireza Fazeli¹⁷, Neža Grgurević¹⁸, Ivo Gut¹⁹, Bastiaan T Heijmans²⁰, Sylvie Hermouet²¹, Jeanine Houwing-Duistermaat²⁰, Ilaria Iacobucci²², Janez Ilaš¹⁸, Raju Kandimalla²³, Susanne Krauss-Etschmann²⁴, Paul Lasko²⁵, Sören Lehmann²⁶, Anders Lindroth²⁷, Gregor Majdic¹⁸, Eric Marcotte²⁸, Giovanni Martinelli²², Nadine Martinet²⁹, Eric Meyer³⁰, Cristina Miceli³¹, Ken Mills³², Maria Moreno-Villanueva³³, Ghislaine Morvan³⁴, Dörthe Nickel¹, Beate Niesler³⁵, Mariusz Nowacki³⁶, Jacek Nowak³⁷, Stephan Ossowski¹⁶, Mattia Pelizzola³, Roland Pochet³⁸, Uroš Potočnik³⁹, Magdalena Radwanska⁴⁰, Jeroen Raes^{41,42,43}, Magnus Rattray⁴⁴, Mark D Robinson⁴⁵, Bernard Roelen⁴⁶, Sascha Sauer⁴⁷, Dieter Schinzer⁴⁸, Eline Slagboom²⁰, Tim Spector⁴⁹, Hendrik G Stunnenberg¹³, Ekaterini Tiligada⁵⁰, Maria-Elena Torres-Padilla⁵¹, Roula Tsonaka²⁰, Ann Van Soom⁵², Melita Vidaković⁵³ and Martin Widschwendter^{23*}

Abstract

Understanding the links between genetic, epigenetic and non-genetic factors throughout the lifespan and across generations and their role in disease susceptibility and disease progression offer entirely new avenues and solutions to major problems in our society. To overcome the numerous challenges, we have come up with nine major conclusions to set the vision for future policies and research agendas at the European level.

Keywords: Genome, Epigenome, Microbiome, Environment

The Human Genome Project was completed in 2003 and led to the identification of all human genes. However, the fundamental question that remains unanswered is how do genes function and how are they regulated? Epigenetics may provide many crucial answers. Epigenetics encompasses all processes that lead to heritable changes in gene expression as cells divide, while epigenomics refers to analysis of epigenetic changes across the whole genome in a cell or entire organism [1,2]. Typically, in a multi-cellular organism, each cell type will be characterised by the same genome, along with as many epigenomes as there are distinct cell types. Epigenetics combined with genetics is a rapidly growing field

with promising implications for health and disease because many common diseases result from the interplay between the genetic make-up of individuals and the environmental factors to which they are exposed [3]. Currently, however, there is limited knowledge on the combined role of genetic and non-genetic factors thus hampering personalised medicine. A conceptual goal is to identify a cascade of genetic/epigenetic factors that underlie the development of chronic diseases. For example, a number of candidate genes have been associated with irritable bowel syndrome, but little research has examined the mechanistic impact on epigenetics [4]. Likewise, even though environmental factors such as stress, life-style, nutrition, air pollution and infections lead to allergies, the genetic and epigenetic contributions are not well understood [5,6].

* Correspondence: m.widschwendter@ucl.ac.uk

²³Department of Women's Cancer, UCL Elizabeth Garrett Anderson Institute for Women's Health, University College London, 74 Huntley Street, London WC1E 6AU, UK

Full list of author information is available at the end of the article

The reversible nature of epigenetic changes has attracted interest in exploring their potential as targets for the development of novel and more individualised medical treatments.

Europe, with additional effort from Member States, is showing leadership in the field of epigenetics and epigenomics and more than €200 Million were invested in research projects and infrastructure through Framework Programmes 6 and 7 (Table 1). For example, the BLUE-PRINT project is focusing on distinct types of haematopoietic cells from healthy individuals and their malignant leukaemic counterparts with the aim of generating at least 100 reference epigenomes and studying them to advance and exploit knowledge of the underlying biological processes and mechanisms in health and disease [7].

With this aim, the European Commission's Directorate General for Research and Innovation (DG RTD) and Cooperation in Science and Technology (COST) organised a joint strategic workshop "Relationship between genome and epigenome". The workshop addressed the links between genetic, epigenetic and non-genetic factors throughout the lifespan and across generations, their role in health and disease including disease susceptibility and progression, and the associated challenges of data handling/storage and interpretation. The outcomes of the workshop will inform future research priorities and are summarised in Figure 1.

Major issues for future research include the following points:

- 1) In order to identify good surrogate epigenomic marks that would corroborate the influence of environmental exposure on the epigenome (including periconception environment, lifestyle, reproductive factors, microbiome etc.) and allow for the prediction and prevention of the development of chronic diseases, detailed research in humans and model organisms and careful sample acquisition (more tissue and cell specific epigenomes, time series, epigenomic variation etc.) is required. Parental conditions before, during and after conception (periconception period) may induce epigenetic changes in gametes and embryos [8]. Such changes may adversely affect the offsprings' future health, development, productivity and fertility [3]. The connection between the perinatal factors and later outcomes in life was illustrated by describing the relationship between birth weight and incidence of diseases in older age such as cardiac disease [9]. Studies of historical famines already yielded key evidence for the association of early life environmental exposure and differences in the adult epigenome [10]. Like the field itself, these studies are in their infancy and ongoing genome-wide studies

are expected to result in the identification of epigenetic alterations that are triggered by non-genetic factors leading to particular disease phenotype. The microbiome has strong parallels with the epigenome in that it is complex and may reflect environmental exposure (of the host from which the microbiome was obtained) and might also impact on how non-genetic factors lead to epigenetic changes (i.e. by modulating hormonal levels [11]). Accumulating data demonstrate a crucial impact of the microbiome on health and disease.

- 2) With the increase of chronological age, an increase of gene promoter methylation paralleled by global hypomethylation across the genome can be observed. This is remarkably similar to the DNA methylation changes seen in cancer [12] suggesting that similar underlying mechanisms may be involved. More age-stratified data are required to understand the relationship between the epigenome, the microbiome and the environment during the course of life and its impact on allergy and chronic diseases.
- 3) The genome-epigenome interaction is also crucially involved in the biology, character and extent of an established disease and not just in disease development. This is reflected for instance in the role that the chromatin and epigenome plays in DNA damage repair [13]. Epigenetic markers allow for the prediction of the natural behaviour of a disease (prognostic markers) and the likelihood of responding to a specific treatment (predictive markers). Testing and validating these markers in clinical trials and benchmarking against established strategies will be crucial in order to improve disease outcome.
- 4) Studies of the effects and the mechanistic impact of epigenetic drugs (drugs that can effect epigenomic modifications) and their impact on the genome, development and validation of new epigenetic drug candidates and rational design of combination therapies of genetic and epigenetic drugs should be encouraged to cure diseases or at least improve the efficacy of current treatment modalities as recently demonstrated [14]. Structural and functional information from chromatin and DNA modifying enzymes and the development of small molecules active on specific epi-targets are crucial for the development of new therapeutic approaches. Epigenetic therapy tries to reverse such aberrations following disruption of the epigenetic signal balance through the use of both natural compounds and synthetic molecules [15]. For instance, pharmacological inhibition of EZH2 (enhancer of zeste homolog 2, a Histone-lysine N-methyltransferase) was recently shown as a promising new tool with which to treat cancer [16]. Many clinical trials are already ongoing, and epigenetic therapy (azacytidine) has recently been

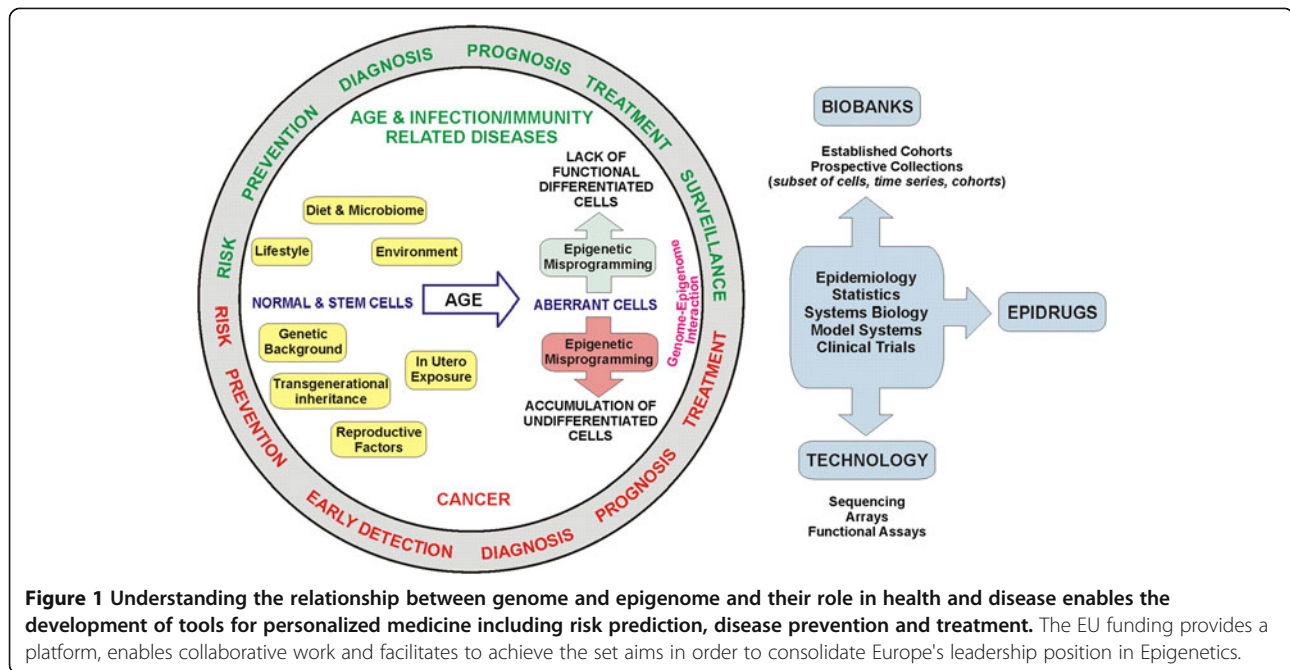
Table 1 FP7 Cooperation projects and network of excellence that were represented at the workshop

Acronym	Project description	Website
ATLAS	Development of Laser-Based Technologies and Prototype Instruments for Genome-Wide Chromatin ImmunoPrecipitation Analyses	http://www.atlas-eu.com/
BLUEPRINT	A BLUEPRINT of haematopoietic Epigenomes	http://www.blueprint-epigenome.eu/
CANCERDIP	The use of Methylated DNA Immunoprecipitation MeDIP in cancer for better clinical management	http://www.cancerdip.eu/
CELLOMATIC	High Throughput Systematic Single Cell Genomics using Micro/Nano-Fluidic Chips for Extracting, Pre-analysing, Selecting and Preparing Sequence-ready DNA	http://www.cellomatic.eu/
CURELUNG	Epigenetic therapeutic strategies for improving lung cancer diagnosis	http://www.curelung.eu/
ELIXIR	European Life-Science Infrastructure	http://www.elixir-europe.org/about
EPIFEMCARE	Epigenetics for Female Personalised Cancer Care	http://www.epifemcare.eu/
EPIGENESYS	Epigenetics towards systems biology	http://www.epigenesys.eu/
ESGI	European Sequencing and Genotyping Infrastructure	http://www.esgi-infrastructure.eu/
EUROBATS	Identifying biomarkers of ageing using whole transcriptome sequencing	http://www.eurobats.eu/
GENCODYS	Genetic and Epigenetic Networks in Cognitive Dysfunction	http://www.gencodys.eu/index.php
GENICA	Genomic instability in cancer and pre-cancer	http://genica.unige.ch/
GEUVADIS	Genetic European Variation in Disease	http://www.geuvas.org/
IDEAL	Integrated research on developmental determinants of Aging and Longevity	http://www.ideal-ageing.eu/
MARK-AGE	European study to establish biomarkers for human aging	http://www.mark-age.eu/
MEDALL	Mechanisms of the Development of ALLergy	http://medall-fp7.eu/
MODHEP	An integrative genomic-epigenomic approach to liver cancer	http://www.modhep.eu/
NGS-PTL	Next Generation Sequencing platform for targeted Personalized Therapy of Leukemia	http://www.ngs-ptl.com/
RADIANT	Rapid development and distribution of statistical tools for high-throughput sequencing data	http://www.radiant-project.eu/
READNA	REvolutionary Approaches and Devices for Nucleic Acid Analysis	http://www.cng.fr/READNA/
SETTREND	Schistosoma epigenetics: targets, regulation, new drugs	http://settrend.cebio.org/
SIROCCO	Silencing RNAs: organisers and coordinators of complexity in eukaryotic organisms	http://www.sirocco-project.eu/
SWITCHBOX	Homeostatic mechanisms to facilitate maintenance of health from early life through to aging	http://www.switchbox-online.eu/
International consortia		
IHEC	International Human Epigenome Consortium	http://www.ihec-epigenomes.org/

Table 1 FP7 Cooperation projects and network of excellence that were represented at the workshop (Continued)

Cost actions

TD0905 Epigenetics from bench to bedside	http://www.cost.eu/domains_actions/cmst/Actions/TD0905
COST- FA1201– Epigenetics and periconception environment	http://www.cost.eu/domains_actions/fa/Actions/FA1201
COST-BM– 1201 Developmental origins of chronic lung diseases	http://www.cost.eu/domains_actions/bmbs/Actions/BM1201
COST- BM1102 Ciliates as model systems to study genome evolution, mechanisms of non-Mendelian inheritance, and their roles in environmental adaptation	http://www.cost.eu/domains_actions/bmbs/Actions/BM1102
COST Action BM1106 'The Genes in Irritable Bowel Syndrome Research Network Europe (GENIEUR)	http://www.cost.eu/domains_actions/bmbs/Actions/BM1106
COST-BM1007 – Mast cells and basophils – targets for innovative therapies	http://www.cost.eu/domains_actions/bmbs/Actions/BM1007
BM1006 Next Generation Sequencing Data Analysis network (SeqAhead)	http://www.cost.eu/domains_actions/bmbs/Actions/BM1006
BM0806 - Recent advances in histamine receptor H4R research	http://www.cost.eu/domains_actions/bmbs/Actions/BM0806
BM0801 Translating Genomic and epigenetic Studies of MDS and AML (EUGESMA)	http://www.cost.eu/domains_actions/bmbs/Actions/BM0801



approved by the United States Food and Drug Administration (US FDA) for use in the treatment of Myelodysplastic Syndrome (MDS) and Primary Cutaneous T-cell Lymphoma (CTCL) [17].

- 5) Studies to identify functional relationships between epigenetics and genetics require analysis of ex vivo samples of primary cells, and therefore the sampling, sorting and analytical procedures need to be optimised and adapted. Cell heterogeneity (variation among cells) is a challenge in gaining a thorough understanding of genome status, gene expression and the role of underlying epigenetic mechanisms. This is true for many cellular processes, such as genome remodeling during reprogramming or the conversion of somatic cells to pluripotent cells. Therefore collecting the most appropriate samples in order to address a specific set of questions and miniaturization of technologies for the analyses of single cells [18,19] is crucial.
- 6) Epigenomic and genomic data sets are complex and multi-dimensional, and their interpretation requires the further development of data analysis tools/software. A large amount of data has already been acquired and is highly multidimensional and multi-modal; therefore it is the analysis that remains the challenge. DNA and chromatin exist in a 3D space. Transcriptome data are complex: all transcripts, including non-coding (nc) RNAs, overlap other transcripts and quantification is not trivial. Performing data analysis by integrating data from different repositories (some of which are difficult to find) is problematic because of the different methodologies

used to acquire the data sets [20]. There is a need to establish robust benchmarks for data analysis for the comparison of different analytical approaches/software.

- 7) Integrating the findings from -omics research into clinical practice is one of the major challenges of the future. Systems biology approaches are advantageous in providing predictive models of associations between epigenomic/genomic data and phenotypes offering an entry point for assays into functional relationships. Understanding the functional/mechanistic role of epigenetic marks is highly desirable, but that in many cases it may be difficult to directly obtain such insight. Systems biological approaches could identify predictive models from multi-modal data to support associations that can then be tested in functional models.
- 8) Improved collaborations should be fostered by the establishment and harmonization of standard operating procedures for sample processing, data acquisition and formatting; and by the development of software that is user-friendly for the non-specialist as well as facilitating an Open Access policy to allow free data sharing and automatic mining of publications. Current European effort should be aligned with those of the International Human Epigenome Consortium (<http://www.ihec-epigenomes.org/>) coordinating epigenome mapping and characterisation worldwide to avoid redundant research effort, to implement high data quality standards, to coordinate data storage, management and analysis and to provide free access to the epigenomes produced.

9) European Union (EU) consortia and COST Actions have tremendously shaped and consolidated Europe's leadership position in Epigenetics and can provide indispensable means for young researchers to become principal investigators and future European leaders by integrating them into networks of experienced scientists/clinicians. EC funding schemes should devote further effort to principal investigators career development.

The European Union is currently funding over 300 epigenetics projects (a High Impact Project, Collaborative Projects, Networks of Excellence, ERC (European Research Council) Starting Grants, ERC Advanced Grants, Marie Curie Actions) with a total contribution of more than €200 Million.

Abbreviations

EC-COST: European Commission's Cooperation in Science and Technology; DG RTD: European Commission's Directorate General for Research and Innovation; DNA: Deoxyribonucleic acid; EZH2: Enhancer of zeste homolog 2; US FDA: United States Food and Drug Administration; MDS: Myelodysplastic Syndrome; CTCL: Primary Cutaneous T-cell Lymphoma; nc: Non-coding; RNAs: Ribonucleic acids; EU: European Union; ERC: European Research Council.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

All authors, GA, LA, BA, NA, DB, NB, CB, EB-R, JB, SB, BB-deP, MB, LC, AC, XE, AF, NG, IG, BTH, SH, JH-D, II, JI, RK, SK-E, PL, SL, AL, GM, EM, GM, NM, EM, CM, KM, MM-V, GM, DN, BN, MN, JN, SO,MP, RP, UP, MR, JR, MR, MDR, BR, SS, DS, ES, TS, HGS, ET, M-ET-P, RT, AVS, MV and MW, contributed to this report equally as members of the workshop. All authors read and approved the final manuscript.

Author details

¹Institut Curie – Research Center, UMR3664 CNRS/IC, 26 rue d'Ulm, Paris cedex 05 F-75248, France. ²Seconda Università degli Studi di Napoli, Naples, IT, Italy. ³Istituto Italiano di Tecnologia (IIT), Milan, IT, Italy. ⁴Istituto Europeo di Oncologia (IEO), Milan, IT, Italy. ⁵University of Oxford, Oxford, UK. ⁶Cambridge University, Cambridge, UK. ⁷INRA, UMR 1198 Biologie du Développement et Reproduction, Jouy-en-Josas, FR F-78350, France. ⁸CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, AT, Austria. ⁹Swedish University of Agricultural Sciences, Uppsala, SE, Sweden. ¹⁰University of Montpellier, Montpellier, FR, France. ¹¹Ludwig Maximilians University of Munich, Munich, DE, Germany. ¹²Gustave-Roussy, Villejuif, FR, France. ¹³Radboud University Nijmegen, Nijmegen, NL, Netherlands. ¹⁴European Molecular Biology Laboratory, European Bioinformatics Institute, Hinxton, Cambridge, UK. ¹⁵Centro de Investigación Príncipe Felipe, Valencia, ES, Spain. ¹⁶Centre for Genomic Regulation (CRG), Barcelona, Spain and Universitat Pompeu Fabra (UPF), Barcelona, Spain. ¹⁷University of Sheffield, Sheffield, UK. ¹⁸Center for Animal Genomics, Institute of physiology, Veterinary Faculty, University of Ljubljana and Medical school, University of Maribor, Ljubljana, Slovenia. ¹⁹Centre Nacional d'Anàlisi Genòmica, Barcelona, ES, Spain. ²⁰Leiden University Medical Center, Leiden, NL, Netherlands. ²¹Centre Hospitalier Universitaire, Nantes, FR, France. ²²University of Bologna, Bologna, IT, Italy. ²³Department of Women's Cancer, UCL Elizabeth Garrett Anderson Institute for Women's Health, University College London, 74 Huntley Street, London WC1E 6AU, UK. ²⁴Helmholtz Center, Munich, DE, Germany. ²⁵Department of Biology, McGill University, Montreal, QC, Canada. ²⁶Karolinska Institute, Stockholm, SE, Sweden. ²⁷German Cancer Research Centre, Heidelberg, DE, Germany. ²⁸Canadian Institutes of Health Research, Ottawa, CA, Canada. ²⁹Institut de Chimie, UMR CNRS 7272/UNSA, Nice, FR, France. ³⁰Centre National de la Recherche Scientifique, Paris, FR, France. ³¹University of Camerino, Camerino, IT, Italy. ³²Queen's University Belfast,

Belfast, UK. ³³University of Konstanz, Konstanz, DE, Germany. ³⁴CNRS UMR7221, Museum National d'Histoire Naturelle, Paris, FR, France. ³⁵Universitäts Klinikum Heidelberg, Heidelberg, DE, Germany. ³⁶University of Bern, Bern, CH, Switzerland. ³⁷Institute of Biochemistry and Biophysics, PAS, Warsaw, PL, Poland. ³⁸Université Libre de Bruxelles, Bruxelles, BE, Belgium. ³⁹University of Maribor, Maribor, SI, Slovenia. ⁴⁰Science Europe, Brussel, Europe, BE, Belgium. ⁴¹Vrije Universiteit Brussel, Brussel, BE, Belgium. ⁴²Katholieke Universiteit Leuven, Leuven, BE, Belgium. ⁴³Vlaams Instituut voor Biotechnologie, Gent, BE, Belgium. ⁴⁴University of Manchester, Manchester, UK. ⁴⁵University of Zurich, Zurich, CH, Switzerland. ⁴⁶Utrecht University, Utrecht NL, The Netherlands. ⁴⁷Max-Planck-Institute for Molecular Genetics, Berlin, DE, Germany. ⁴⁸University of Magdeburg, Magdeburg, DE, Germany. ⁴⁹Kings College London, London, UK. ⁵⁰Medical School University of Athens, Athens, GR, Greece. ⁵¹Institut de Génétique et de Biologie Moléculaire et Cellulaire, Strasbourg, FR, France. ⁵²University of Gent, Gent, BE, Belgium. ⁵³Institute for Biological Research, Belgrade, RS, Serbia.

Received: 20 February 2014 Accepted: 28 May 2014

Published: 18 June 2014

References

1. Lister R, Pelizzola M, Dowen RH, Hawkins RD, Hon G, Tonti-Filippini J, Nery JR, Lee L, Ye Z, Ngo QM, Edsall L, Antosiewicz-Bourget J, Stewart R, Ruotti V, Millar AH, Thomson JA, Ren B, Ecker JR: **Human DNA methylomes at base resolution show widespread epigenomic differences.** *Nature* 2009, **462**:315–322. 10.1038/nature08514 [doi].
2. Bird A: **Perceptions of epigenetics.** *Nature* 2007, **447**:396–398. 10.1038/nature05913 [doi].
3. Mill J, Heijmans BT: **From promises to practical strategies in epigenetic epidemiology.** *Nat Rev Genet* 2013, **14**:585–594. 10.1038/nrg3405 [doi].
4. Kapeller J, Houghton LA, Monnikes H, Walstab J, Moller D, Bonisch H, Burwinkel B, Autschbach F, Funke B, Lasitschka F, Gassler N, Fischer C, Whorwell PJ, Atkinson W, Fell C, Buchner KJ, Schmidtman M, Van DV I, Wisser AS, Berg T, Rappold G, Niesler B: **First evidence for an association of a functional variant in the microRNA-510 target site of the serotonin receptor-type 3E gene with diarrhea predominant irritable bowel syndrome.** *Hum Mol Genet* 2008, **17**:2967–2977. 10.1093/hmg/ddn195 [doi].
5. Anto JM, Pinart M, Akdis M, Auffray C, Bachert C, Basagana X, Carlsen KH, Guerra S, Von HL, Illi S, Kauffmann F, Keil T, Kiley JP, Koppelman GH, Lupinek C, Martinez FD, Nawijn MC, Postma DS, Siroux V, Smit HA, Sterk PJ, Sunyer J, Valenta R, Valverde S, Akdis CA, Annesi-Maesano I, Ballester F, Benet M, Cambon-Thomsen A, Chatzi L, et al: **Understanding the complexity of IgE-related phenotypes from childhood to young adulthood: a Mechanisms of the Development of Allergy (MeDALL) seminar.** *J Allergy Clin Immunol* 2012, **129**:943–954. 10.1016/j.jaci.2012.01.047 [doi].
6. Krauss-Etschmann S, Bush A, Bellucci S, Brusselle GG, Dahlen SE, Demhel S, Eickelberg O, Gibson G, Hylkema MN, Knaus P, Konigshoff M, Lloyd CM, Macciarini P, Mailleux A, Marsland BJ, Postma DS, Roberts G, Samakovlis C, Stocks J, Vandesompele J, Wjst M, Holloway J: **Of flies, mice and men: a systematic approach to understanding the early life origins of chronic lung disease.** *Thorax* 2013, **68**:380–384. 10.1136/thoraxjnl-2012-201902 [doi].
7. Adams D, Altucci L, Antonarakis SE, Ballesteros J, Beck S, Bird A, Bock C, Boehm B, Campo E, Caricasole A, Dahl F, Dermitzakis ET, Enver T, Esteller M, Estivill X, Ferguson-Smith A, Fitzgibbon J, Flicek P, Giehl C, Graf T, Grosveld F, Guigo R, Gut I, Helin K, Jarvius J, Koppers R, Lehrach H, Lengauer T, Lernmark A, Leslie D, et al: **BLUEPRINT to decode the epigenetic signature written in blood.** *Nat Biotechnol* 2012, **30**:224–226. 10.1038/nbt.2153 [doi].
8. Habibi E, Brinkman AB, Arand J, Kroeze LI, Kerstens HH, Matarese F, Lepikhov K, Gut M, Brun-Heath I, Hubner NC, Benedetti R, Altucci L, Jansen JH, Walter J, Gut IG, Marks H, Stunnenberg HG: **Whole-genome bisulfite sequencing of two distinct interconvertible DNA methylomes of mouse embryonic stem cells.** *Cell Stem Cell* 2013, **13**:360–369. 10.1016/j.stem.2013.06.002 [doi].
9. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ: **Weight in infancy and death from ischaemic heart disease.** *Lancet* 1989, **2**:577–580.
10. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH: **Persistent epigenetic differences associated with prenatal exposure to famine in humans.** *Proc Natl Acad Sci U S A* 2008, **105**:17046–17049. 10.1073/pnas.0806560105 [doi].
11. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, Von BM, McCoy KD, Macpherson AJ, Danska JS: **Sex differences in the gut**

- microbiome drive hormone-dependent regulation of autoimmunity. *Science* 2013, **339**:1084–1088. 10.1126/science.1233521 [doi].
12. Teschendorff AE, Menon U, Gentry-Maharaj A, Ramus SJ, Weisenberger DJ, Shen H, Campan M, Noushmehr H, Bell CG, Maxwell AP, Savage DA, Mueller-Holzner E, Marth C, Kocjan G, Gayther SA, Jones A, Beck S, Wagner W, Laird PW, Jacobs IJ, Widschwendter M: **Age-dependent DNA methylation of genes that are suppressed in stem cells is a hallmark of cancer.** *Genome Res* 2010, **20**:440–446. 10.1101/gr.103606.109 [doi].
 13. Soria G, Polo SE, Almouzni G: **Prime, repair, restore: the active role of chromatin in the DNA damage response.** *Mol Cell* 2012, **46**:722–734. 10.1016/j.molcel.2012.06.002 [doi].
 14. Schenk T, Chen WC, Gollner S, Howell L, Jin L, Hebestreit K, Klein HU, Popescu AC, Burnett A, Mills K, Casero RA Jr, Marton L, Woster P, Minden MD, Dugas M, Wang JC, Dick JE, Muller-Tidow C, Petrie K, Zelent A: **Inhibition of the LSD1 (KDM1A) demethylase reactivates the all-trans-retinoic acid differentiation pathway in acute myeloid leukemia.** *Nat Med* 2012, **18**:605–611. 10.1038/nm.2661 [doi].
 15. Dell'Aversana C, Lepore I, Altucci L: **HDAC modulation and cell death in the clinic.** *Exp Cell Res* 2012, **318**:1229–1244. 10.1016/j.yexcr.2012.01.025 [doi].
 16. McCabe MT, Ott HM, Ganji G, Korenchuk S, Thompson C, Van Aller GS, Liu Y, Graves AP, Della PA III, Diaz E, LaFrance LV, Mellinger M, Duquenne C, Tian X, Kruger RG, McHugh CF, Brandt M, Miller WH, Dhanak D, Verma SK, Tummino PJ, Creasy CL: **EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations.** *Nature* 2012, **492**:108–112. 10.1038/nature11606 [doi].
 17. Gronbaek K, Hother C, Jones PA: **Epigenetic changes in cancer.** *APMIS* 2007, **115**:1039–1059.
 18. Bock C, Tomazou EM, Brinkman AB, Muller F, Simmer F, Gu H, Jager N, Gnirke A, Stunnenberg HG, Meissner A: **Quantitative comparison of genome-wide DNA methylation mapping technologies.** *Nat Biotechnol* 2010, **28**:1106–1114. 10.1038/nbt.1681 [doi].
 19. Stunnenberg HG, Hubner NC: **Genomics meets proteomics: identifying the culprits in disease.** *Hum Genet* 2013, **10**: 1007/s00439-013-1376-2 [doi].
 20. Pettifer S, Ison J, Kalas M, Thorne D, McDermott P, Jonassen I, Liaquat A, Fernandez JM, Rodriguez JM, Pisano DG, Blanchet C, Uludag M, Rice P, Bartaseviciute E, Rapacki K, Hekkelman M, Sand O, Stockinger H, Clegg AB, Bongcam-Rudloff E, Salzemann J, Breton V, Attwood TK, Cameron G, Vriend G: **The EMBRACE web service collection.** *Nucleic Acids Res* 2010, **38**:W683–W688. 10.1093/nar/gkq297 [doi].

doi:10.1186/1471-2164-15-487

Cite this article as: Almouzni *et al.*: Relationship between genome and epigenome - challenges and requirements for future research. *BMC Genomics* 2014 **15**:487.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

