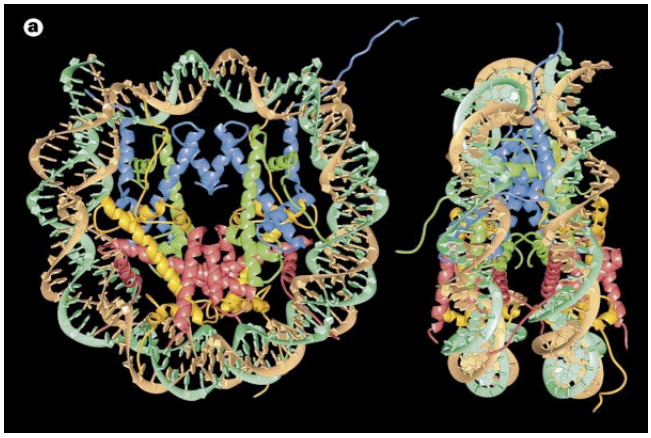
BIOD19H3 Epigenetics in Health and Disease

Winter 2017

Professor: Dr. David Ashbrook; **TA:** Sameera Abuaish



A lecture/seminar/discussion class on the emerging field of environmental epigenetics. Course will cover basic epigenetic mechanisms, methods in epigenetic research, epigenetic control of gene function, and the role of epigenetics in normal development and human disease.

Environmental epigenetics is a new field of study focusing on mitotically or meiotically heritable changes in gene regulation caused by *environmental factors*. There is evidence that epigenetic changes can occur through diet, toxicants (xenobiotics) and social factors (e.g. parental care). When such factors influence brain development, they can increase the risk for psychopathology throughout the lifespan. This course will focus on the environmental epigenetic mechanisms that impact human health and disease.

Office hours: Wednesday 9-11 or by appointment. My office is in PO104 - RM110.

Course email address: epigeneticsD19@gmail.com

Lectures: MV-120 Fridays 10-12

A course calendar with the schedule for lectures and presentations will be available on Blackboard. This schedule is subject to change, so check back regularly.

- Weeks 1-2: Lectures on **(1)** foundation topics in environmental epigenetics, **(2)** how to read/present a research article, **(3)** how to write a minireview
- Weeks 3-12: Student seminars on research articles.

Textbook: There is NO textbook for this class. PowerPoint presentations and journal articles will be supplied on Blackboard as PDF files or linked.

Exams: There are NO exams in this class.

Anticipated Outcomes

1. You will gain breadth and depth of knowledge about basic concepts and ideas in epigenetics.
2. You will gain exposure to the current research in the field of Epigenetics
3. You will learn how to critically read scientific articles
4. You will develop presentation skills delivering scientific knowledge to specialized audiences through oral presentations
5. You will learn how to critically review a topic in epigenetics

Grading scheme overview:

Assignments (4x2.5%)	10%
Seminar presentations	35%
Seminar questions	15%
Minireview	35%
Attendance	5%
	100%

Deadlines (3PM to course email):

Take-home assignments (4): Variable, but one week after assignment.
Seminar Presentation: Choice of articles (top 3): *Monday 16th January 2017*, 11am
Minireview: Topic choice: *Monday 23rd January 2017, 11am*
Abstract and Title: Monday 30th January 2017, 11am
First Full Paragraph (5-6 sentences) and reference list (10): 27th February
Final Document (including hardcopy): *Friday 31st March 2017, 11am*

Take-home assignments: Four take-home assignments of short answer questions (brief: 3-5 sentences each question) addressing one of the articles presented in the class. You will be required to answer basic questions about the background, methods used, results and conclusions of the paper. The specific paper used for the questions is Dr. Ashbrook's choice, and you will have one week after assignment to submit your answers. Each assignment will contribute to 2.5% of your final grade (total **10%**).

Seminar Presentation: Seminars will be based on research articles chosen by Dr. Ashbrook, or you can suggest an article. Each person and a classmate will lead a 15 min discussion of a research article, followed by a 10 min question period. Only a maximum of 5 minutes should be spent on the introduction. When presenting, students are expected to provide handouts, which will be given to the class at the beginning of the seminar. Seminars will be graded based on clarity, style and delivery, use of visual aids, content, and ability to answer questions. Your slides and handout document must be submitted the night before your presentation via email (epigeneticsD19@gmail.com). The handout documents will be made available to the class by the instructor via Blackboard before the presentation. The seminar will contribute to **35%** of your final grade.

Seminar Questions: An important part of your mark in this class is based on contribution to discussions. For each article presented, 4 students will be randomly assigned

one week before the presentation to lead a 10-minute discussion (you won't present and lead the discussion on the same article). Each student will lead 2 paper discussions during the course. You will be graded based on your capacity to engage other students into discussion, as well as on your critical analysis and understanding of the article. This mark contributes **15%** to your final grade.

Minireview: You will complete a summary/analysis of a topic in environmental epigenetics. This could stem from the article that you will present, but it could also be on another topic (note: must at least be related to a foundation review). Choose your topic by week 3 of class (11AM 23rd Jan) and email us with your topic choice. Your Title and Abstract must be submitted by 11AM 30th Jan. The first full paragraph of your introduction (5-6 sentences) and a list of 10 references must be submitted by 11AM 27th Feb. The final document will be due the final week of class (11AM, 31st March) both as a hard copy and emailed as a PDF file to the class email address. See the Minireview Guidelines section for detailed instructions. The minireview contributes 35% to your final grade.

Attendance: You are expected to be present on time in this seminar/discussion class. Attendance contributes **5%** to your final grade.

Minireview Guidelines: A minireview is a concise, focused summary of the literature related to a question of current interest in environmental epigenetics. Scientists may read minireviews to quickly get up to speed on a particular topic that may not be their area of specialty. Sometimes minireviews also raise questions or suggest new hypotheses or attempt to reconcile conflicting data that has recently been published. Writing a minireview is a good way to organize your thoughts and summarize the knowledge you have obtained about a particular topic that you have acquired from reading the literature and thinking and discussing with others and is a good exercise in scientific writing.

Example description of a minireview (from the Journal of Biological Chemistry): "The goal of the Minireviews is to provide a concise summary of a particular field in a manner understandable to [scientists] working in any area."

The sections of your minireview will be as follows:
Title page (not numbered). The title page includes a clear, concise title that is comprehensible to all readers with the purpose of quickly identifying the focus of the reported work. Also, include your name, student number, course (BioD19), prof, TA and date.
Body of the minireview (10 pages double spaced). Start with a **Brief Abstract**: Summarize what the minireview is about as concisely as possible in an introductory paragraph. Provide necessary background/context for the reader. Should indicate why the chosen topic is important and timely. **Body of the review:** This section should contain the most relevant aspects and achievements in the reviewed scientific area. The review itself should not be an assembly of detailed information but present a summarization of critically selected and evaluated literature, which should reflect the most important findings. It may be subdivided with short, informative headings.
References. You will be obliged to perform literature searches and to cite original research articles. Aim for about 20 references, at least 15 of which are **primary research articles.** Include a reference list at the end, in one of the following styles: American Psychological Association (APA), Vancouver, Nature, or PLoS.

Additional guidelines. Submit your minireview double-spaced, with pages numbered, using 12 point font (Arial), 2 cm margins. The maximum length for the minireview is 10 pages including any Figures you make yourself and EXCLUDING the title page and references. **Endnote** or **Mendeley** (free) are useful programs for generating a reference list.

Foundation Reviews (Optional reading for background information):

Jirtle, Randy L, and Michael K Skinner. 2007. "Environmental Epigenomics and Disease Susceptibility." *Nature Reviews. Genetics* 8 (4): 253–62. doi:10.1038/nrg2045.

Fagiolini, Michela, Catherine L Jensen, and Frances A Champagne. 2009. "Epigenetic Influences on Brain Development and Plasticity." *Current Opinion in Neurobiology* 19 (2): 207–12. doi:10.1016/j.conb.2009.05.009.

Petronis, Arturas. 2010. "Epigenetics as a Unifying Principle in the Aetiology of Complex Traits and Diseases." *Nature* 465 (7299): 721–27. doi:10.1038/nature09230.

Youngson, Neil A, and Emma Whitelaw. 2008. "Transgenerational Epigenetic Effects." *Annual Review of Genomics and Human Genetics* 9 (1): 233–57. doi:10.1146/annurev.genom.9.081307.164445.

Epigenetics, Second Edition. 2015. Eds. CD Allis, M Caparros, T Jenuwein, D Reinberg. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

Articles:

Articles to present will be assigned on a first-come first-served basis (so get this in before the deadline!).
Send an email with your top 3 choices to: epigeneticsD19@gmail.com
YOU CAN ALSO SUGGEST AN ARTICLE (but please justify why you have chosen this).
Deadline: *Monday 16th January*. After the deadline, an article will be assigned to you.

Nutrition:

1. Lillycrop, Karen A, Jo L Slater-Jefferies, Mark A Hanson, Keith M Godfrey, Alan A Jackson, and Graham C Burdge. 2007. "Induction of Altered Epigenetic Regulation of the Hepatic Glucocorticoid Receptor in the Offspring of Rats Fed a Protein-Restricted Diet during Pregnancy Suggests That Reduced DNA Methyltransferase-1 Expression Is Involved in Impaired DNA Methylation and ." *The British Journal of Nutrition* 97 (6): 1064–73. doi:10.1017/S000711450769196X.
Illustrates the impact of methyl donors in the maternal diet on offspring DNA methylation and histone acetylation patterns, providing an important link between nutrition and gene regulation.

2. Weaver, Ian C G, Frances A Champagne, Shelley E Brown, Sergiy Dymov, Shakti Sharma, Michael J Meaney, and Moshe Szyf. 2005. "Reversal of Maternal Programming of Stress Responses in Adult Offspring through Methyl Supplementation: Altering Epigenetic Marking Later in Life." *The*

Journal of Neuroscience : The Official Journal of the Society for Neuroscience 25 (47): 11045–54. doi:10.1523/JNEUROSCI.3652-05.2005.

Describes the role of methyl donors in altering epigenetic programming of the stress response and behaviours in adult rats.

3. Dunn, Gregory A, and Tracy L Bale. 2011. "Maternal High-Fat Diet Effects on Third-Generation Female Body Size via the Paternal Lineage." *Endocrinology* 152 (6): 2228–36. doi:10.1210/en.2010-1461.

This study implicates environmental influences on developmental regulation of growth and body size as the result of broad programming events at imprinted loci.

4. Kucharski, R, J Maleszka, S Foret, and R Maleszka. 2008. "Nutritional Control of Reproductive Status in Honeybees via DNA Methylation." *Science (New York, N.Y.)* 319 (5871): 1827–30. doi:10.1126/science.1153069.

Early life nutrition induces epigenetic changes that determine whether a honeybee will become a queen or worker bee.

5. Gao, Yuan, Zhuo Han, Qian Li, Yongyan Wu, Xiaoyan Shi, Zhiying Ai, Juan Du, Wenzhong Li, Zekun Guo, and Yong Zhang. 2015. "Vitamin C Induces a Pluripotent State in Mouse Embryonic Stem Cells by Modulating microRNA Expression." *The FEBS Journal* 282 (4): 685–99. doi:10.1111/febs.13173.

Examines the effects of vitamin C on the epigenetic machinery, including micro RNA expression, in embryonic stem cells.

6. Dominguez-Salas, Paula, Sophie E Moore, Maria S Baker, Andrew W Bergen, Sharon E Cox, Roger A Dyer, Anthony J Fulford, et al. 2014. "Maternal Nutrition at Conception Modulates DNA Methylation of Human Metastable Epialleles." *Nature Communications* 5 (April): 3746. doi:10.1038/ncomms4746.

Study of seasonal variations in methyl-donor nutrient intake of mothers in rural Gambia around the time of conception and their influence on 13 plasma biomarkers and DNA methylation.

<u>Xenobiotics:</u>

7. Anway, Matthew D, Charles Leathers, and Michael K Skinner. 2006. "Endocrine Disruptor Vinclozolin Induced Epigenetic Transgenerational Adult-Onset Disease." *Endocrinology* 147 (12): 5515–23. doi:10.1210/en.2006-0640.

Demonstrates the ability of an endocrine disruptor to induce an epigenetic transgenerational disease phenotype for four generations.

8. Dolinoy, Dana C, Dale Huang, and Randy L Jirtle. 2007. "Maternal Nutrient Supplementation Counteracts Bisphenol A-Induced DNA Hypomethylation in Early Development." *Proceedings of the National Academy of Sciences of the United States of America* 104 (32): 13056–61. doi:10.1073/pnas.0703739104.

Shows that early developmental exposure to an environmental toxin can change offspring phenotype by stably altering the epigenome, an effect that can be counter-acted by maternal dietary supplements.

9. Wu, Jinfang, Md Riyaz Basha, Brian Brock, David P Cox, Fernando Cardozo-Pelaez, Christopher A McPherson, Jean Harry, et al. 2008. "Alzheimer's Disease (AD)-like Pathology in Aged Monkeys after Infantile Exposure to Environmental Metal Lead (Pb): Evidence for a Developmental Origin and Environmental Link for AD." *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience* 28 (1): 3–9. doi:10.1523/JNEUROSCI.4405-07.2008.

This study in primates finds that early exposure to lead (Pb) results in decreased DNA methyltransferase activity in the brain 23 years later.

Stress:

10. Weaver, Ian C G, Nadia Cervoni, Frances A Champagne, Ana C D'Alessio, Shakti Sharma, Jonathan R Seckl, Sergiy Dymov, Moshe Szyf, and Michael J Meaney. 2004. "Epigenetic Programming by Maternal Behavior." *Nature Neuroscience* 7 (8): 847–54. doi:10.1038/nn1276.
Describes the role of maternal care in epigenetic programming of the stress response and behaviours in rats.

11. Franklin, Tamara B, Holger Russig, Isabelle C Weiss, Johannes Gräff, Natacha Linder, Aubin Michalon, Sandor Vizi, and Isabelle M Mansuy. 2010. "Epigenetic Transmission of the Impact of Early Stress across Generations." *Biological Psychiatry* 68 (5): 408–15. doi:10.1016/j.biopsych.2010.05.036.
These findings highlight the negative impact of early stress on behavioral responses across generations and on the regulation of DNA methylation in the germline.

12. Mueller, Bridget R, and Tracy L Bale. 2008. "Sex-Specific Programming of Offspring Emotionality after Stress Early in Pregnancy." *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience* 28 (36): 9055–65. doi:10.1523/JNEUROSCI.1424-08.2008.
Illustrates alterations in DNA methylation of placental and brain tissue following exposure to gestational stress, providing a possible mechanism mediating the long-term neurobiological effects of prenatal exposure to elevated maternal stress response activity.

13. Roth, Tania L, Farah D Lubin, Adam J Funk, and J David Sweatt. 2009. "Lasting Epigenetic Influence of Early-Life Adversity on the BDNF Gene." *Biological Psychiatry* 65 (9): 760–69. doi:10.1016/j.biopsych.2008.11.028.
Study of the transgenerational impact of exposure to maternal abuse in infancy and the role of differential methylation of a growth factor gene in the prefrontal cortex in mediating these effects.

14. Murgatroyd, Chris, Alexandre V Patchev, Yonghe Wu, Vincenzo Micale, Yvonne Bockmühl, Dieter Fischer, Florian Holsboer, Carsten T Wotjak, Osborne F X Almeida, and Dietmar Spengler. 2009. "Dynamic DNA Methylation Programs Persistent Adverse Effects of Early-Life Stress." *Nature Neuroscience* 12 (12): 1559–66. doi:10.1038/nn.2436.
Shows that early life stress can dynamically control DNA methylation in neurons to generate stable changes in gene expression and phenotypic alterations that are frequent features in depression.

15. Cao-Lei, Lei, Renaud Massart, Matthew J Suderman, Ziv Machnes, Guillaume Elgbeili, David P Laplante, Moshe Szyf, and Suzanne King. 2014. "DNA Methylation Signatures Triggered by Prenatal Maternal Stress Exposure to a Natural Disaster: Project Ice Storm." Edited by Kazuya Iwamoto. *PloS One* 9 (9): e107653. doi:10.1371/journal.pone.0107653.
Study of effects of the 1998 Quebec Ice Storm on methylation in T-cells and saliva of children in utero at the time.

Learning and Memory/Addiction:

16. Fischer, Andre, Farahnaz Sananbenesi, Xinyu Wang, Matthew Dobbin, and Li-Huei Tsai. 2007. "Recovery of Learning and Memory Is Associated with Chromatin Remodelling." *Nature* 447 (7141): 178–82. doi:10.1038/nature05772.

Rodent study showing that environmental enrichment increases histone acetylation in the hippocampus. Histone deacetylase inhibitors induce increased spatial memory in a neurodegenerative disorder mouse model.

17. Lubin, Farah D, Tania L Roth, and J David Sweatt. 2008. "Epigenetic Regulation of BDNF Gene Transcription in the Consolidation of Fear Memory." *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience* 28 (42): 10576–86. doi:10.1523/JNEUROSCI.1786-08.2008.

Illustrates the dynamic changes to DNA methylation which occur during the process of learning and the critical role of these modifications in the consolidation of memory.

18. Guan, Ji-Song, Stephen J Haggarty, Emanuela Giacometti, Jan-Hermen Dannenberg, Nadine Joseph, Jun Gao, Thomas J F Nieland, et al. 2009. "HDAC2 Negatively Regulates Memory Formation and Synaptic Plasticity." *Nature* 459 (7243): 55–60. doi:10.1038/nature07925.

Study in mice examining the particular histone deacetylase target through which histone deacetylase inhibitors exert enhancements in synaptic plasticity and memory. The authors illustrate the importance of levels of this enzyme in mediating cognitive enhancement.

19. Vassoler, Fair M, Samantha L White, Heath D Schmidt, Ghazaleh Sadri-Vakili, and R Christopher Pierce. 2013. "Epigenetic Inheritance of a Cocaine-Resistance Phenotype." *Nature Neuroscience* 16 (1): 42–47. doi:10.1038/nn.3280.

In a case of sex-linked epigenetic inheritance, paternal cocaine use results in a heritable increase in cortical *Bdnf* gene expression that confers a cocaine-resistant phenotype in male, but not female, progeny.

20. Dias, Brian G, and Kerry J Ressler. 2014. "Parental Olfactory Experience Influences Behavior and Neural Structure in Subsequent Generations." *Nature Neuroscience* 17 (1): 89–96. doi:10.1038/nn.3594.

This study shows that when mice are taught to fear an odor, both their offspring and the next generation are born fearing it. The gene for an olfactory receptor activated by the odor is specifically demethylated in the germ line and the olfactory circuits for detecting the odor are enhanced.

21. Wang, Hui, Florian Duclot, Yan Liu, Zuoxin Wang, and Mohamed Kabbaj. 2013. "Histone Deacetylase Inhibitors Facilitate Partner Preference Formation in Female Prairie Voles." *Nature Neuroscience* 16 (7): 919–24. doi:10.1038/nn.3420.

Examines the epigenetics of pair bond formation in the monogamous prairie vole, and uses a pharmacological method to alter epigenetic status and partner preference.

22. Zovkic IB, Paulukaitis BS, Day JJ, Etikala DM, Sweatt JD. Histone H2A.Z subunit exchange controls consolidation of recent and remote memory. Nature. 2014 Nov 27;515(7528):582-6. doi: 10.1038/nature13707.
Examines the role of histone variant exchange in memory in a mouse model.

<u>Human Transgenerational/Health and Disease:</u>

23. (A) Pembrey, M. E. et al. Sex-specific, male-line transgenerational responses in humans. Eur. J. Hum. Genet. 14, 159–166 (2006).
(B) Kaati G, Bygren LO, Pembrey M, Sjöström M. Transgenerational response to nutrition, early life circumstances and longevity. Eur J Hum Genet 2007; 15:784-90.

These two short reports (A-B) should be considered together. The first study demonstrates an inherited disease phenotype in humans that is potentially induced by an epigenetic phenomena. The second study follows on those data with evidence of a transgenerational response to ancestors' nutrition as a main influence on longevity.

24. Tobi EW, Goeman JJ, Monajemi R, Gu H, Putter H, Zhang Y, Slieker RC, Stok AP, Thijssen PE, Müller F, van Zwet EW, Bock C, Meissner A, Lumey LH, Eline Slagboom P, Heijmans BT. DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nat Commun. 2014 Nov 26;5:5592.
A genome-scale analysis of differential DNA methylation in whole blood after periconceptional exposure to famine during the Dutch Hunger Winter of World War II.

<u>Human Development/Health and Disease:</u>

25. Kaminsky, Z. A. et al. DNA methylation profiles in monozygotic and dizygotic twins. Nature Genet. 41, 240–245 (2009).
A study of genome-wide epigenetic differences among twins.

26. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suner D, Cigudosa JC, Urioste M, Benitez J, et al. 2005. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci 102: 10604– 10609.
This study examined the global and locus-specific differences in DNA methylation and histone acetylation of a large cohort of monozygotic twins. They find that, compared to differences in the early years of life, older monozygous twins exhibit greater differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, affecting their gene-expression portrait.

27. Katari S, Turan N, Bibikova M, et al. DNA methylation and gene expression differences in children conceived in vitro or in vivo. Hum Mol Genet 2009;18:3769–78.
This study examined DNA methylation at more than 700 genes in placenta and cord blood and measured gene expression levels of a subset of genes that differed in methylation levels between children conceived in vitro versus in vivo.

28. Lam LL, Emberly E, Fraser HB, Neumann SM, Chen E, Miller GE, Kobor MS. Factors underlying variable DNA methylation in a human community cohort. Proc Natl Acad Sci U S A. 2012 Oct 16;109 Suppl 2:17253-60. doi: 10.1073/pnas.1121249109. Epub 2012 Oct 8.
Genome-wide epigenetic study of the contributions of stress and other factors in early life to epigenetic variability in humans stratified by socio-economic position.

29. Borghol N, Suderman M, McArdle W, Racine A, Hallett M, Pembrey M, Hertzman C, Power C, Szyf M. Associations with early-life socio-economic position in adult DNA methylation. Int J Epidemiol. 2012 Feb;41(1):62-74.
Study reporting that adult blood DNA methylation profiles show more associations with childhood socio-economic position than adult socio-economic position.

30. Petropoulos, S., Edsgärd, D., Reinius, B., Deng, Q., Panula, S. P., Codeluppi, S., ... & Lanner, F. (2016). Single-Cell RNA-Seq Reveals Lineage and X Chromosome Dynamics in Human Preimplantation Embryos. *Cell*, *165*(4), 1012-1026.
Study of human pre-implantation embryo development at single cell resolution, revealing that the lineage path in the human embryo is distinct from that in the mouse.

<u>Mental health (humans):</u>

31. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics. 2008 Mar-Apr;3(2):97-106. PubMed PMID: 18536531.
This study examined relationships between prenatal exposure to maternal mood and the methylation status of the human glucocorticoid receptor gene in newborns and HPA stress reactivity at age three months.

32. Davies MN, Krause L, Bell JT, Gao F, Ward KJ, Wu H, Lu H, Liu Y, Tsai PC, Collier DA, Murphy T, Dempster E, Mill J; UK Brain Expression Consortium, Battle A, Mostafavi S, Zhu X, Henders A, Byrne E, Wray NR, Martin NG, Spector TD, Wang J. Hypermethylation in the ZBTB20 gene is associated with major depressive disorder. Genome Biol. 2014 Apr 2;15(4):R56. doi: 10.1186/gb-2014-15-4-r56.
Reports that aberrant methylation profiles affecting the hippocampus are associated with major depressive disorder and shows the potential of the epigenetic twin model in neuro-psychiatric disease.

33. Lunnon K, Smith R, Hannon E, De Jager PL, Srivastava G, Volta M, Troakes C, Al-Sarraj S, Burrage J, Macdonald R, Condliffe D, Harries LW, Katsel P, Haroutunian V, Kaminsky Z, Joachim C, Powell J, Lovestone S, Bennett DA, Schalkwyk LC, Mill J. Methylomic profiling implicates cortical deregulation of ANK1 in Alzheimer's disease. Nat Neurosci. 2014 Sep;17(9):1164-70.
The first epigenome-wide association study of AD employing a sequential replication design across multiple tissues.

34. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, Pace TW, Rex-Haffner M, Loeschner A, Gonik M, Mercer KB, Bradley B, Müller-Myhsok B, Ressler KJ, Binder EB. Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. Proc Natl Acad Sci U S A. 2013 May 14;110(20):8302-7.
Study of the interaction between childhood maltreatment and PTSD, examining genome-wide gene expression and epigenetic signatures.

35. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009; 12: 342-8.
This study shows epigenetic alterations of a stress-sensitive gene in the brains of suicide victims in association with early life abuse or neglect.

Genetic, tissue-specific, and intergenerational sources of epigenetic variation:

36. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol 2013; 14: R115.
Uses computational methods and DNA methylation microarray data to examine DNA methylation status as a predictor of chronological age in a variety of tissues.

37. Orozco LD, Rubbi L, Martin LJ, Fang F, Hormozdiari F, Che N, Smith AD, Lusis AJ, Pellegrini M. Intergenerational genomic DNA methylation patterns in mouse hybrid strains. Genome Biol. 2014 Apr 30;15(5):R68.
Concludes that the majority of DNA methylation differences among individuals are associated with genetic differences, and a much smaller proportion of these epigenetic differences are due to sex, imprinting or stochastic intergenerational effects.

38. Heijmans, B. T., Kremer, D., Tobi, E. W., Boomsma, D. I. & Slagboom, P. E. Heritable rather than age-related environmental and stochastic factors dominate variation in DNA methylation of the human IGF2/H19 locus. Hum. Mol. Genet. 16, 547–554 (2007).
This study investigated the contribution of heritable influences and the combined effect of environmental and stochastic factors to variation in DNA methylation of the IGF2/H19 locus.

39. Reinius LE, Acevedo N, Joerink M, Pershagen G, Dahlen S-E, Greco D, Soderhall C, Scheynius A, Kere J. Differential DNA methylation in purified human blood cells: Implications for cell lineage and studies on disease susceptibility. PLoS ONE 2012; 7: e41361.
Addresses the tissue-specific nature of epigenetic modifications by examining methylation profiles in subsets of peripheral blood cells, which are commonly used in human clinical investigations.

40. Flanagan, J. M. et al. Intra- and interindividual epigenetic variation in human germ cells. Am. J. Hum. Genet. 79, 67–84 (2006).
This study provides evidence for significant epigenetic variability in human germ cells, which warrants further research to determine whether such epigenetic patterns can be efficiently transmitted across generations and what impact inherited epigenetic individuality may have on phenotypic outcomes in health and disease.

41. Radford EJ, Ito M, Shi H, Corish JA, Yamazawa K, Isganaitis E, Seisenberger S, Hore TA, Reik W, Erkek S, Peters AH, Patti ME, Ferguson-Smith AC. In utero effects. In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. Science. 2014 Aug 15;345(6198):1255903.
Reports that prenatal undernutrition can compromise male germline epigenetic reprogramming and thus permanently alter DNA methylation in the sperm of adult offspring at regions resistant to zygotic reprogramming. However, persistence of altered DNA methylation into late-gestation somatic tissues of the subsequent generation is not observed.

Accessibility: Students with diverse learning styles and needs are welcome in this course. If you have a disability/health consideration that may require accommodations, please notify me and contact the AccessAbility Services Office (located in SW302) as soon as possible. I will work with you and AccessAbility services to ensure you can achieve your learning goals in this course. Enquiries are confidential, and the staff is available to assess your specific needs, provide referrals, and arrange appropriate accommodations (Tel/TTY: 416-287-7560 or ability@utsc.utoronto.ca).