Global Epigenetics
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Modelling emergence of transgenerational schizophrenia

a CSSS 2018 project
Introduction

At the end of the eighteenth century, the French naturalist Jean-Baptiste Lamarck noted that life on earth had evolved over long periods of time into a striking variety of organisms. He sought to explain how they had become more and more complex. Living organisms not only evolved, Lamarck argued; they did so very slowly, “little by little and successively.” In Lamarckian theory, animals became more diverse as each creature strove toward its own “perfection,” hence the enormous variety of living things on earth. Man is the most complex life form, therefore the most perfect, and is even now evolving.

In Lamarck’s view, the evolution of life depends on variation and the accumulation of small, gradual changes. These are also
Epigenetics and mental health

‘Nongenetic influences on gene expression’

Trauma can lead to:

- Methylation: epigenetic modification on the Glucocorticoid receptor gene
- Blocked receptor cannot regulate cortisol effectively
- Cortisol runs up like temperature due to broken thermostat
- Chronic stress linked to worse mental health outcomes
Epigenetics and mental health

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Dutch Hunger Winter (1944–1945)

- Famine in Western provinces of the Netherlands during WWII
- Adult food rations dropped under 1000 cal/day in 1944, and further to 580 cal/day in 1945
- In children of mothers on the third trimester during famine: Increased risk ratio for schizophrenia twofold
- Similar results for schizophrenia following the Chinese Famine of 1959–1961

Hejmans et al., 2008; Lumey et al. 2009; St Clair et al., 2005; Veenendaal et al., 2013
Aetiology of Schizophrenia (a simplified model)
Model

Stress event
(famine)
Model

Demographic model

Netherland census data (fertility, mortality)

Heritability model

Review of schizophrenia heritability studies

Environmental effect

Dutch famine cohort data
Genetic Algorithm to Fit Exponential Model of Mortality Rates

\[ p(\text{death this year}) = p_1 e^{\frac{(\text{age} - p_2)^2}{p_3}} \]
Fitting Exponential Mortality Model With Regression

\[
\text{lm(formula = probDeath.1940 \sim \exp(ageGroup.1940))}
\]

Coefficients:

| Estimate | Std. Error | t value | Pr(>|t|) |
|----------|------------|---------|----------|
| (Intercept) | 2.912e-03  | 2.134e-03 | 1.364  | 0.30571 |
| exp(ageGroup.1940) | 3.344e-33  | 1.393e-34  | 24.009 | 0.00173 ** |

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.003697 on 2 degrees of freedom

**Multiple R-squared: 0.9965, Adjusted R-squared: 0.9948**

F-statistic: 576.4 on 1 and 2 DF,  p-value: 0.00173
Epigenetic mechanism

\[ F_0 \quad F_1 \quad F_2 \]

\[ S = 3.3\% \quad \text{f} \quad S = 1.6\% \quad \text{f} \quad S = 0.6\% \]
Epigenetic mechanism

F₀  F₁  F₂

S = 3.3%  f  S = 1.6%  f  S = 0.6%

Histone Modification

Methylation
Future direction

- Improve the calibration of the demographic model
- Stress scenarios on schizophrenia prevalence
- Cost return of interventions
- Run modelling on real-world issues:
  - Early childhood trauma associated with Trump immigration policy
  - Refugee migration
  - Future mental health impacts of large-scale civil crisis such as Syria

- When data is available - expand model to other mental health issues; anxiety, depression.
References


Veenendaal MV, Painter RC, de Rooij SR, Bossuyt PM, van der Post JA, Gluckman PD, Hanson MA, Roseboom TJ. Transgenerational effects of prenatal exposure to the 1944–45 Dutch famine, BJOG, 2013, 120 (548–553)