Estimating Parental Effects using Polygenic Scores Part I: Model Introduction

Jared V. Balbona | Yongkang Kim | Matthew C. Keller

“Okay yeah, that explains a lot.”





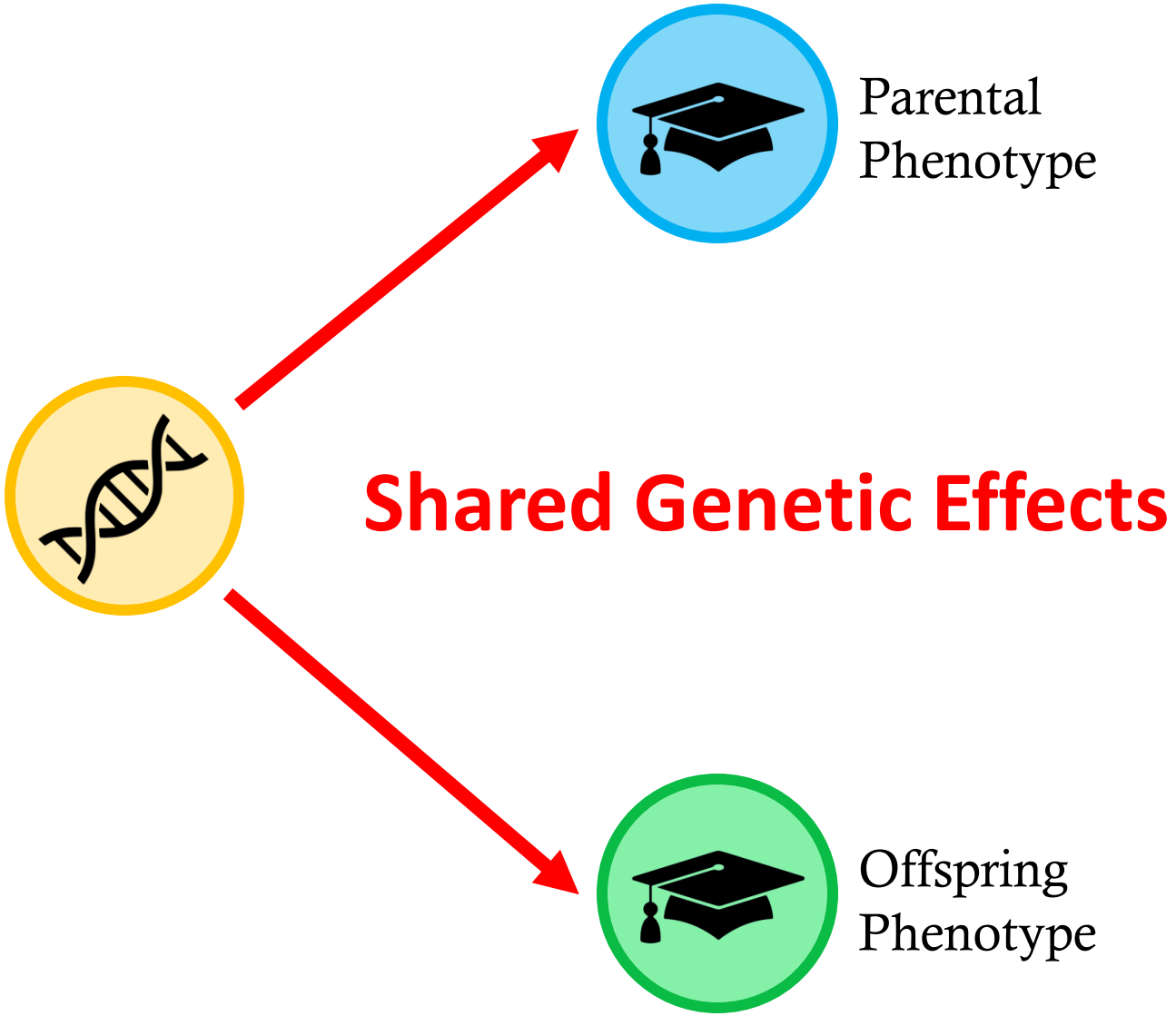
There are so many ways that parents and offspring resemble one another.

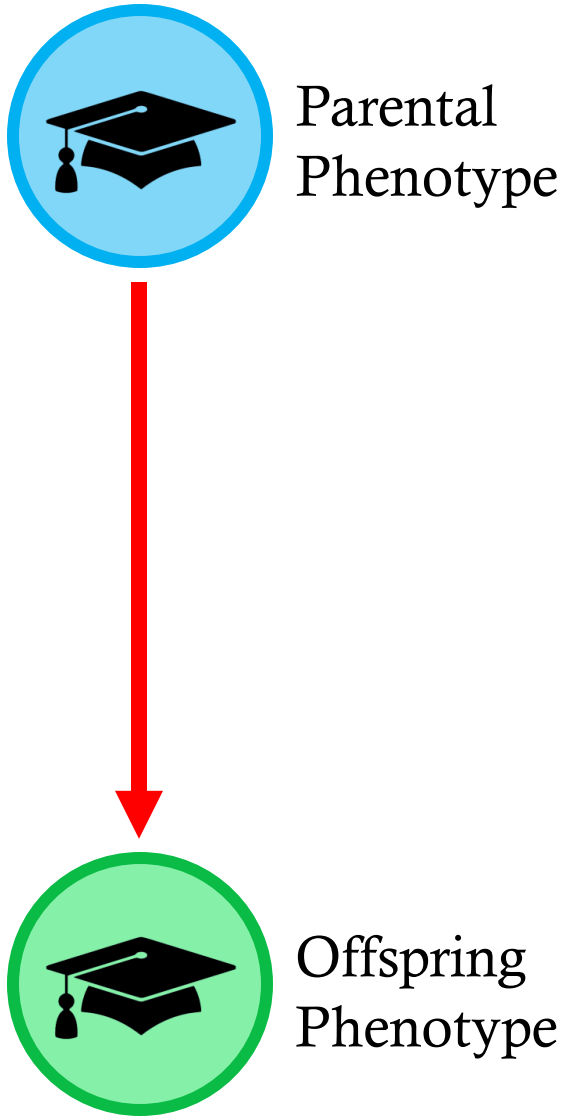


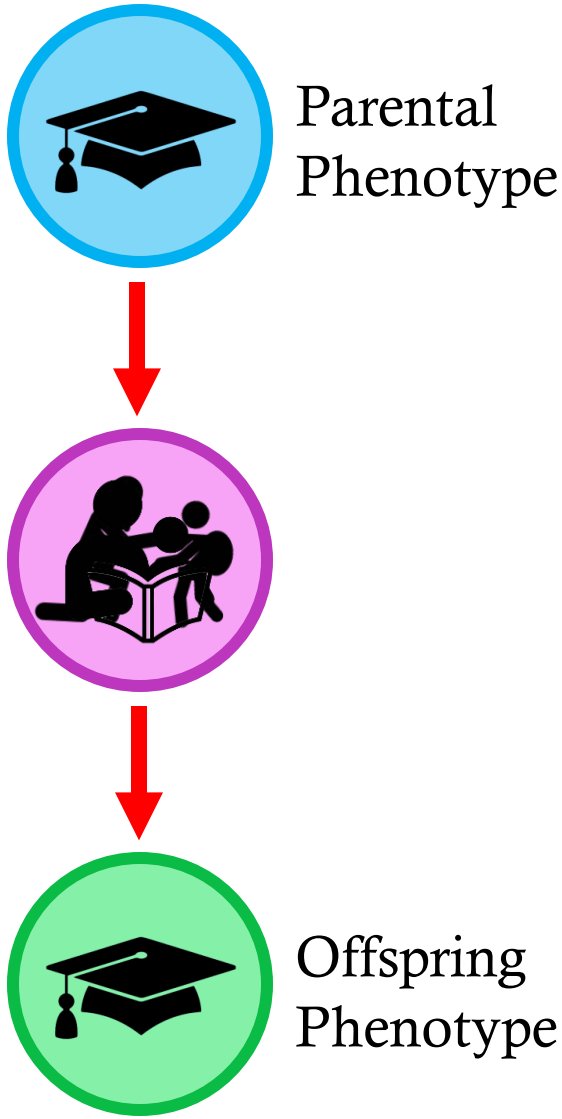


Why?

Education

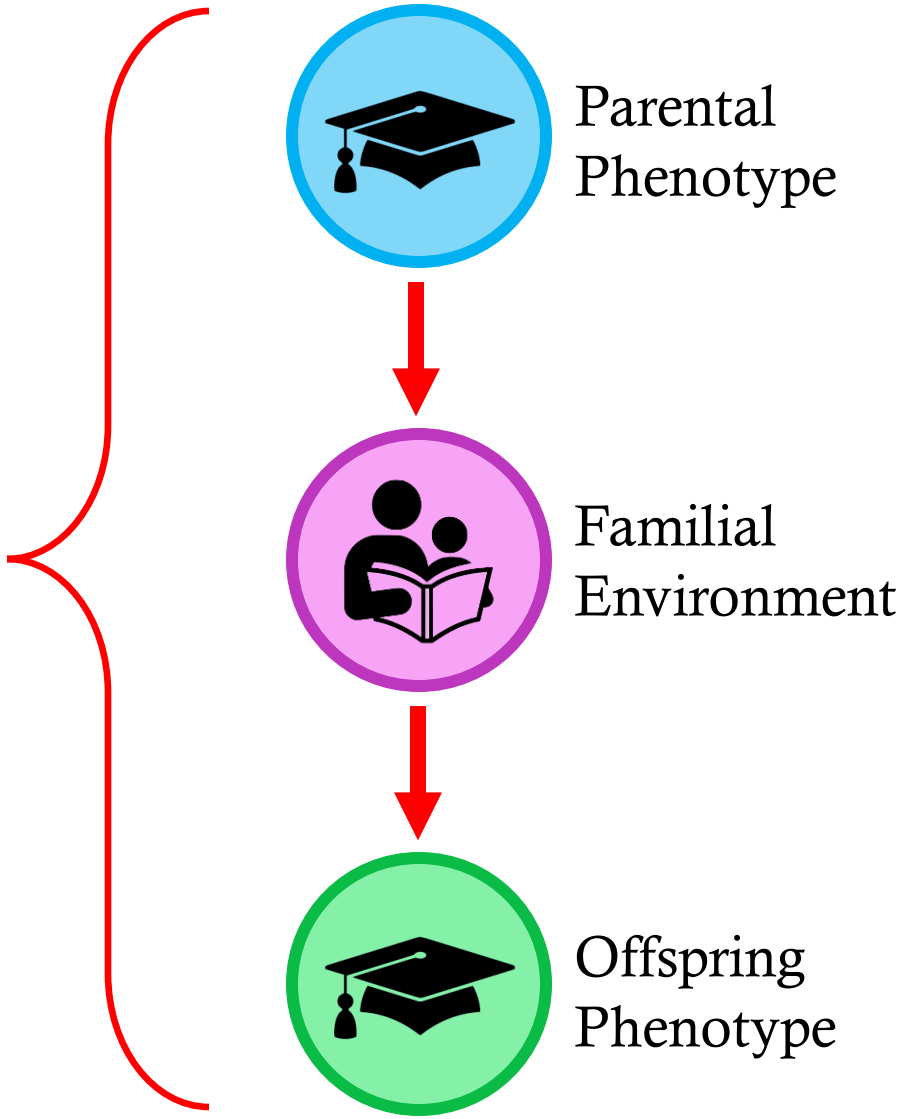

Parental
Phenotype
Shared Genetic Effects
Offspring
Phenotype

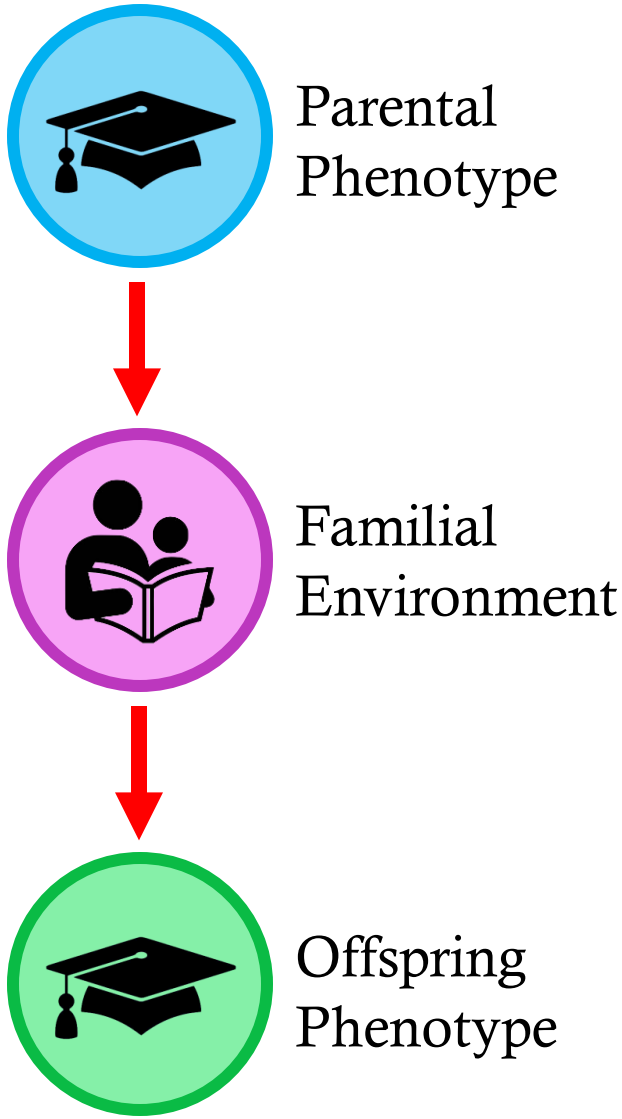

Parental
Phenotype
Offspring
Phenotype

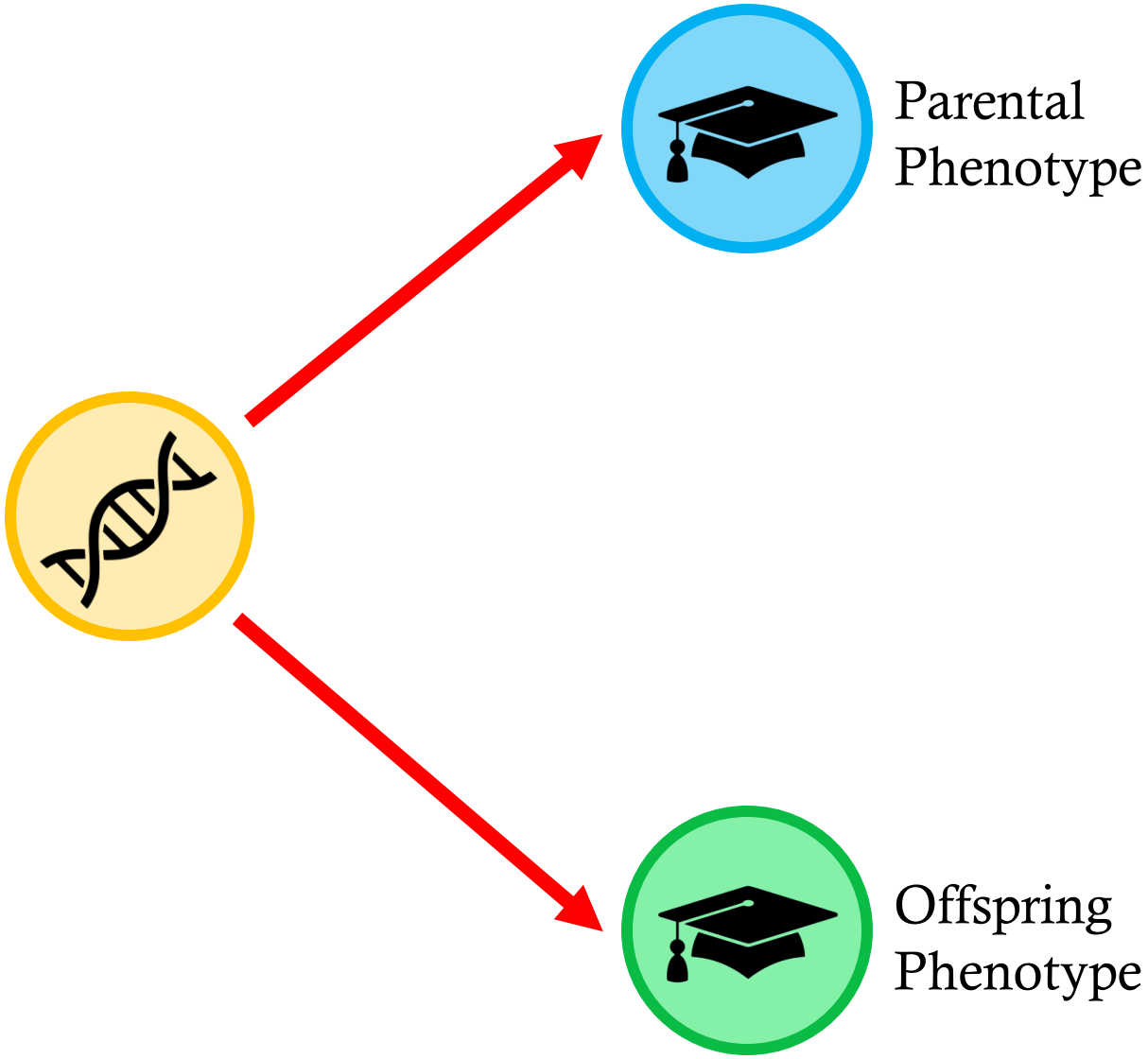

Parental
Phenotype
Offspring
Phenotype

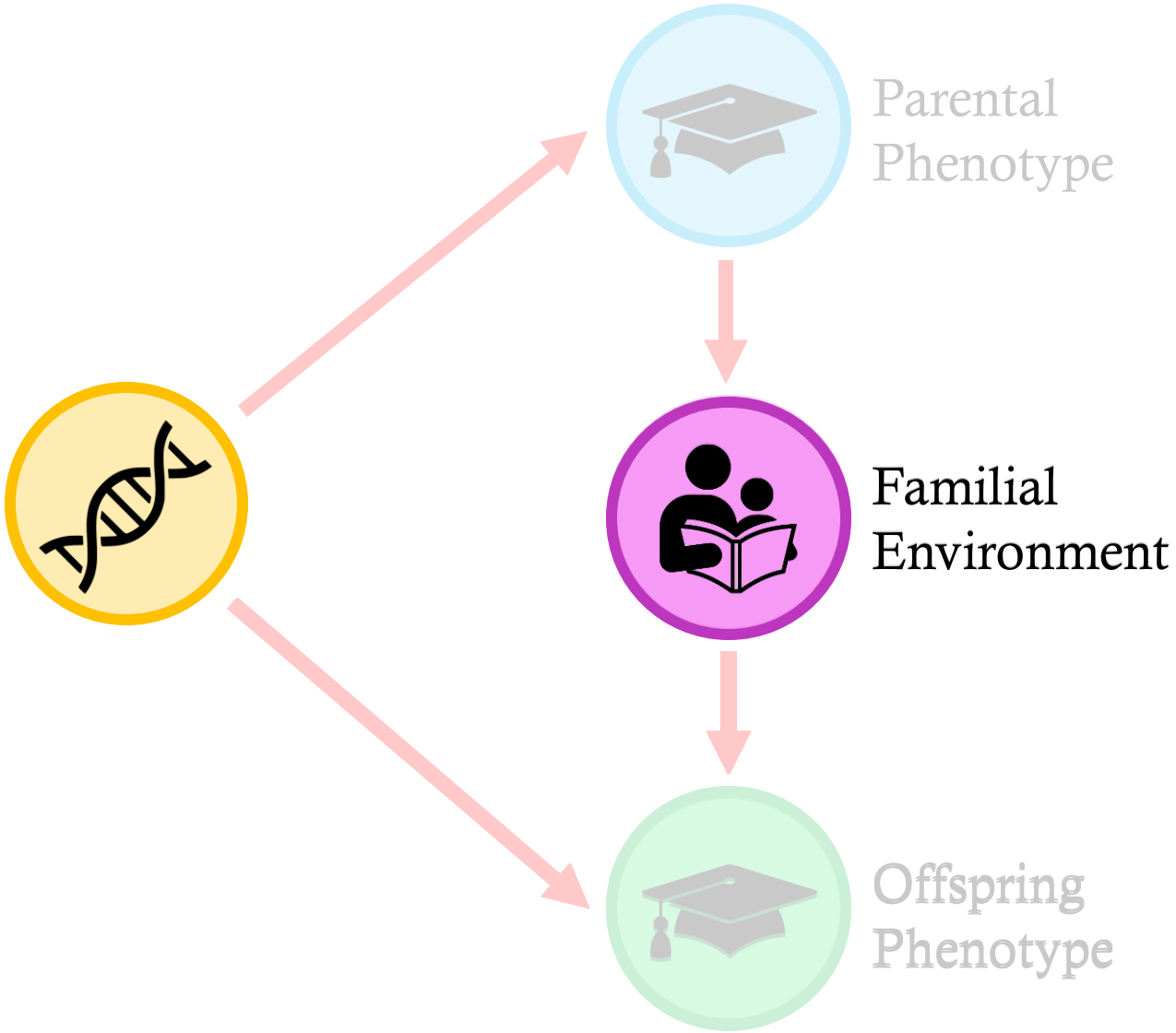
Vertical Transmission

(aka "Cultural Transmission")



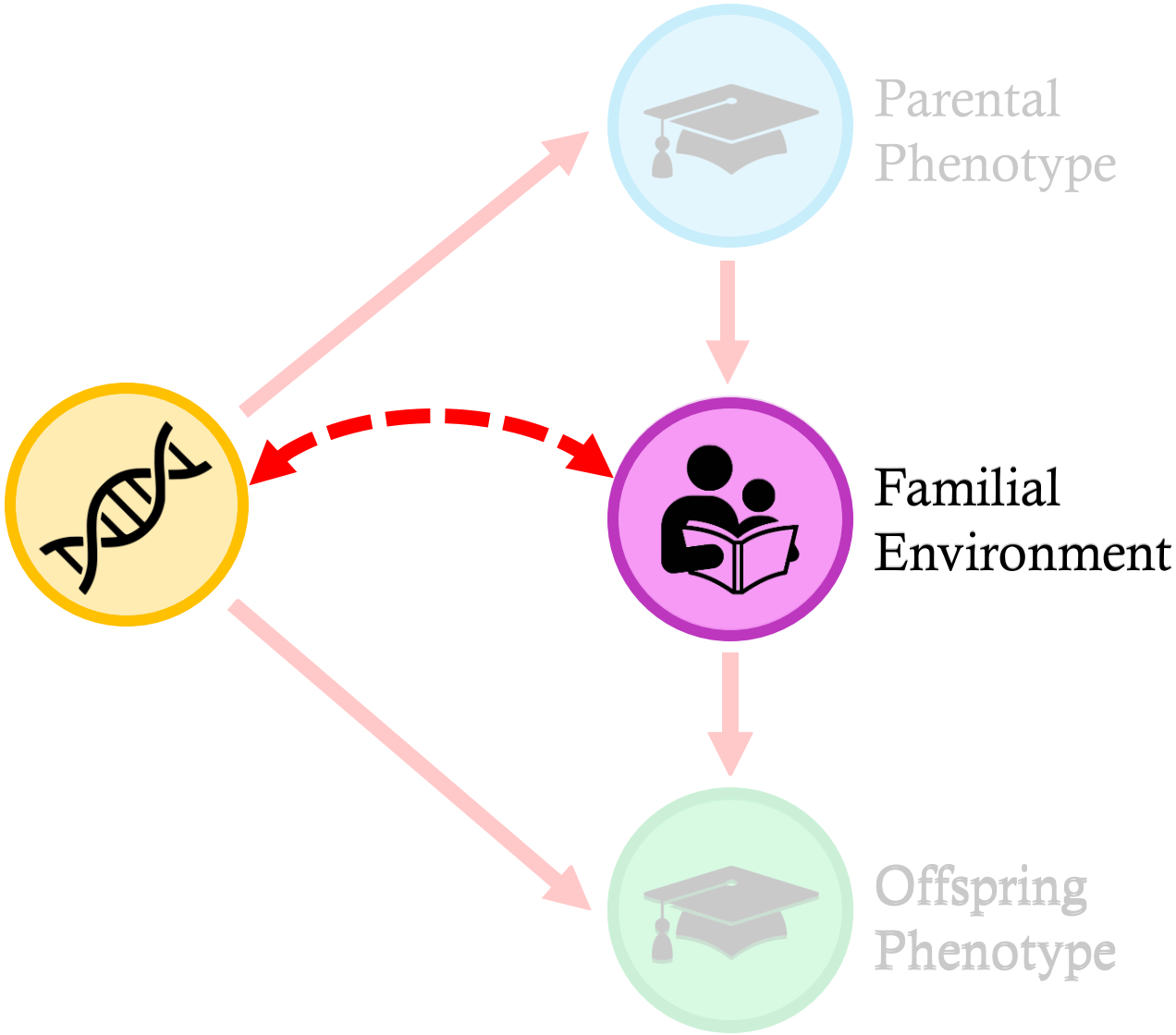

Parental
Phenotype
Familial
Environment
Offspring
Phenotype

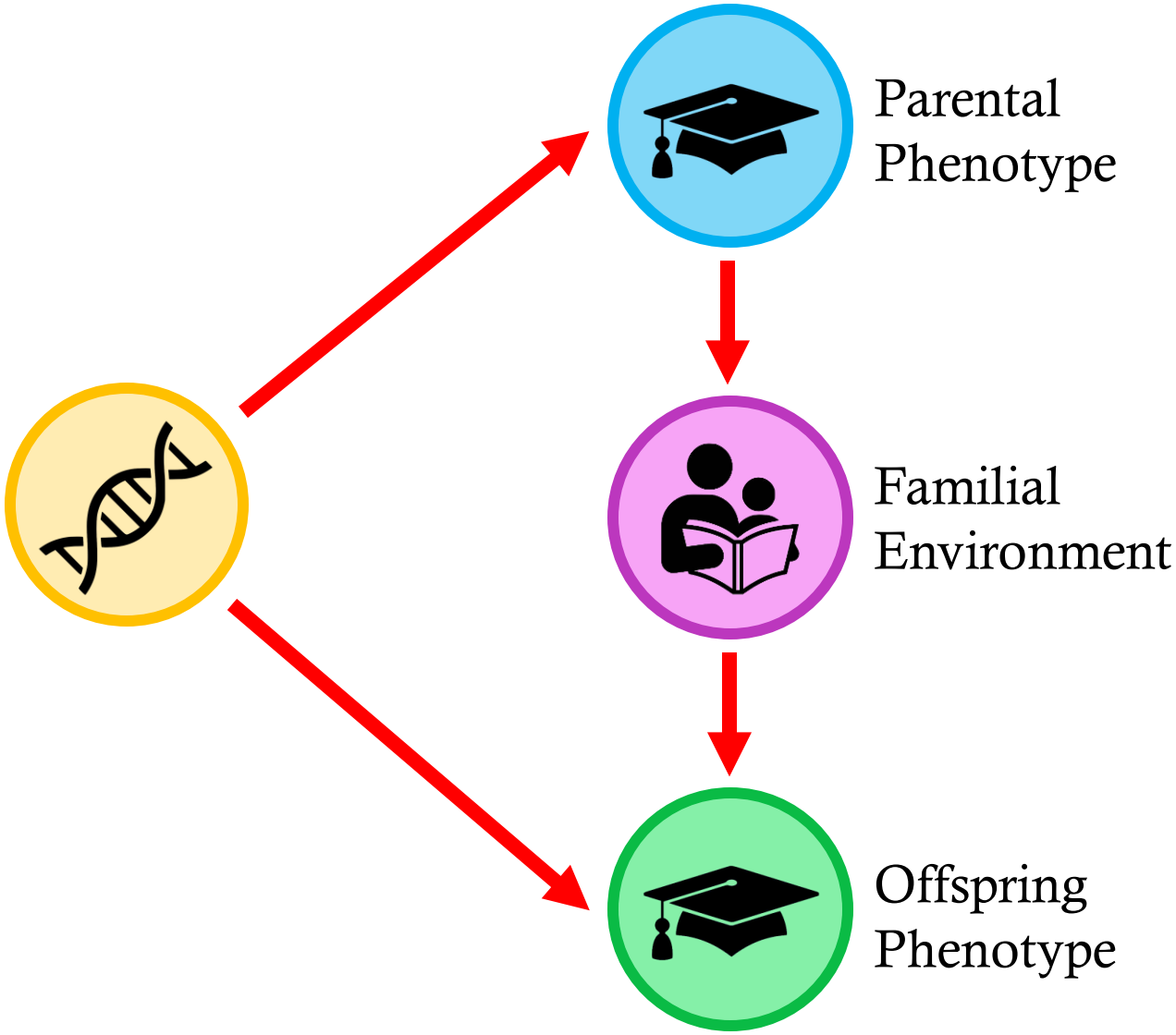

Parental
Phenotype
Offspring
Phenotype


Parental
Phenotype
Familial
Environment
Offspring
Phenotype

Genetic Nurture

aka "Passive Gene-Environment Covariance"




Parental
Phenotype
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Offspring
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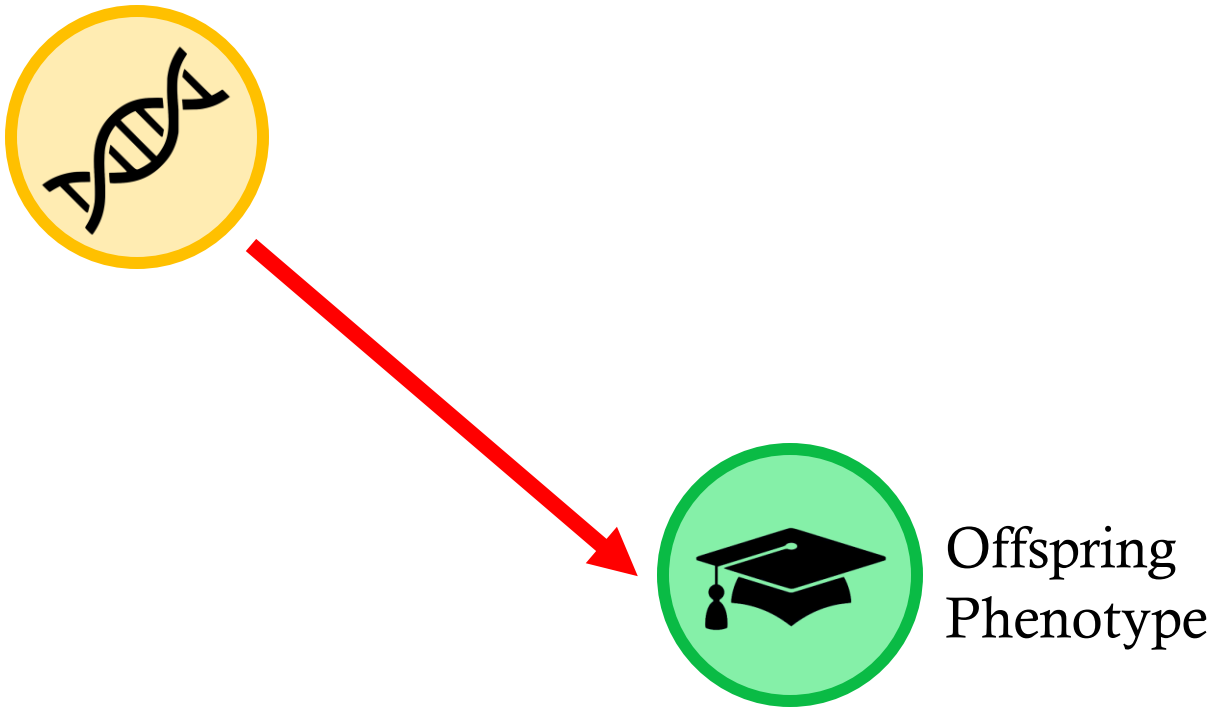
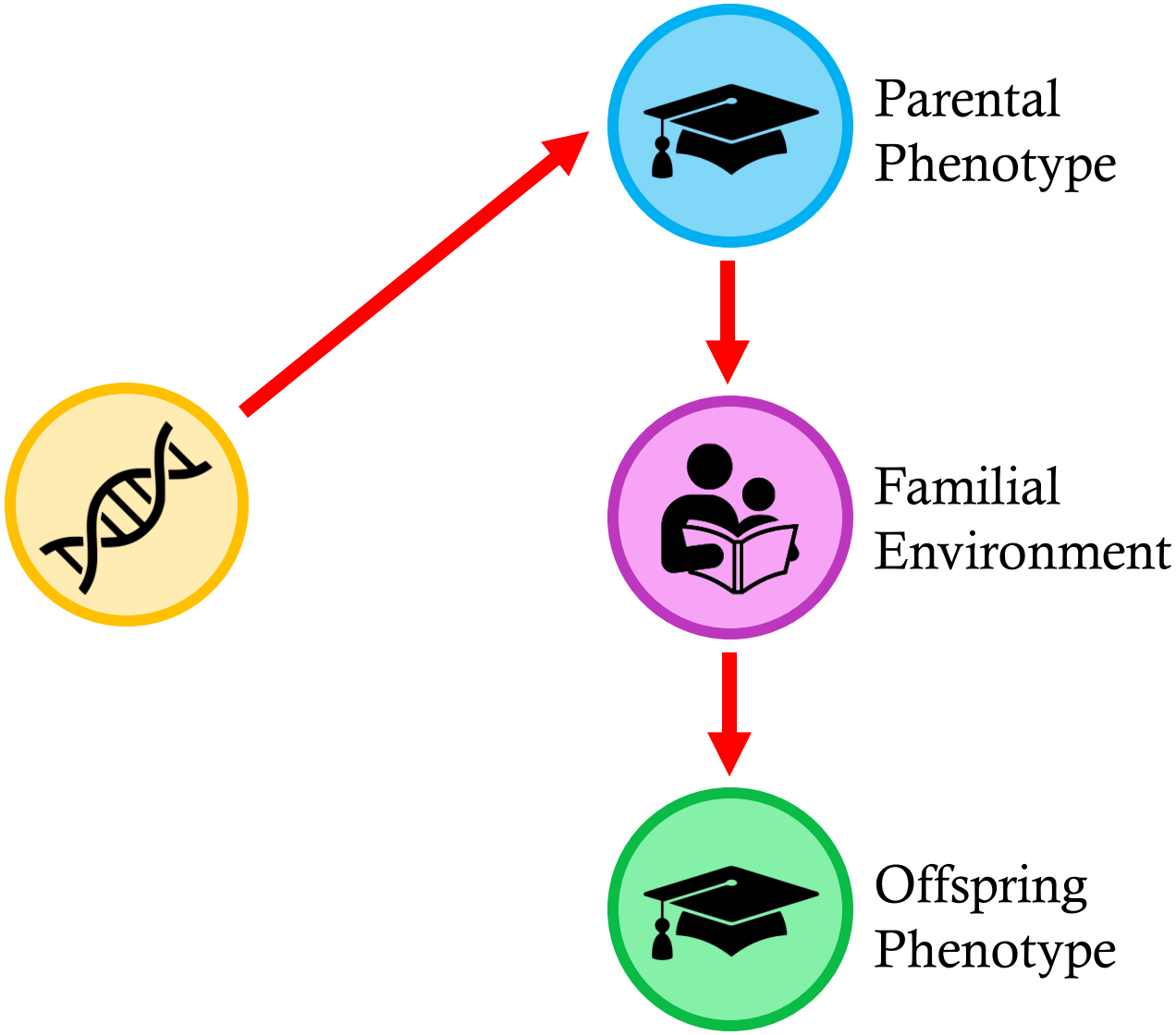
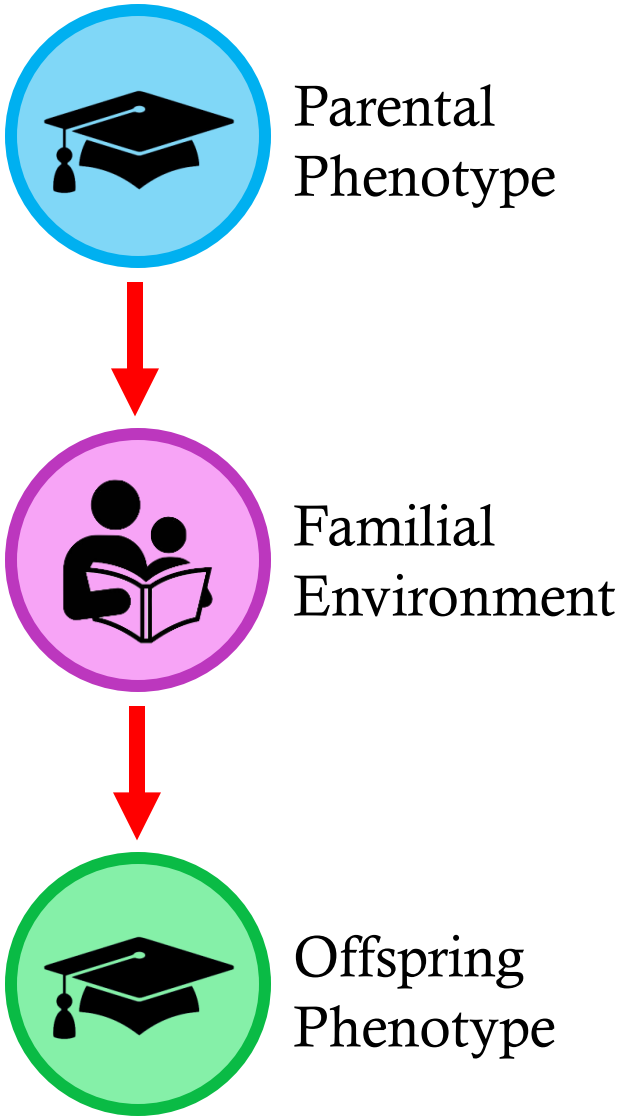
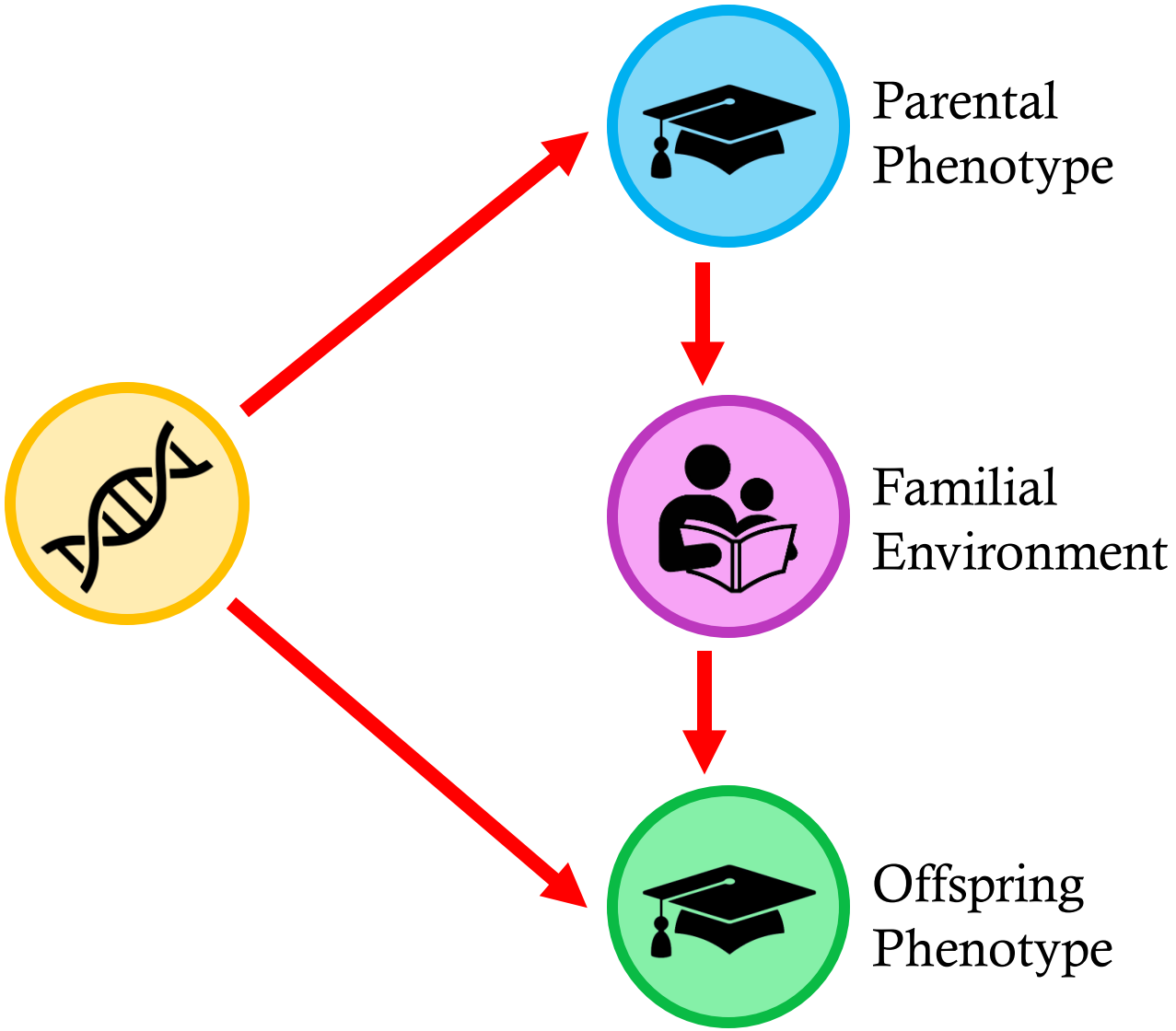

Offspring
Phenotype


Parental
Phenotype
Familial
Environment
Offspring
Phenotype

If unaccounted for, vertical transmission:

- Will upwardly bias estimates of SNP effects from GWAS
- Will upwardly bias estimates of shared environmental effects (C) in twin ACE models
- Will upwardly bias estimates of additive genetic effects (A) in twin AE and ADE models




Parental
Phenotype
Familial
Environment
Offspring
Phenotype

International Journal of Epidemiology, 2018, 1229–1241
doi: 10.1093/ije/dyy015
Advance Access Publication Date: 13 February 2018
Original article

Methods

Using structural equation modelling to jointly estimate maternal and fetal effects on birthweight in the UK Biobank

Nicole M Warrington,[1] Rachel M Freathy,[2,3] Michael C Neale[4] and David M Evans[1,3,5]*

International Journal of Epidemiology, 2019, 861–875
doi: 10.1093/ije/dyz019
Advance Access Publication Date: 27 February 2019
Original article

Mendelian Randomization

Elucidating the role of maternal environmental exposures on offspring health and disease using two-sample Mendelian randomization

David M Evans ,[1,2,3]* Gunn-Helen Moen,[4,5] Liang-Dar Hwang,[1] Debbie A Lawlor[2,3,6] and Nicole M Warrington[1]

PLOS MEDICINE

RESEARCH ARTICLE

Assessing the Causal Relationship of Maternal Height on Birth Size and Gestational Age at Birth: A Mendelian Randomization Analysis

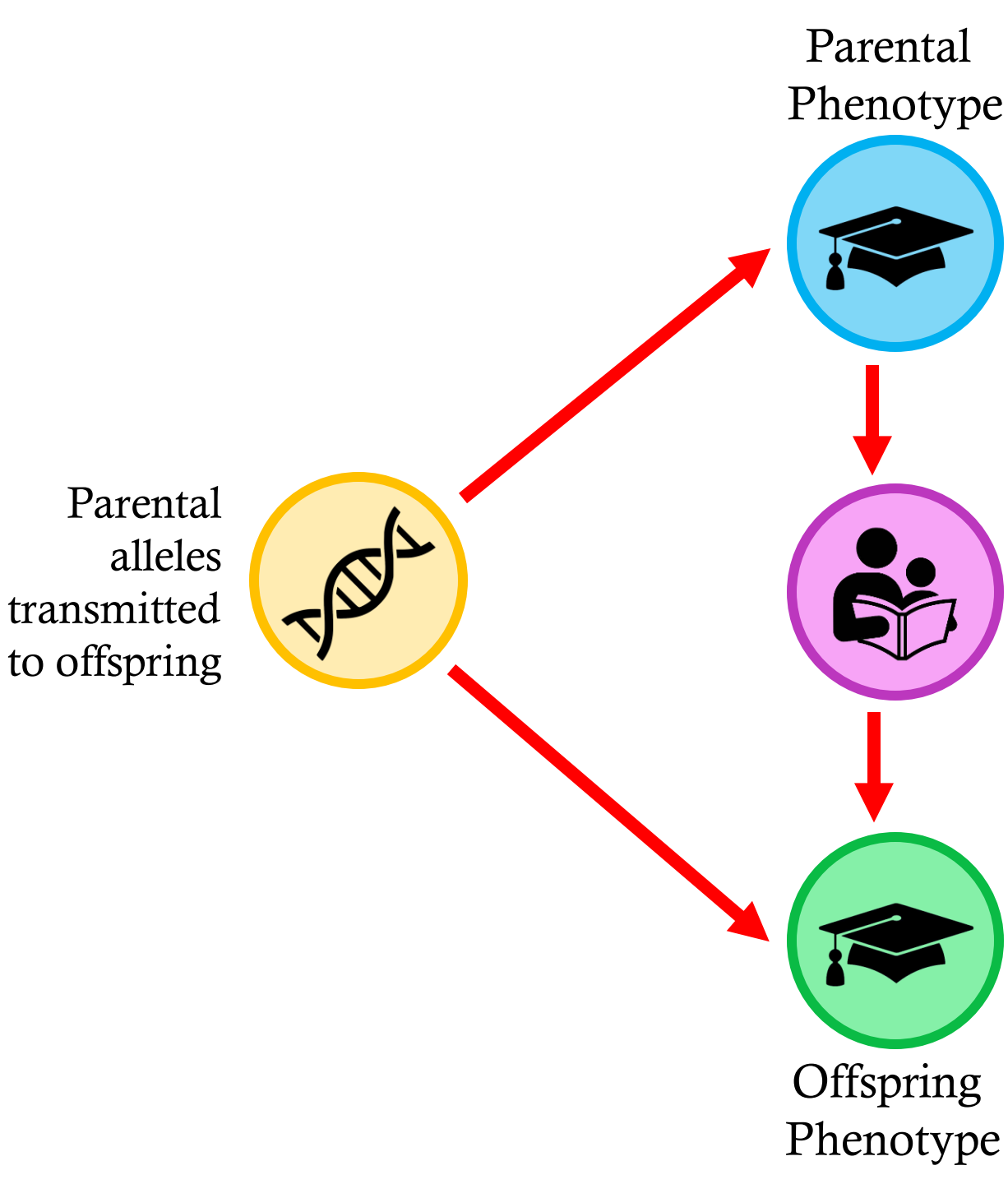
Ge Zhang[1,2]*, Jonas Bacelis[3], Candice Lengyel[2], Kari Teramo[4], Mikko Hallman[5], Øyvind Helgeland[6], Stefan Johansson[6,7], Ronny Myhre[8], Verena Sengpiel[3], Pål Rasmus Njølstad[6,9], Bo Jacobsson[8,10], Louis Muglia[2]*

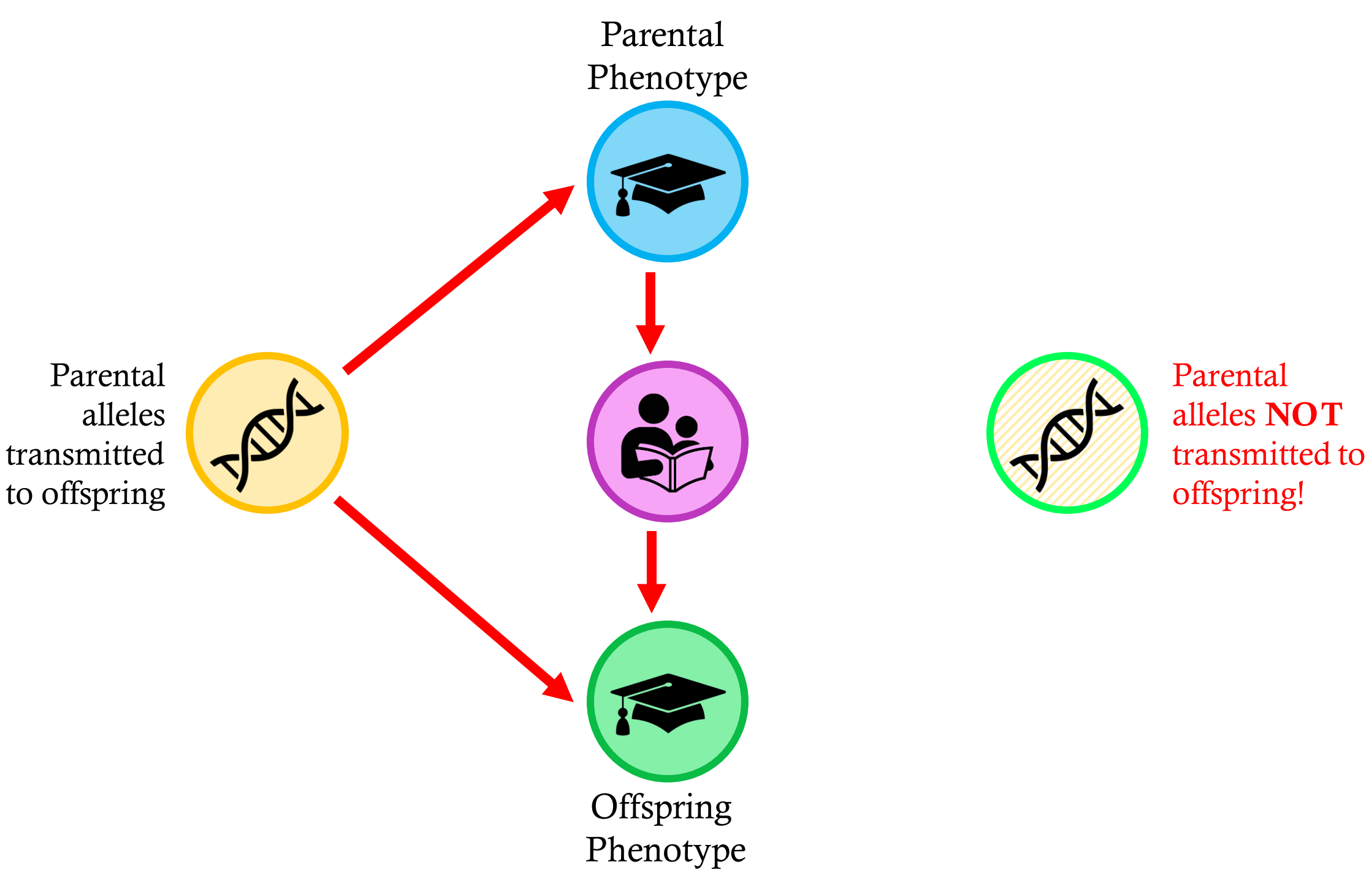
RESEARCH

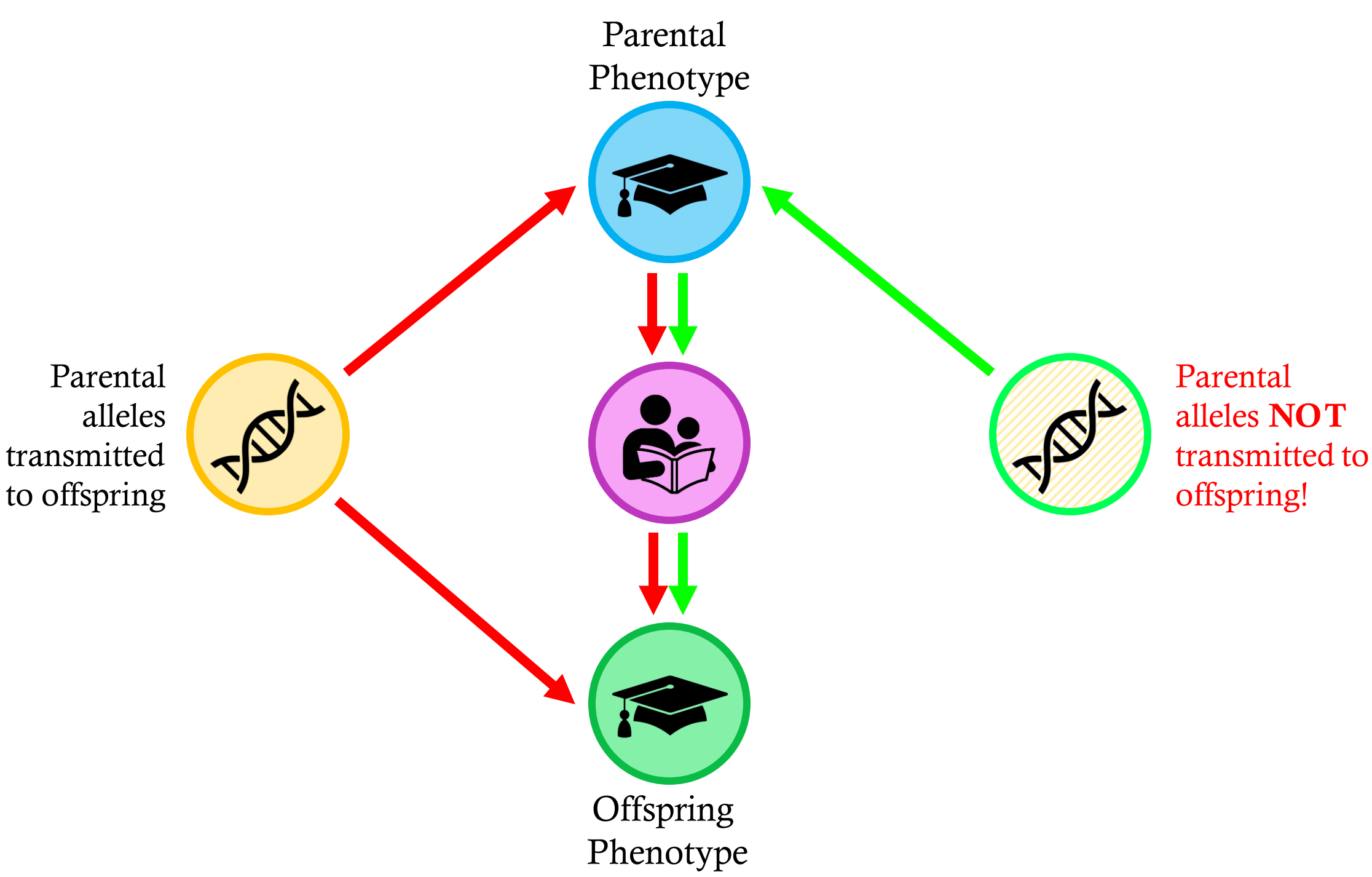
HUMAN GENOMICS

The nature of nurture: Effects of parental genotypes

Augustine Kong,[1,2,3]* Gudmar Thorleifsson,[1] Michael L. Frigge,[1] Bjarni J. Vilhjalmsson,[4,5] Alexander I. Young,[1,2,6] Thorgeir E. Thorgeirsson,[1] Stefania Benonisdottir,[1] Asmundur Oddsson,[1] Bjarni V. Halldorsson,[1] Gisli Masson,[1] Daniel F. Gudbjartsson,[1,3] Agnar Helgason,[1,7] Gyda Bjornsdottir,[1] Unnur Thorsteinsdottir,[1,8] Kari Stefansson[1,8]*


Parental
Phenotype
Parental
alleles
transmitted
to offspring
Offspring
Phenotype


Parental
Phenotype
Parental
alleles
transmitted
to offspring
Parental
alleles NOT
transmitted to
offspring!
Offspring
Phenotype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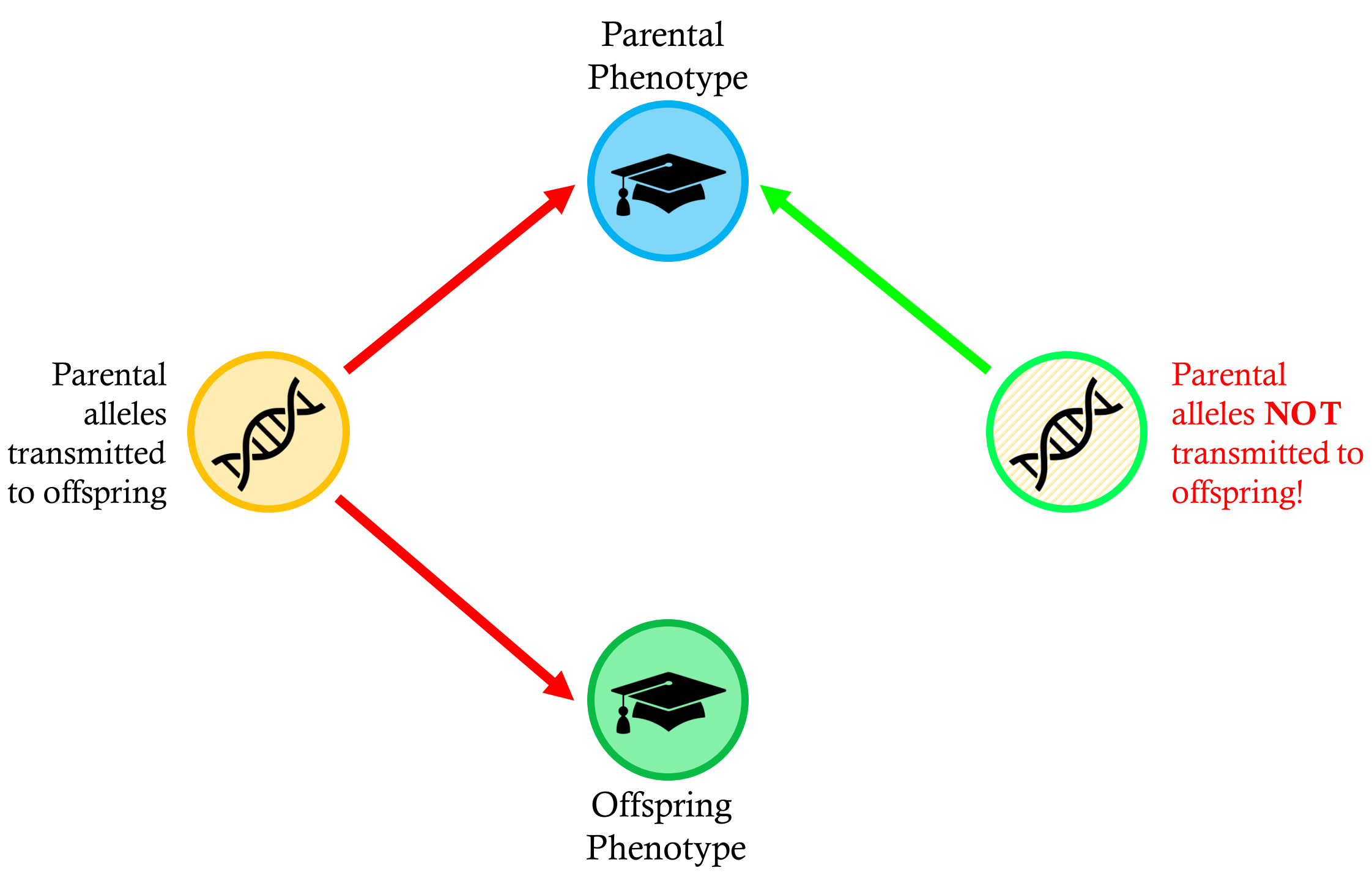
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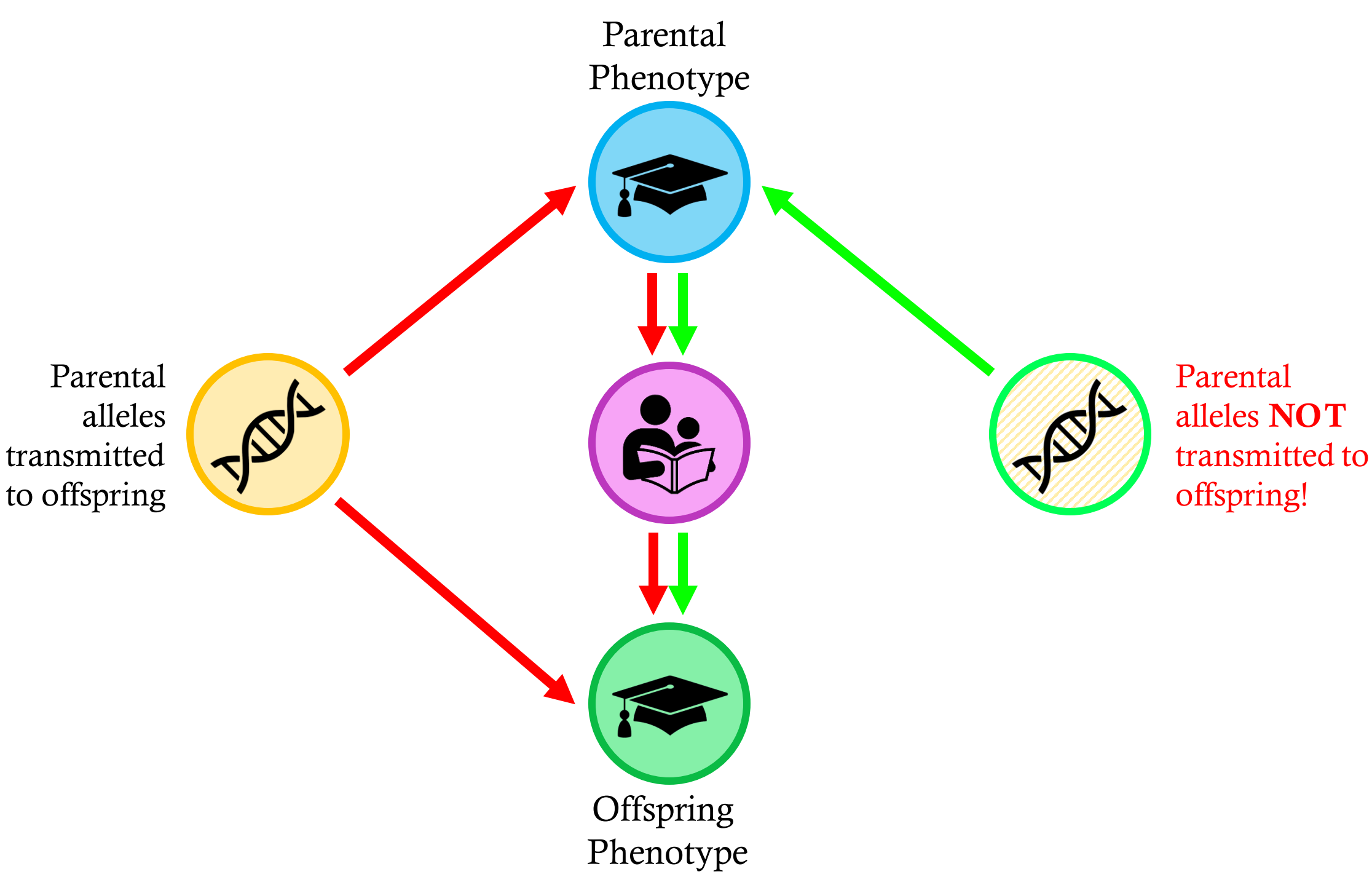
Parental
Phenotype
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Parental
alleles NOT
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offspring!
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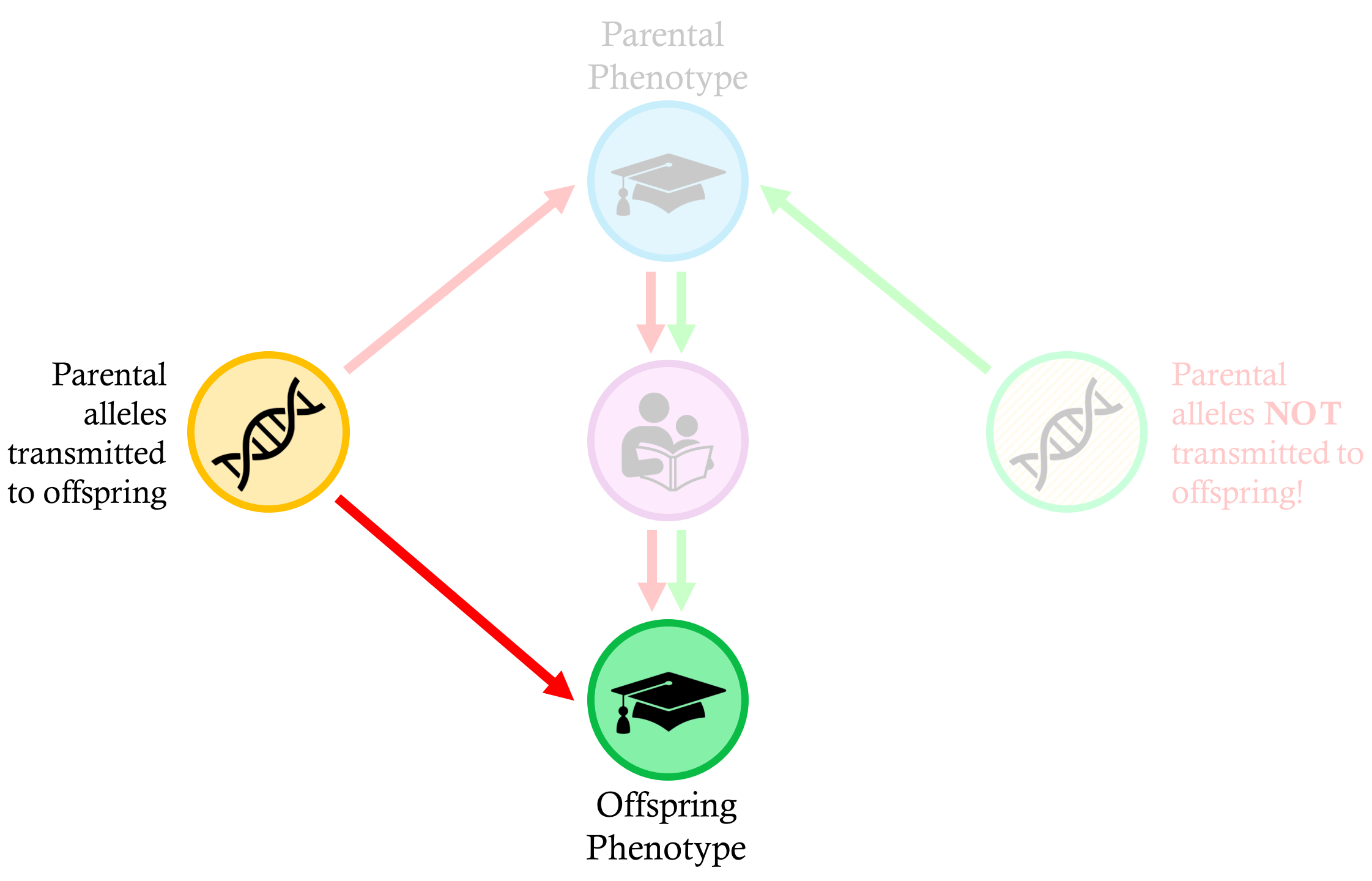
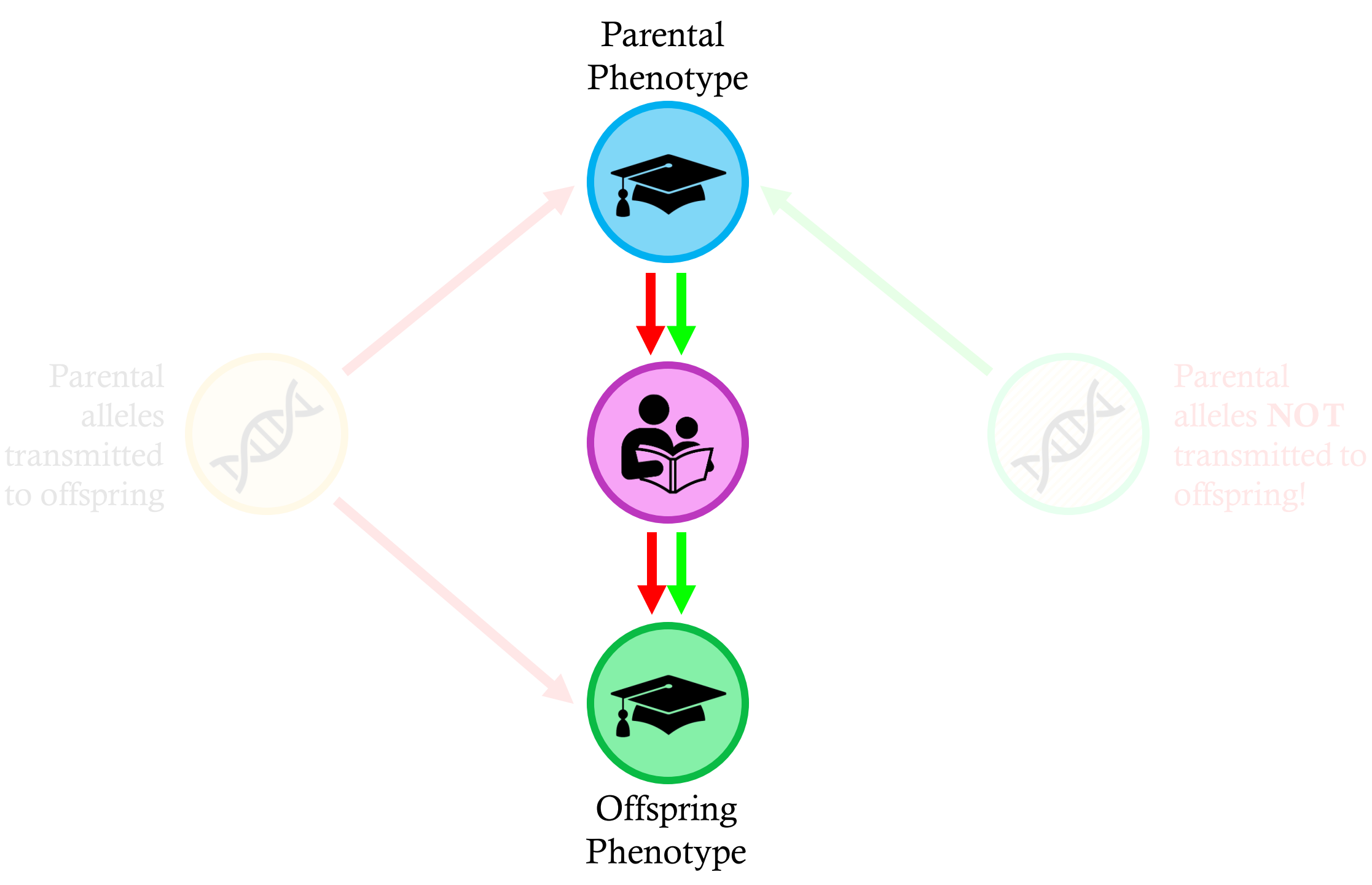
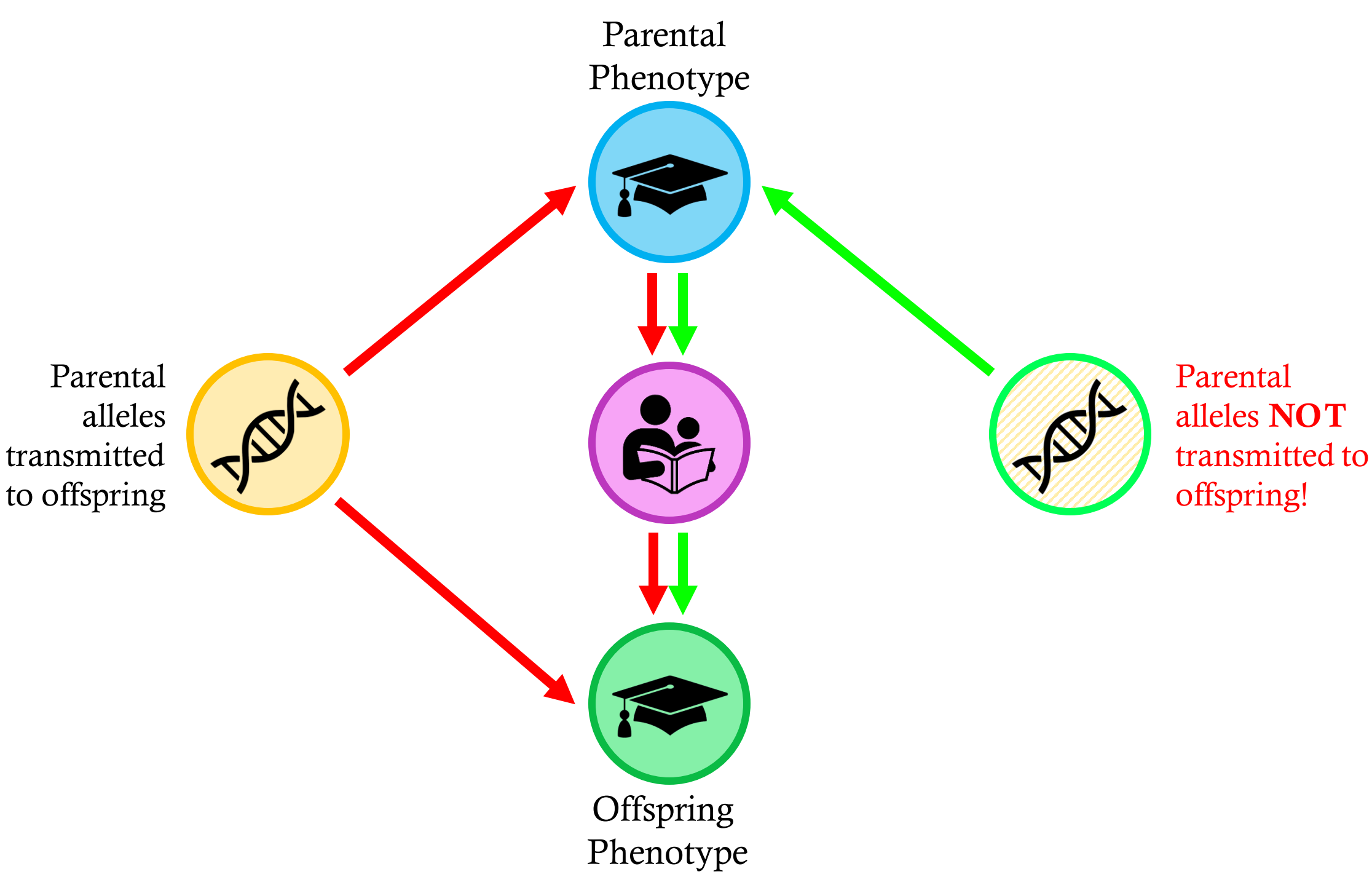
Phenotype


Parental Phenotype
Parental alleles transmitted to offspring
Parental alleles NOT transmitted to offspring!
Offspring Phenotype


Parental
Phenotype
Parental
alleles
transmitted
to offspring
Parental
alleles NOT
transmitted to
offspring!
Offspring
Phenotype


Parental
Phenotype
Parental
alleles
transmitted
to offspring
Parental
alleles NOT
transmitted to
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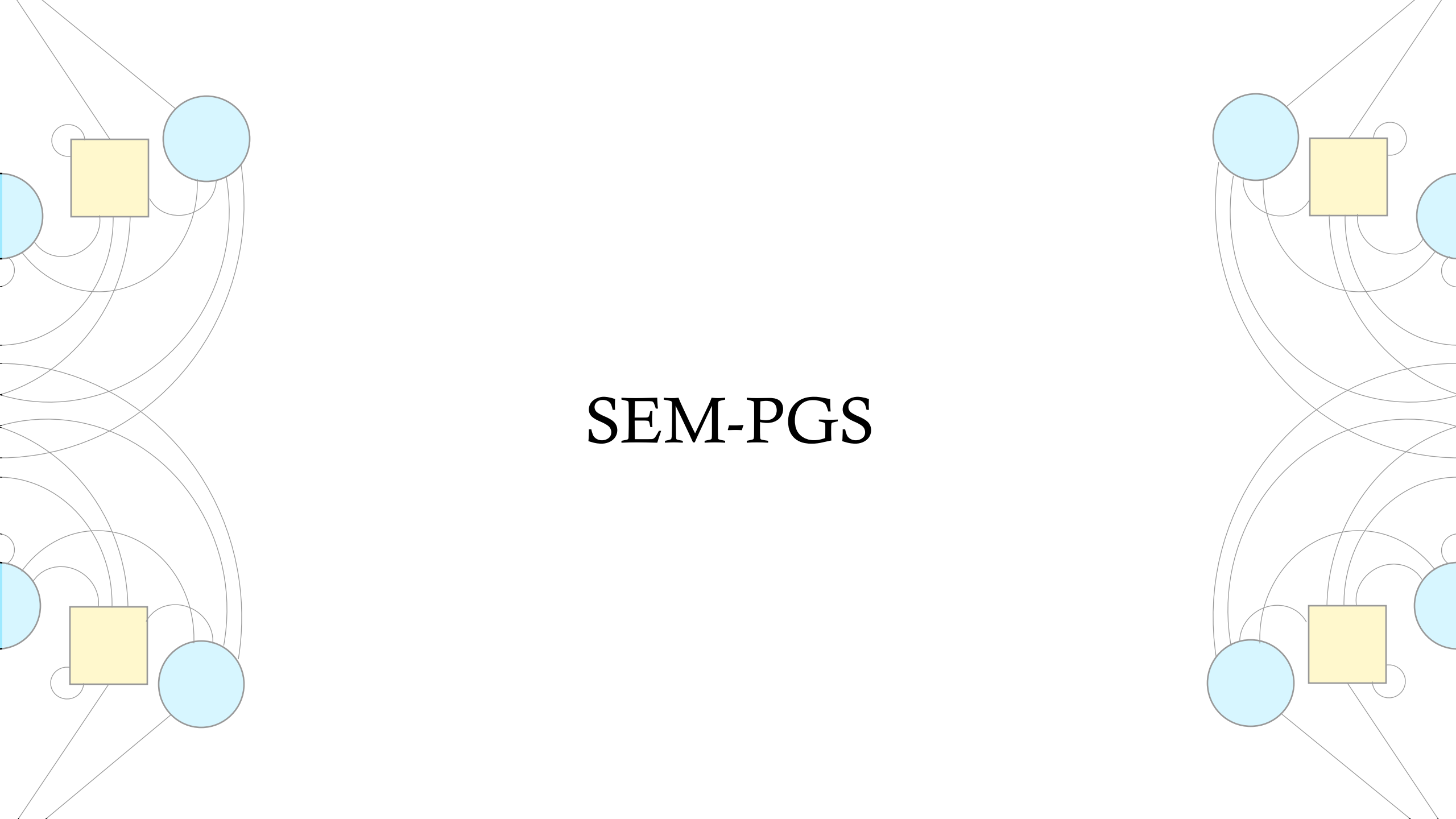
Offspring
Phenotype

ORIGINAL RESEARCH

Estimation of Parental Effects Using Polygenic Scores

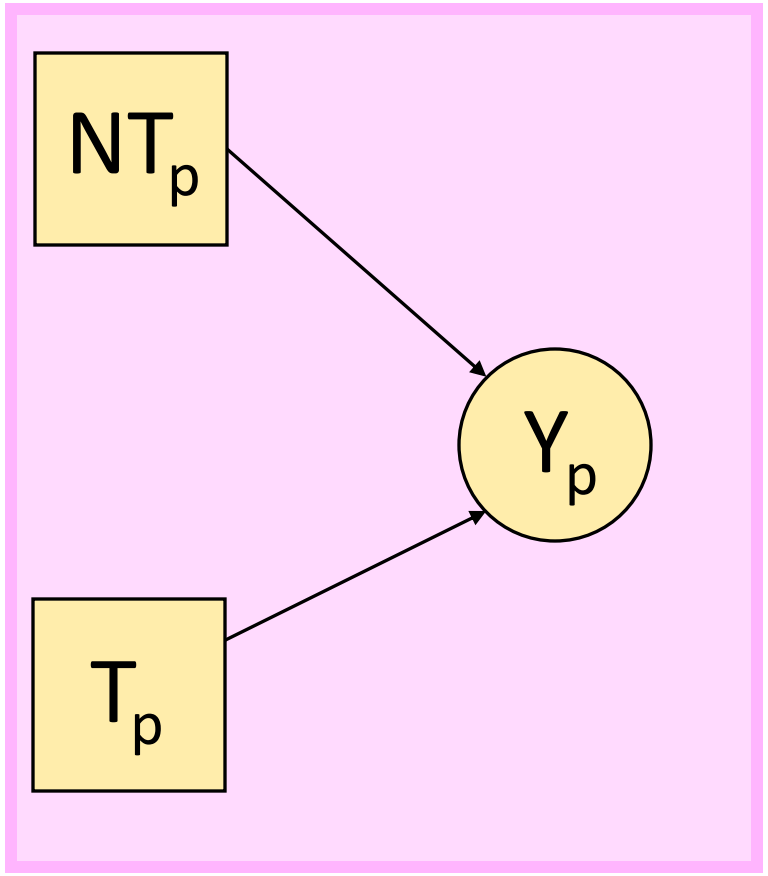
Jared V. Balbona[1,2] · Yongkang Kim[1] · Matthew C. Keller[1,2]

Received: 7 August 2020 / Accepted: 20 November 2020 / Published online: 2 January 2021

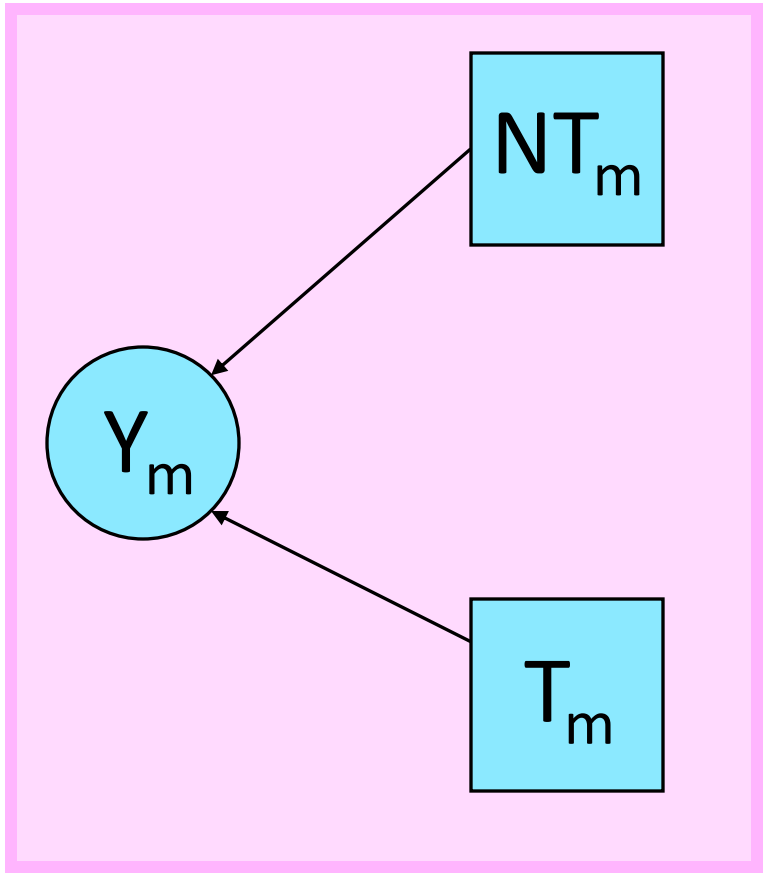

SEM-PGS

SEM-PGS

1. Unbiased estimates of h^2, vertical transmission, and genetic nurture– Even when the PGS being used is not very predictive
2. Properly accounts for various types of assortative mating at both equilibrium and disequilibrium
3. In principle, is not biased by missing data-- Thus, it does not require complete trios
4. Is very easy to use, relying on relatively simple math
5. Allows for a vast number of extensions to best fit the trait and data being worked with



Paternal Genes and Phenotype

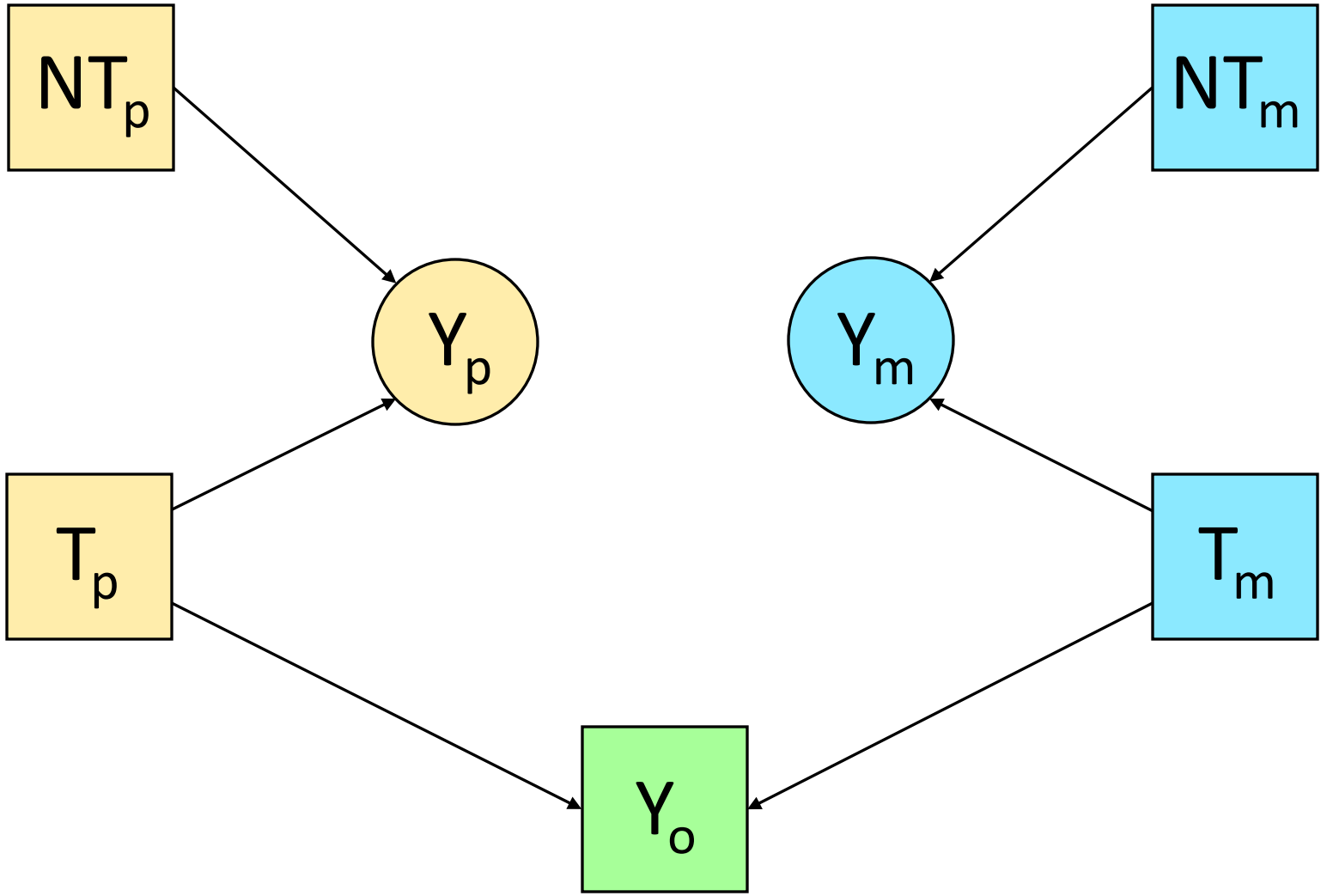


Maternal Genes and Phenotype

Y: Phenotypic Value

T: PGS made from the parent's *transmitted* alleles

NT: PGS made from the parent's *non-transmitted* alleles



Y: Phenotypic Value

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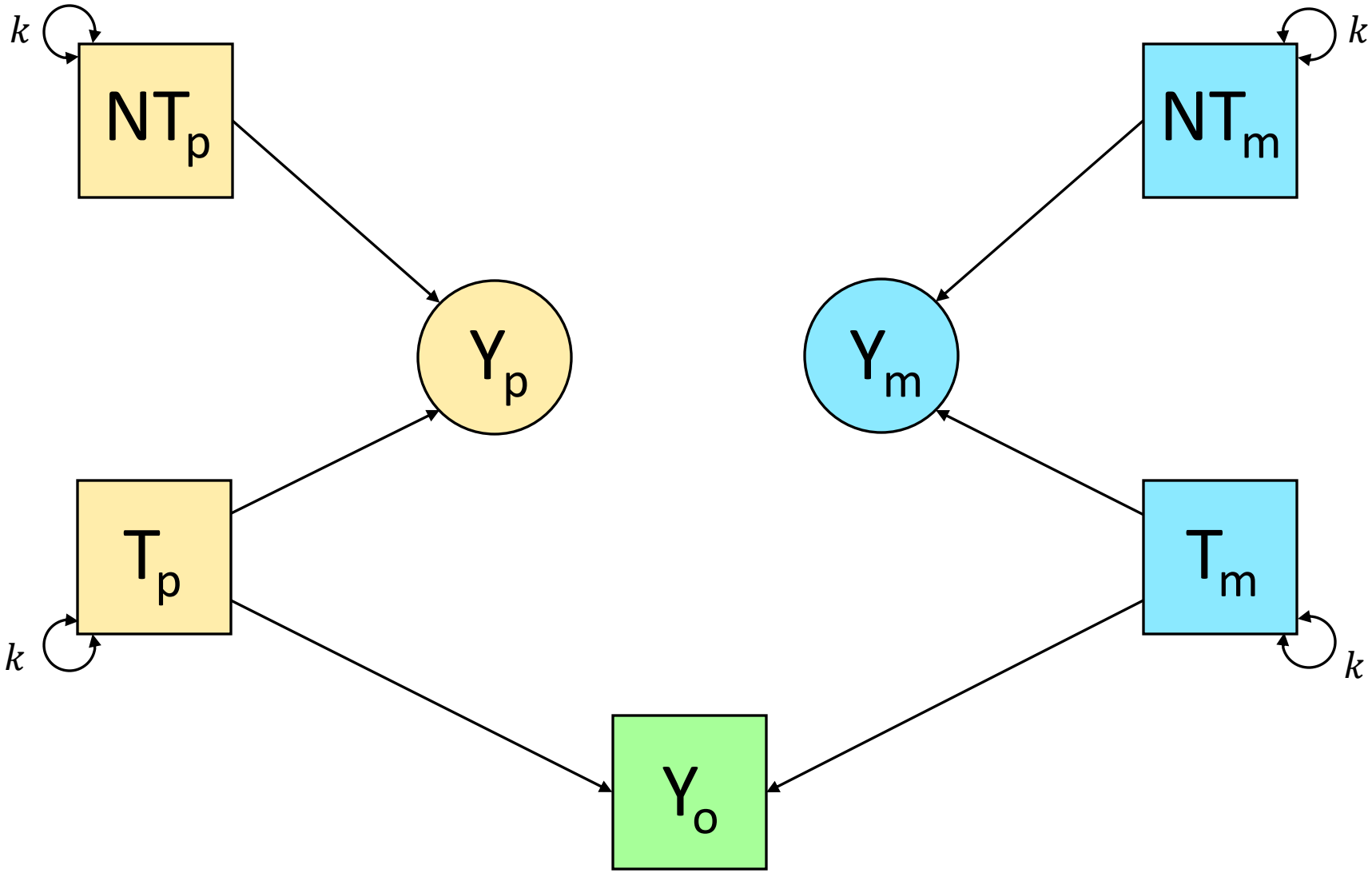

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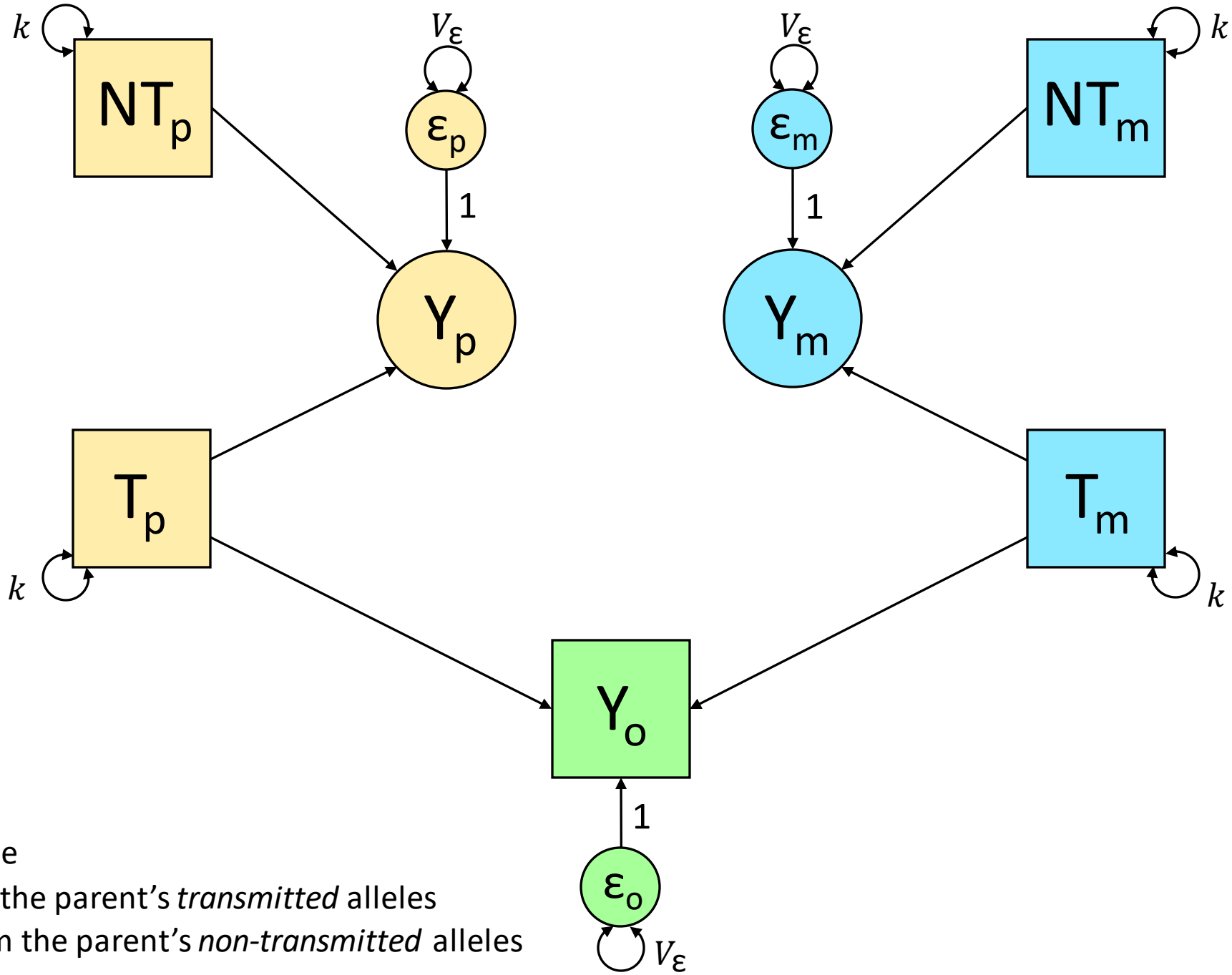

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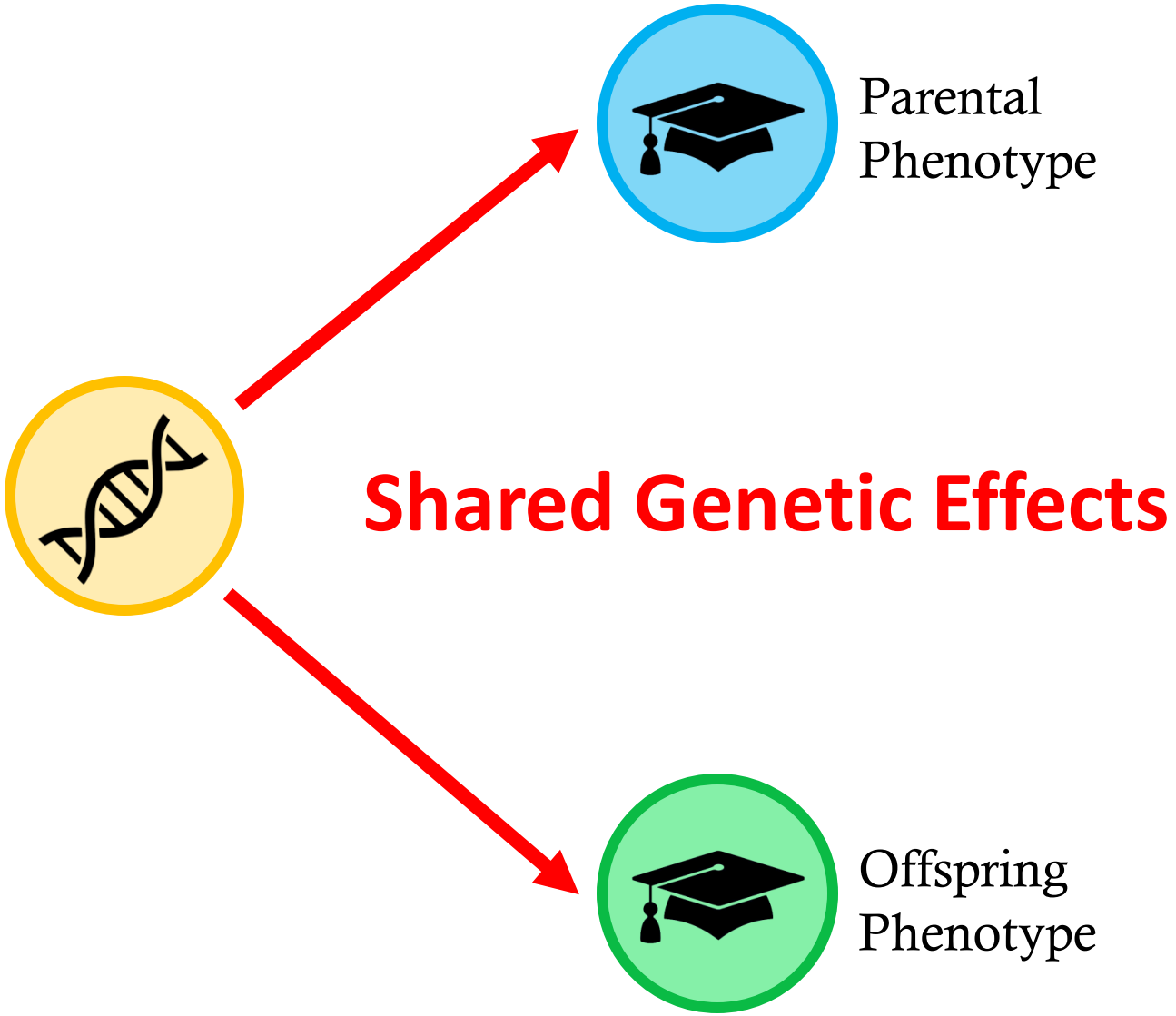
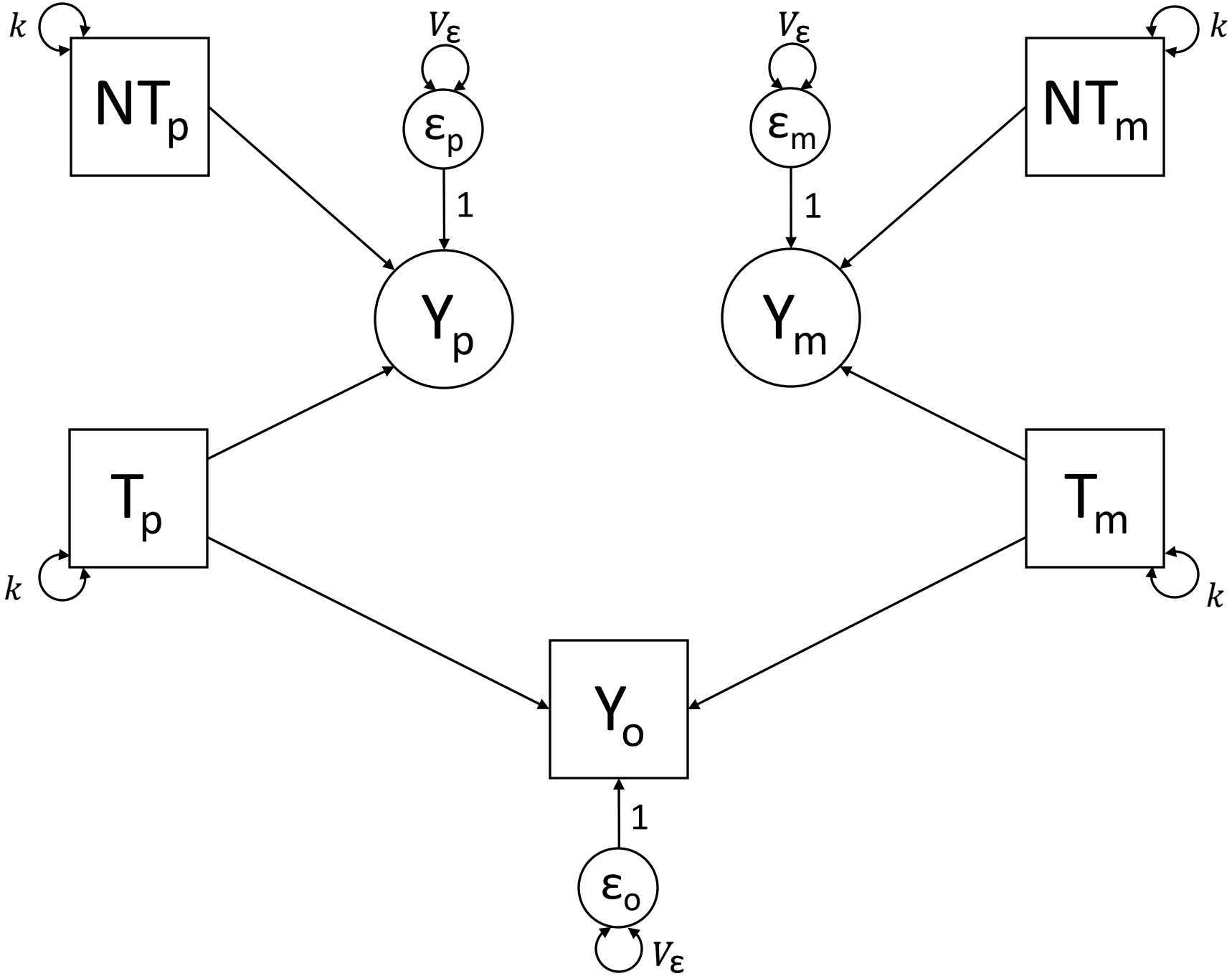
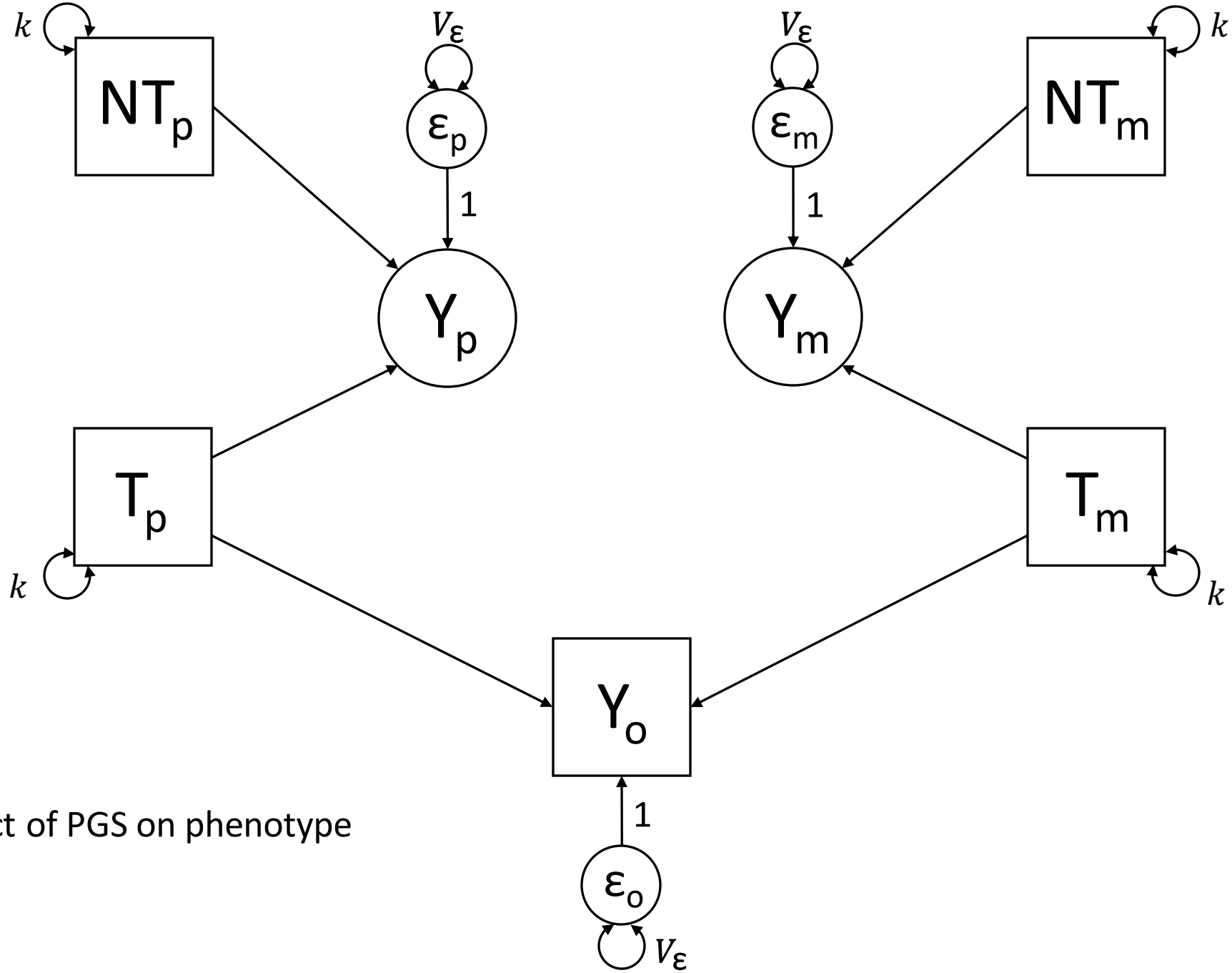
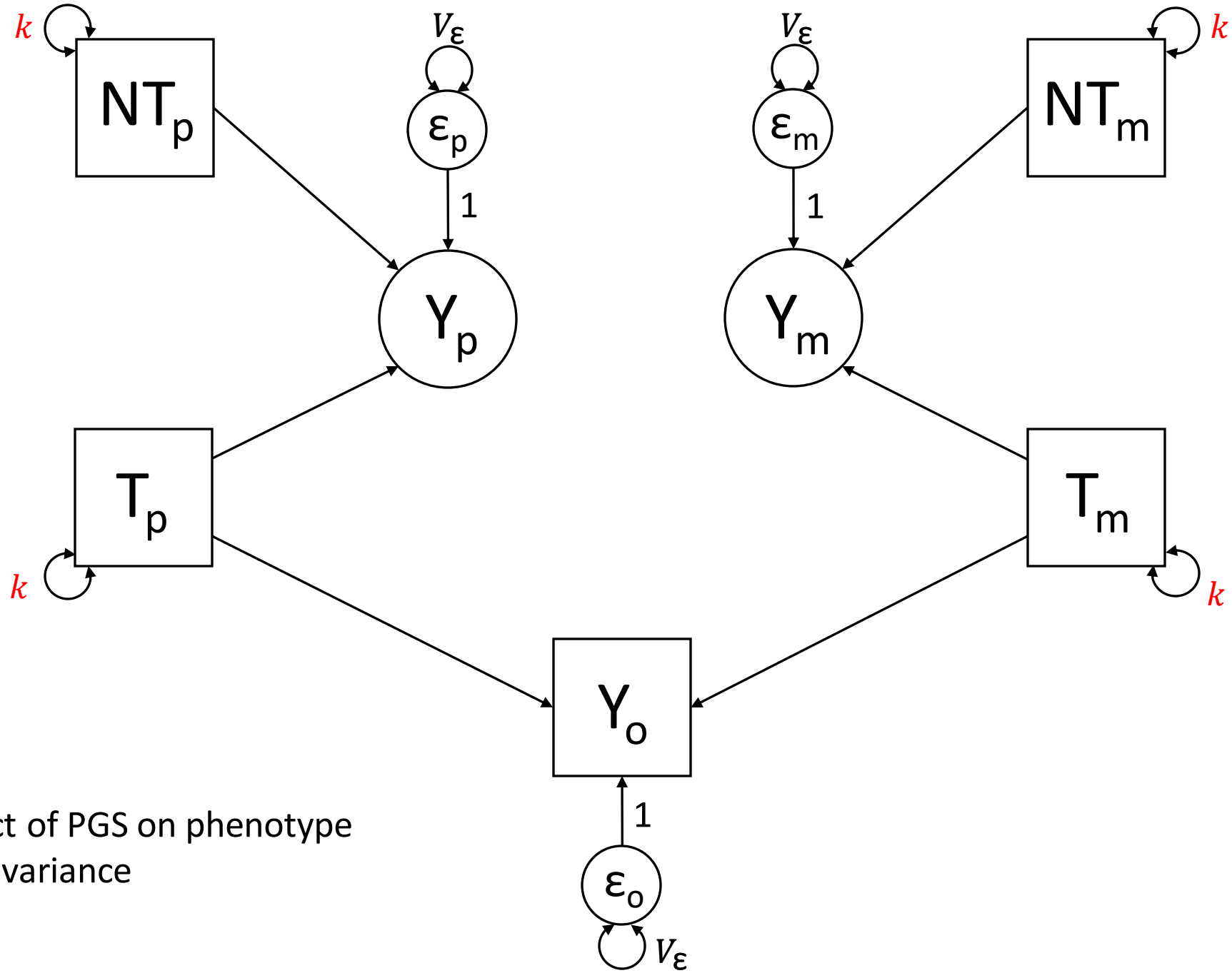

Parental
Phenotype
Shared Genetic Effects
Offspring
Phenotype


k
NT_p
V_ε
ε_p
1
Y_p
T_p
k
V_ε
ε_m
1
NT_m
k
Y_m
T_m
k
Y_o
1
ε_o
V_ε

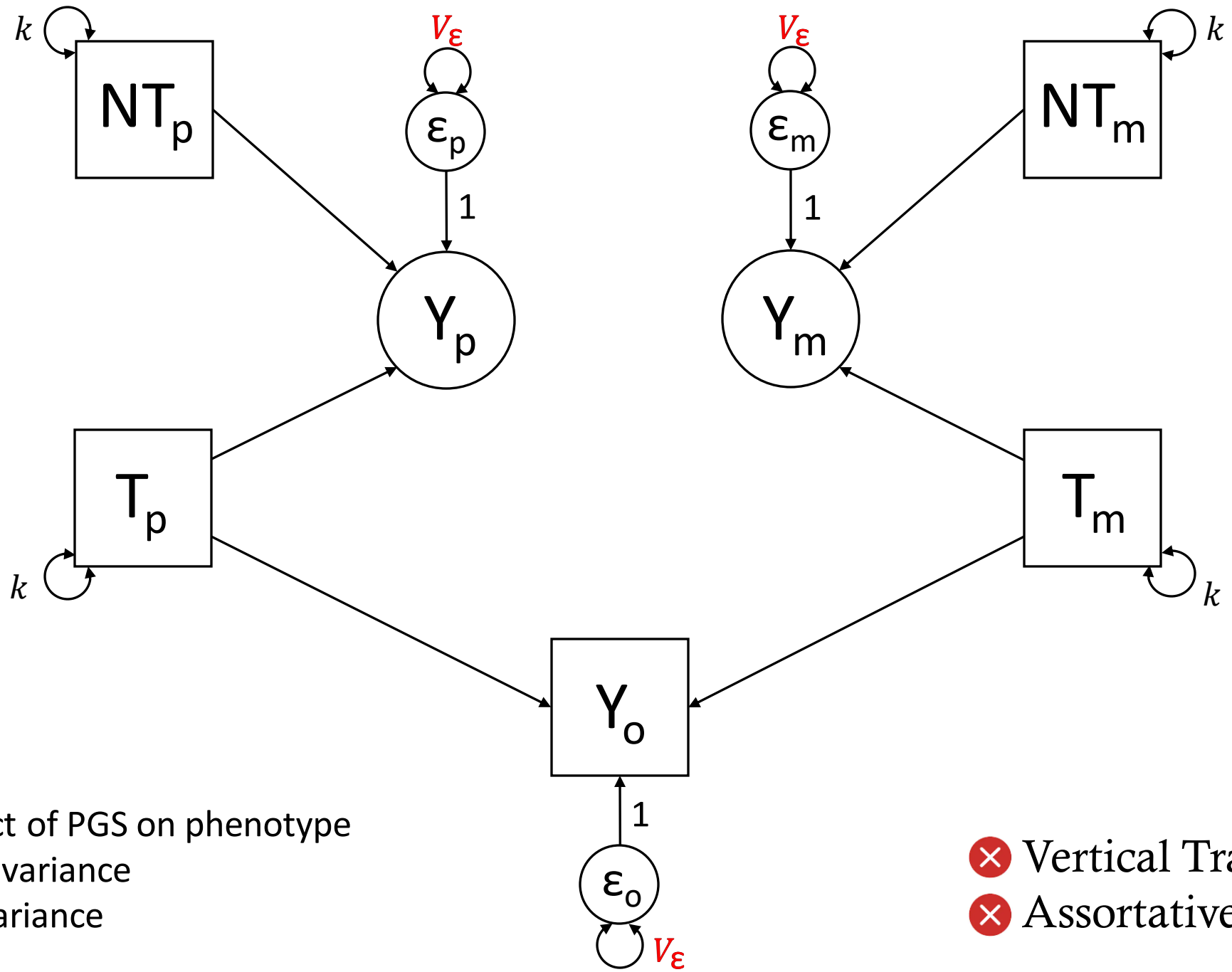


δ : Direct effect of PGS on phenotype



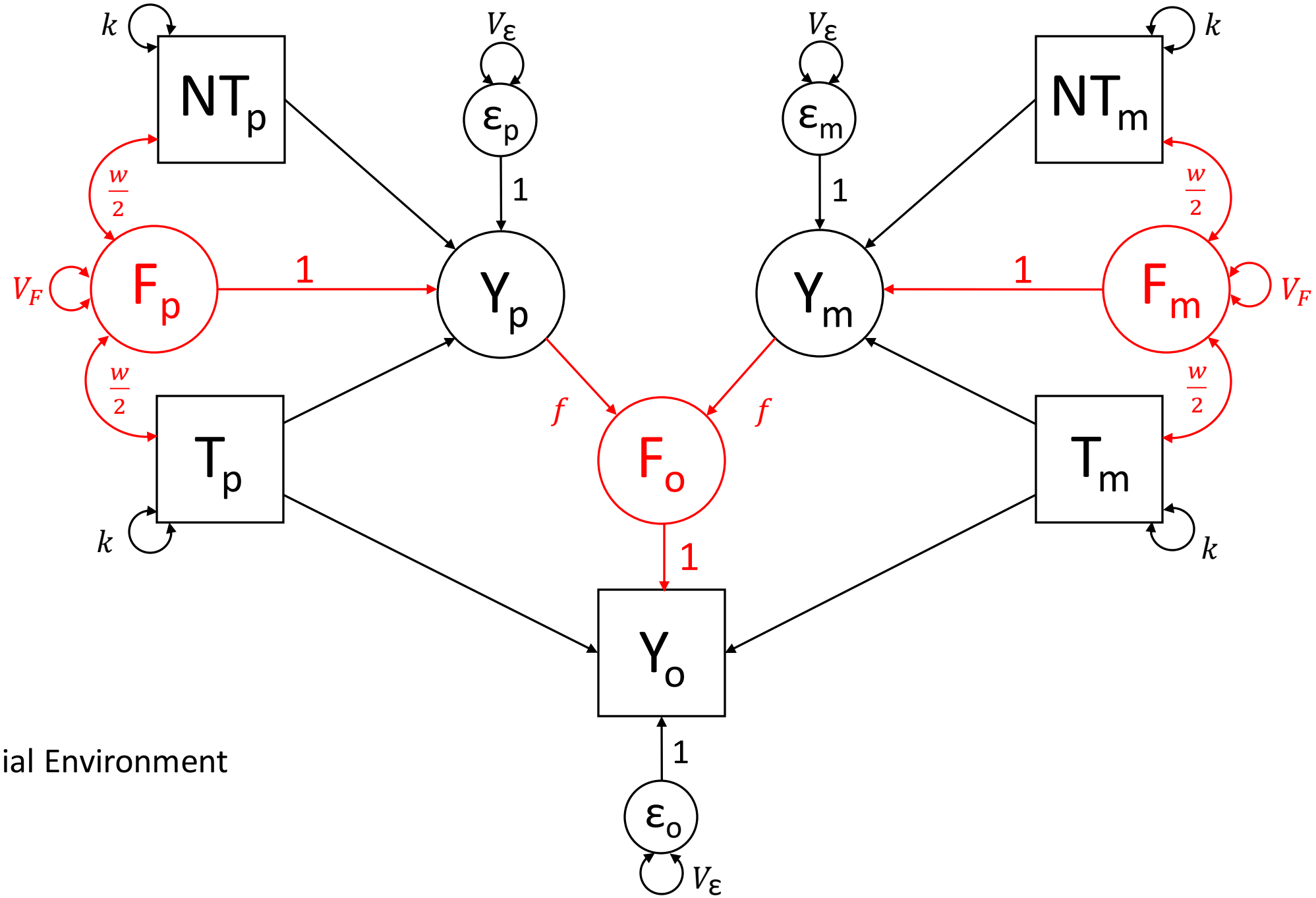
δ : Direct effect of PGS on phenotype

k : Haplotypic variance

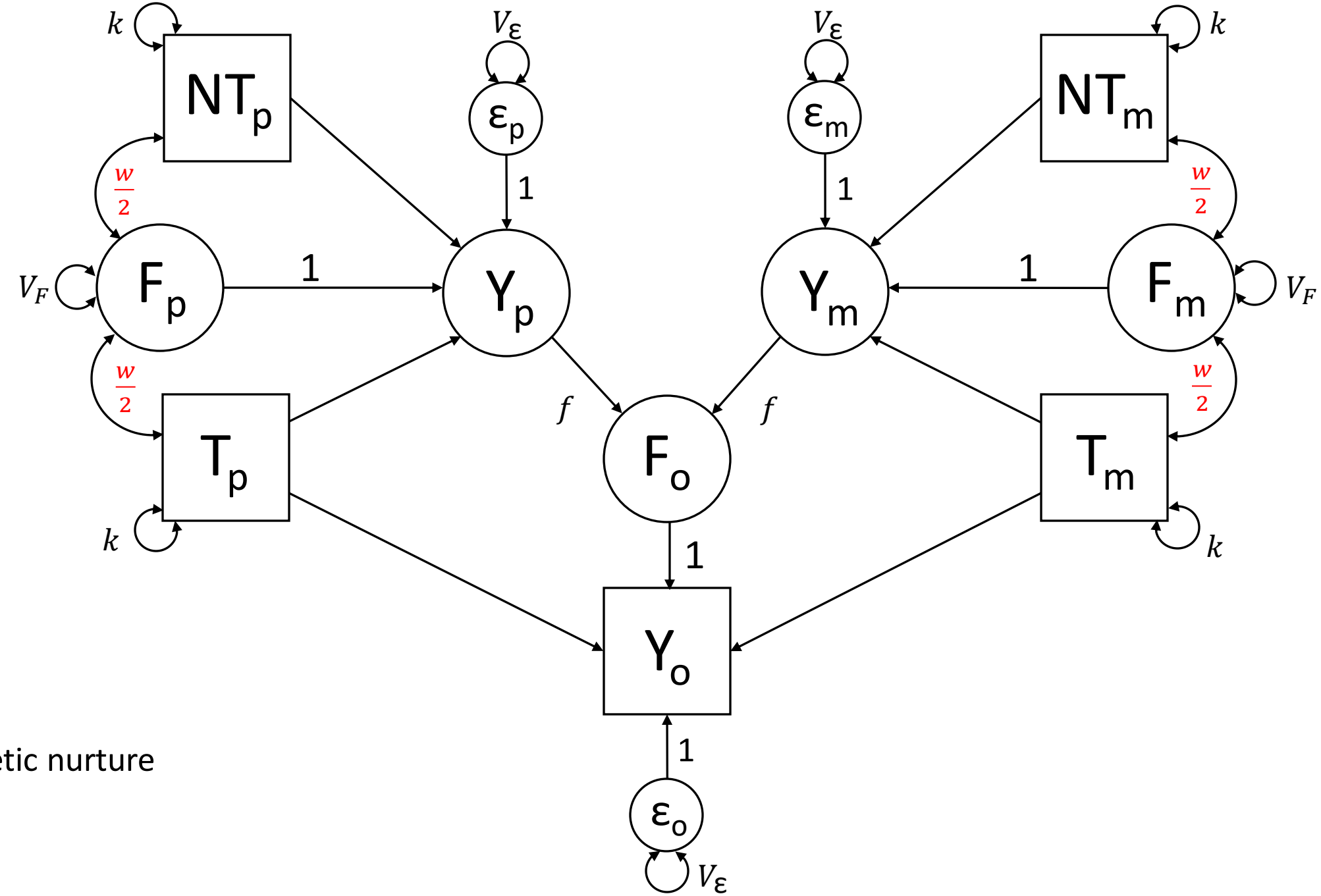


δ : Direct effect of PGS on phenotype
k: Haplotypic variance
V_ε: Residual variance

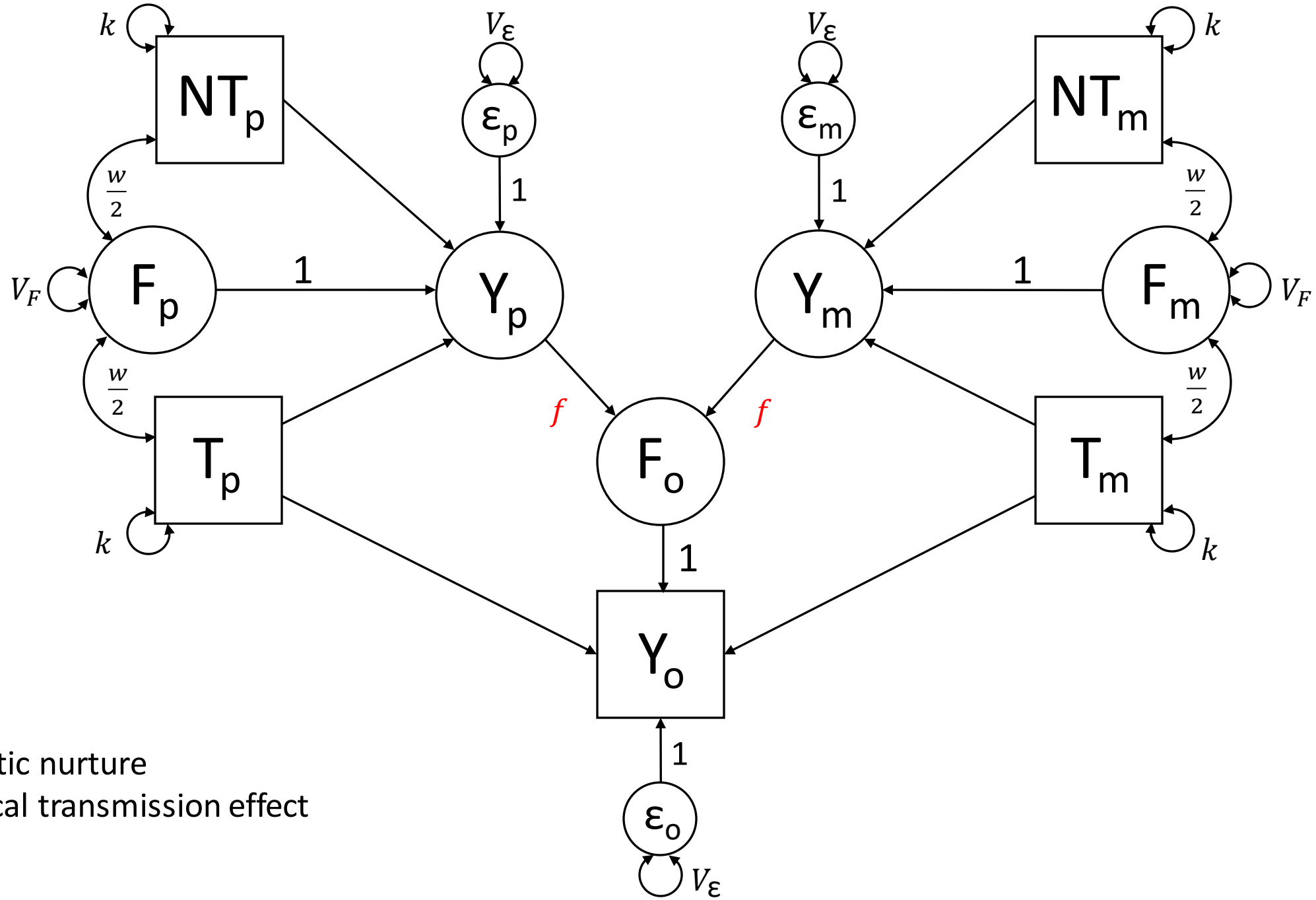
⊗ Vertical Transmission
⊗ Assortative Mating



F : Familial Environment

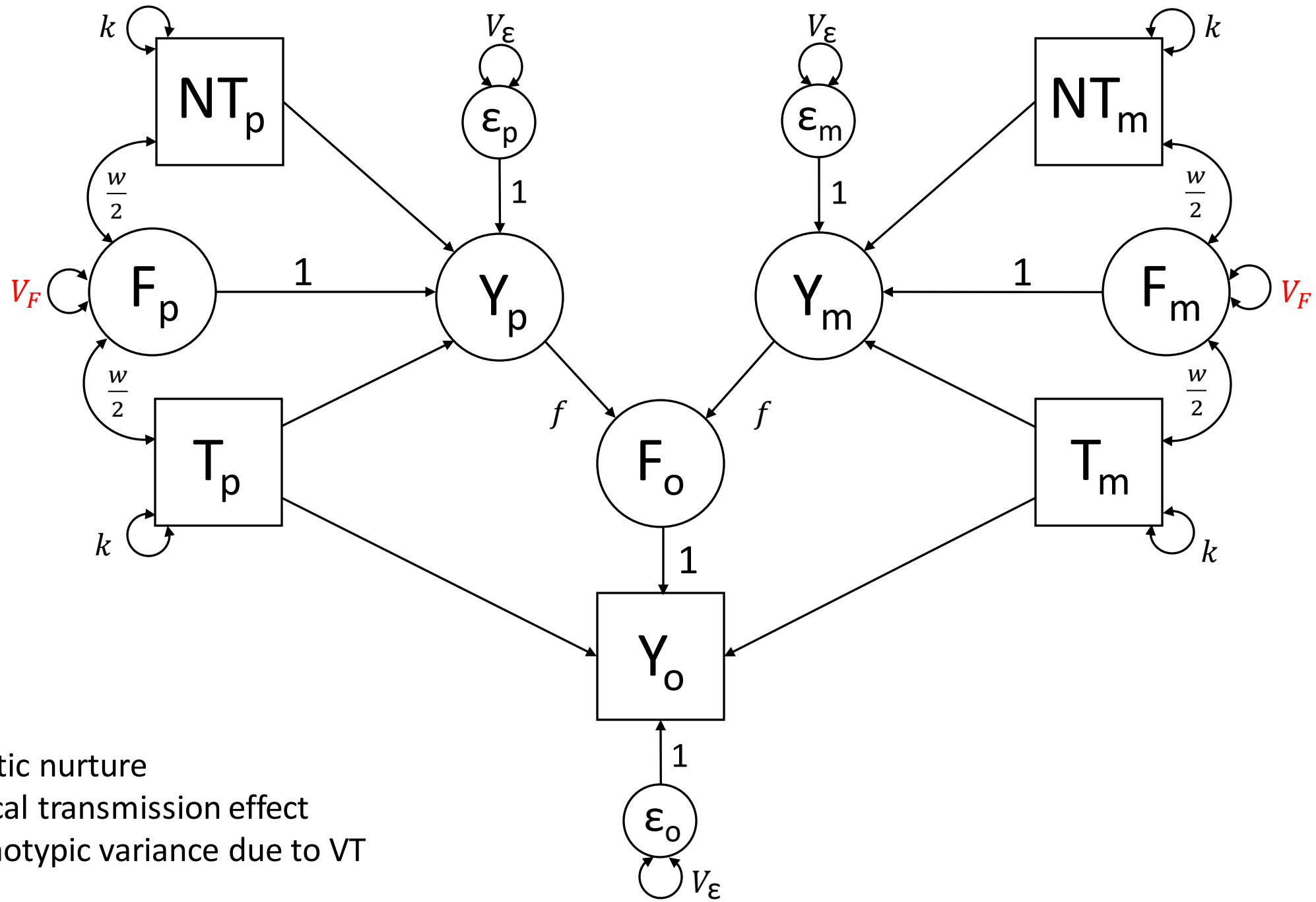


w : Genetic nurture



w : Genetic nurture

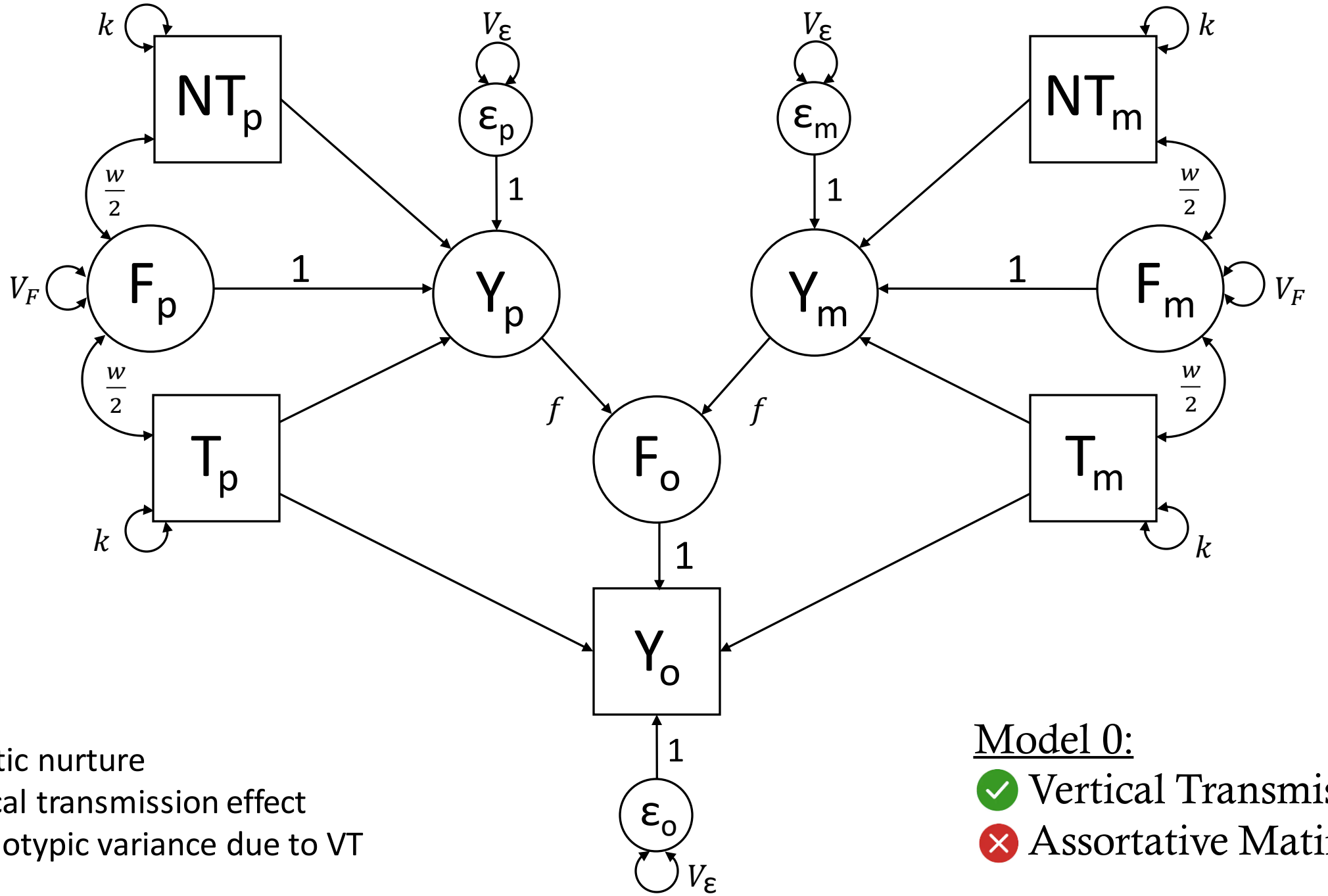
f : Vertical transmission effect



w : Genetic nurture

f : Vertical transmission effect

V_F : Phenotypic variance due to VT



w : Genetic nurture

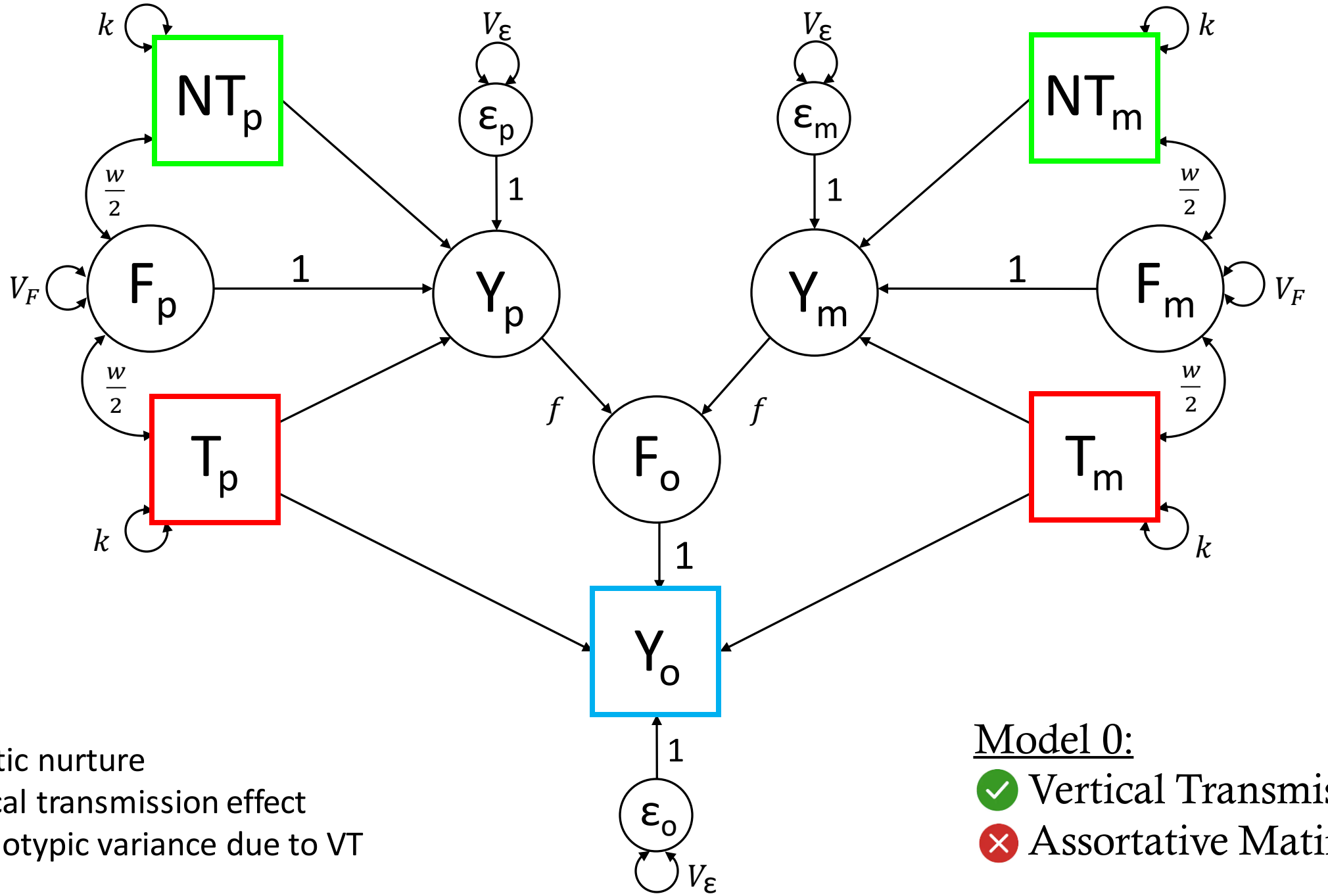
f : Vertical transmission effect

V_F : Phenotypic variance due to VT

Model 0:

✓ Vertical Transmission

✗ Assortative Mating



w : Genetic nurture

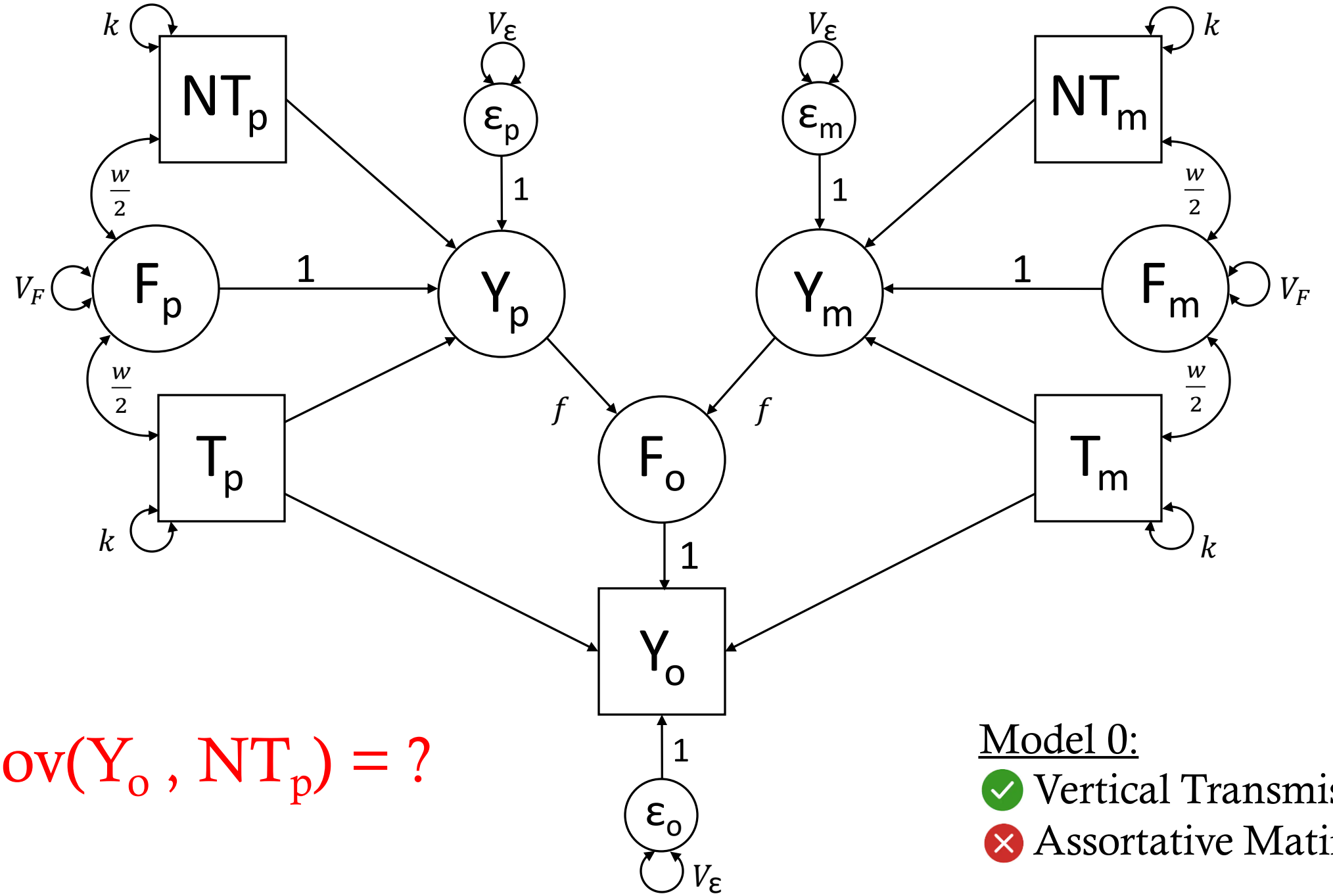
f : Vertical transmission effect

V_F : Phenotypic variance due to VT

Model 0:

✓ Vertical Transmission

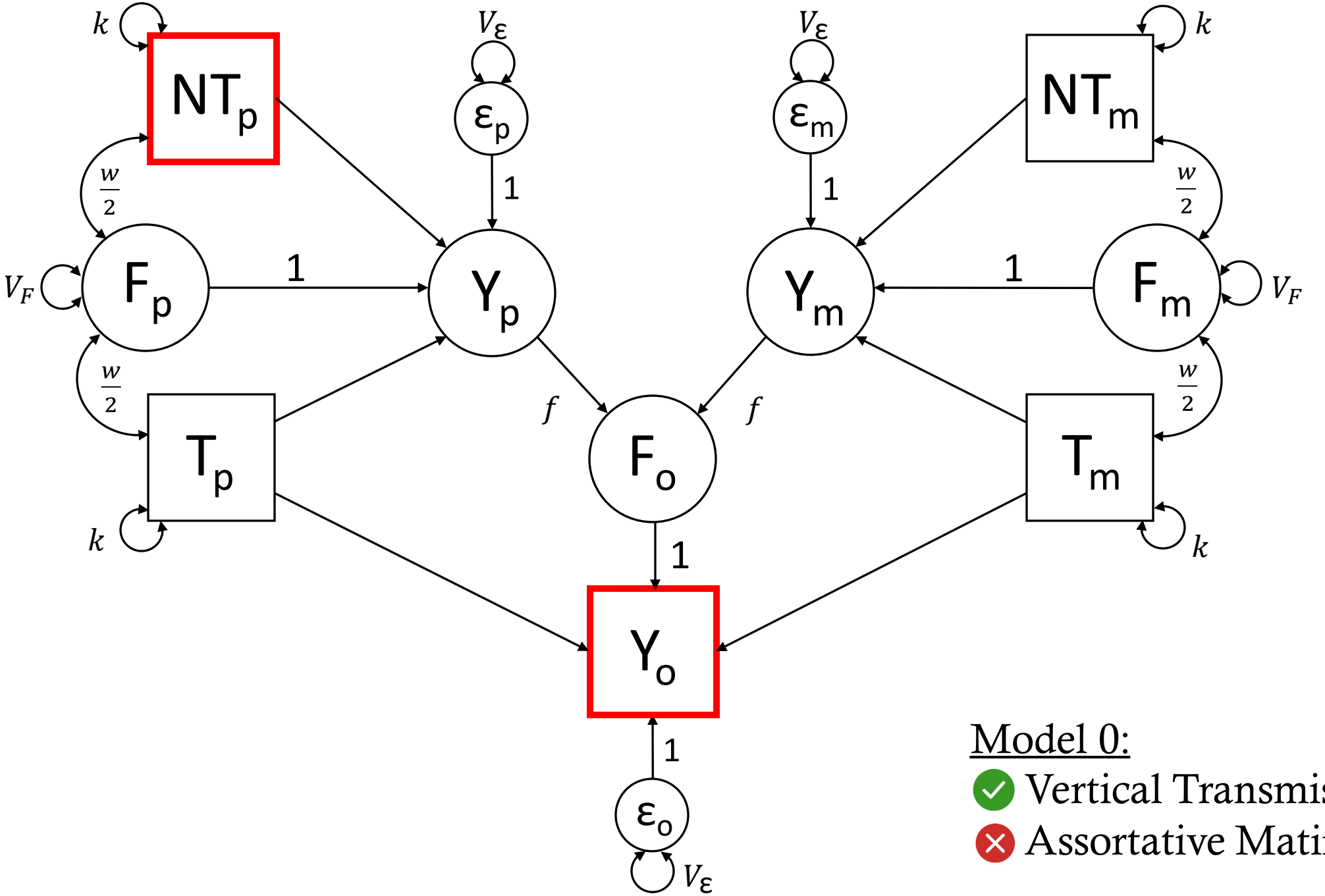
✗ Assortative Mating



$\mathrm{cov}(Y_o , NT_p) = ?$

Model 0:

- ✓ Vertical Transmission
- ✗ Assortative Mating



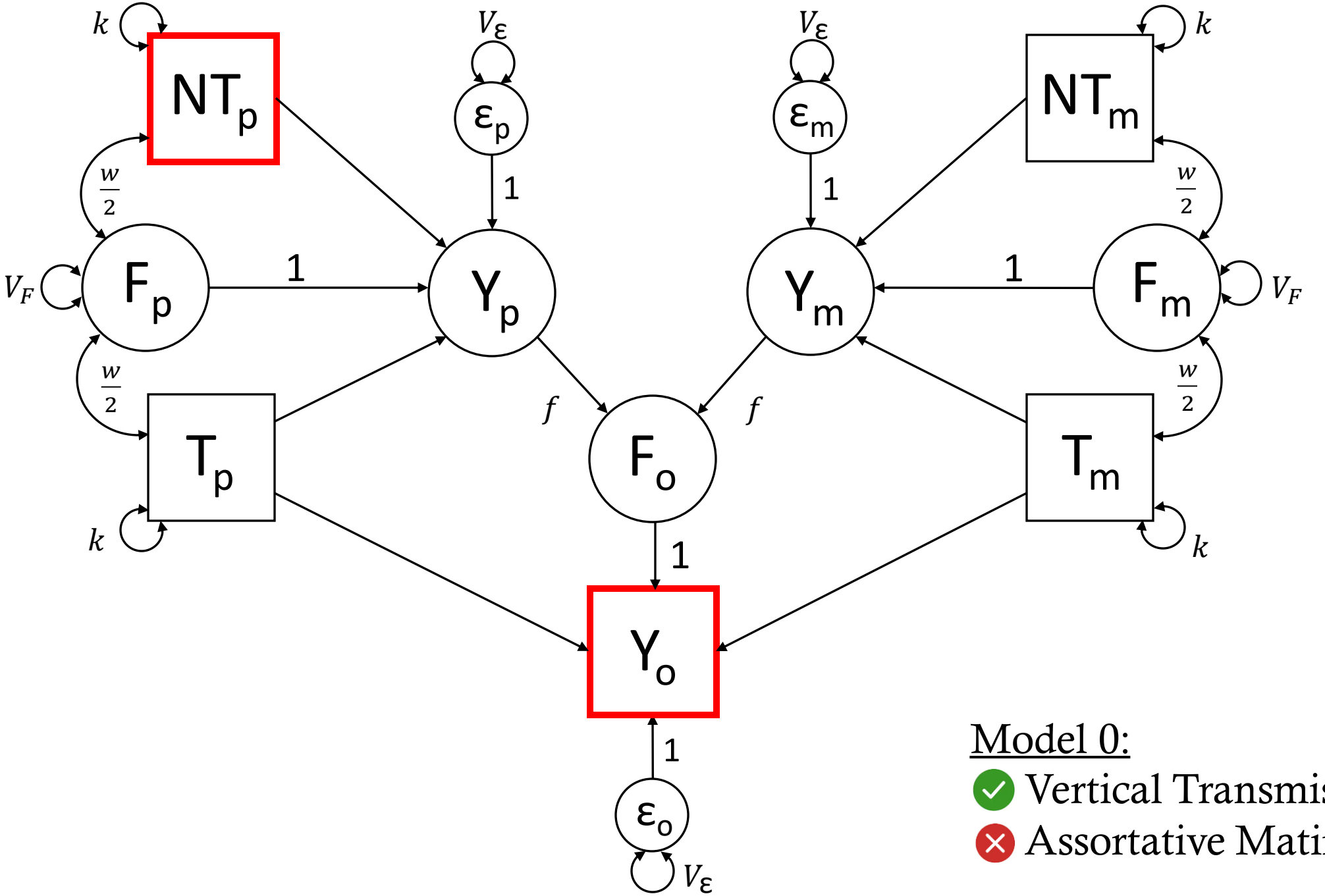
Model 0:

✓ Vertical Transmission

✗ Assortative Mating

Path Tracing Rules (described in Balbona et al., 2021)

1. A chain begins by travelling backwards against the direction of a single or double-headed arrow (from the arrow's head to its tail). However, once a double-headed arrow has been traversed, the direction reverses such that the chain now travels forwards, in the direction of the arrows.
2. A chain must include exactly one double-headed arrow (a variance or a covariance term), which is equivalent to stating that a chain must change directions exactly once. This is necessary because double-headed arrows provide the proper scaling for the coefficients in each chain.
3. All chains must be counted exactly once and each must be unique. However, the order of the links in the chains matters. For example, despite being algebraically equivalent, the chain $Y_p \rightarrow NT_p \rightarrow T_p \rightarrow Y_p$ is distinct from the chain $Y_p \rightarrow T_p \rightarrow NT_p \rightarrow Y_p$ in Figure1. Both are unique and both must be counted in determining the variance of Y_p .
4. Co-paths may only be traversed once in a given chain, and a chain must be legitimate before traversing the co-path. However, once the co-path is crossed, the first two rules above reset. A chain must therefore contain exactly one double-headed arrow before traversing the co-path, and one double-headed arrow after traversing the co-path. Thus, co-paths connect two legitimate chains to create a single, longer chain.



Model 0:

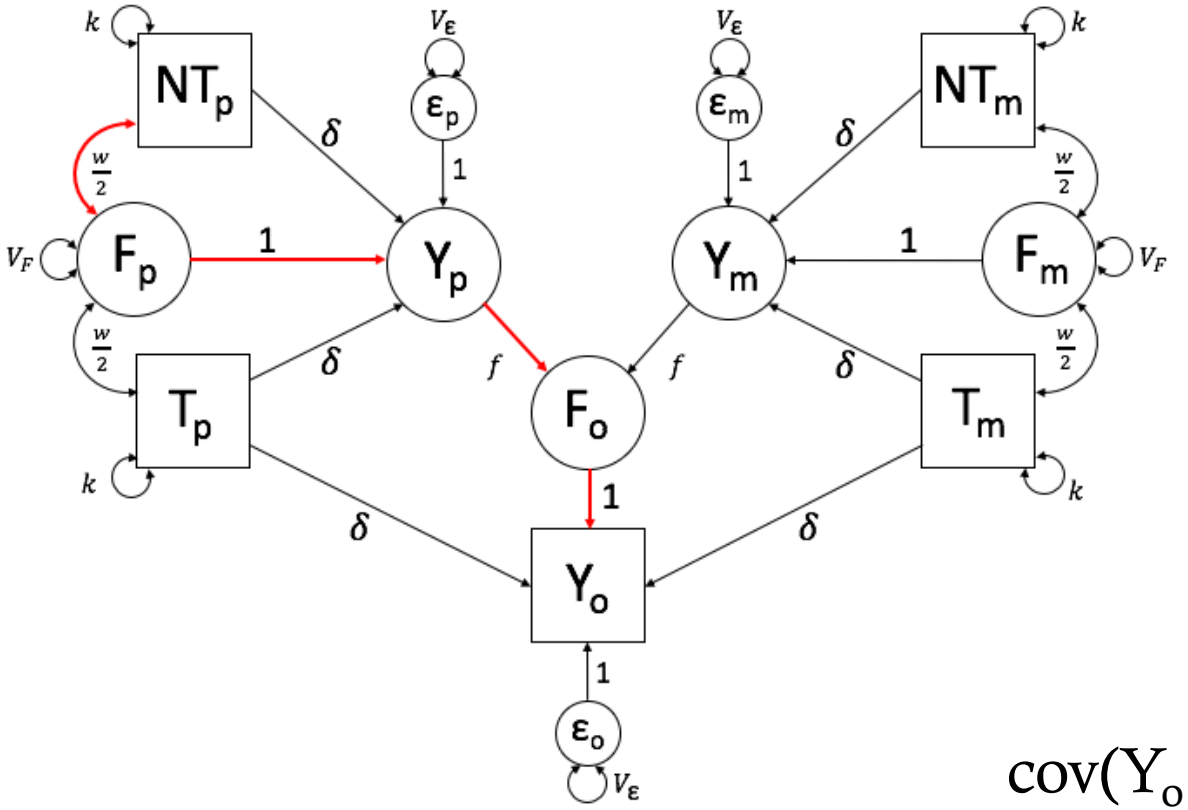
✓ Vertical Transmission

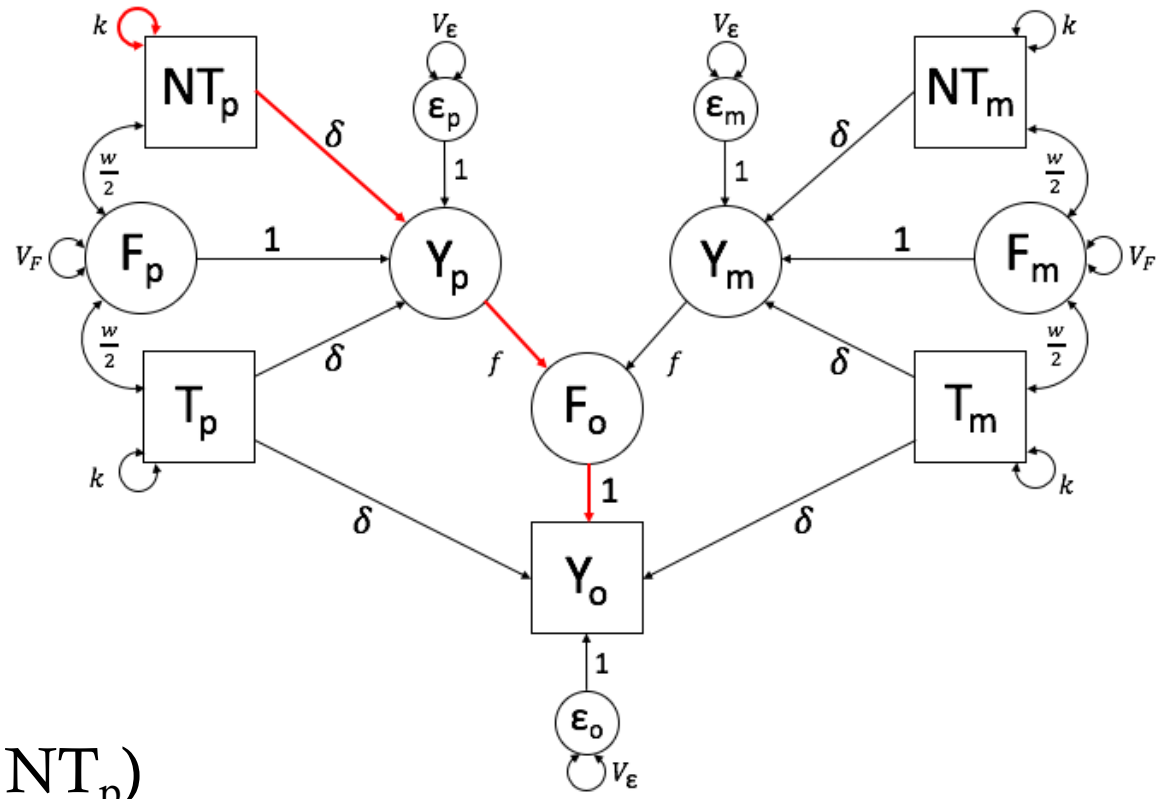
✗ Assortative Mating

Model 0:

✅ Vertical Transmission,

❌ Assortative Mating

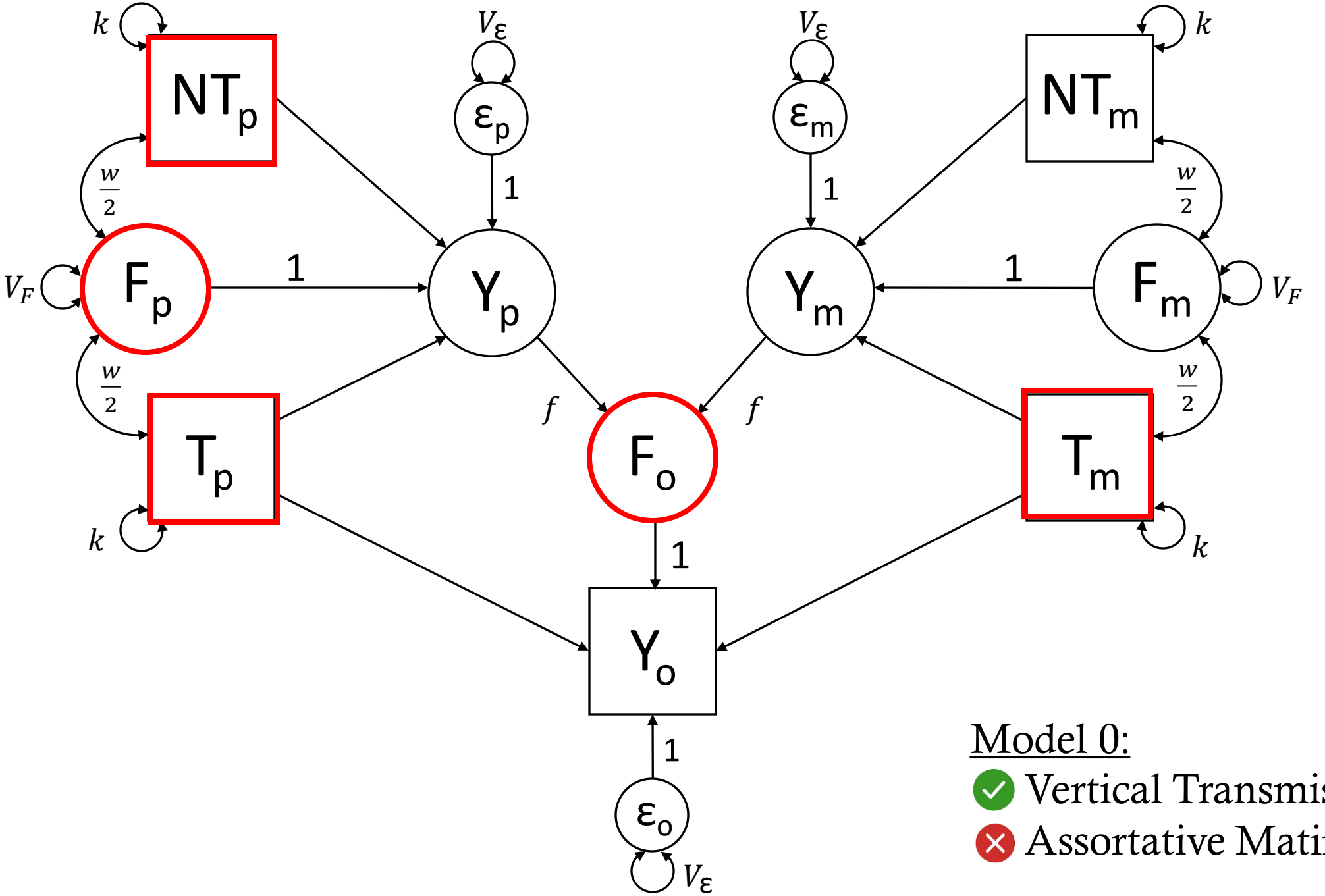




$$\text{cov}(\text{Y}_\text{o}\ ,\ \text{NT}_\text{p})$$

$$= \left(1 * f * 1 * \frac{w}{2}\right) + (1 * f * \delta * k)$$

$$= \frac{1}{2} f w + f \delta \text{k}$$



Model 0:

✓ Vertical Transmission

✗ Assortative Mating


Thank you!