HOMOSEXYALITY AS A CONSEQUENCE OF EPIGENETICALLY CANALIZED SEXUAL DEVELOPMENT

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Used terms:

<u>Epi-marks</u> – means changes in chromatin structure that influence the transcription rate of genes, changes in DNA sequence not included.

<u>Homosexuality</u> – any same-sex partner preference, spanning all Kinsey scores>0.

 \underline{T} – testosterone

<u>DHT</u> – dihydrotestosterone (more potent androgen than testosterone)

<u>SHBG</u> – sex hormone binding globuline

<u>AR</u> – androgen receptor

<u>ARE</u> – androgen response element

<u>SA-epi-marks</u> – sexually antagonistic epi-marks

Homosexuality is quite common in human populations – ca 8% in both sexes was reported in a large and systematic sample in Australia (Bailey et al. 2000)

Two major classes of existing genetic models for the evolution of human homosexuality:

- One based on kin selection
- Second based on sexually antagonistic alleles and/or overdominance





• Differential sensitivity of XY and XX fetuses to androgenes.

T concentrations overlap between sexes during weeks 9-15 of gestation.

 $5-\alpha$ -reductase-2 convert T to DHT and is three time higher in XY fetuses within the urogenital swellings and tubercles.

Higher conversion of T to DHT would permit XY fetuses to develop male traits. Lower 5-α-reductase-2 production in XX fetuses prevent or reduce masculinization of the vulva.

SHBG binds circulating T and makes it unavailable for uptake by cells.

Mechanisms by witch sex-specific epi-marks can canalize androgen sensitivity



Steps in the androgen signaling pathway that can boost or blunt signal transduction.

T = testosterone; AR = androgen receptor; ARE = androgen response element (DNA); CoFacts = androgen receptor cofactors.

During early development there is a nearly global erasure of epi-marks

Dimorphic epi-marks are produced during nearly genome wide episode of epigenetic reprogramming

Epi-marks produced during this early embryonic stage are known to strongly influence gene expression later in development

XX and XY embryos are epigenetically differentiated by the stem cell stage of the blastocyst

Potential for epi-marks lays down during very early development to influence androgen signalling later in development

Heritable epi-marks

Epi-marks have potential to be transmitted across generations, but only when the cycle of epi-mark erasure and renewal, within and between generations, is somehow circumvented

Sexually antagonistic epi-marks can be favored across the entire genome under feasible selective parameters

Mutations causing SA-epi-marks can invade even when the cost to the harmed sex far exceeds the benefit to the favored sex

Homosexuality and SA-epi-marks

Probability that both monozygotic twins are homosexuals is surprisingly low in both sexes – ca 20% for a trait predominantly influenced by genetic factors

Monozygotic twins share inherited SA-epi-marks, but don't share one or more de novo gonad concordant epi-marks

Empirical studies indicate that epigenetics can contribute substantially to similarity and dissimilarity of identical twins

Hypospadias and cryptorchidism

Androgen-influenced Prevalence in population (3-4% / 2-9%) Usually not shared among monozygotic twins Loss of function at some candidate gene can lead to disease, but majority of cases are not associated with any known mutations Inherited Big role of nonshared environment during gestation

SA-epi-marks and homosexuality

Epigenetic female homosexuality



Epigenetic male homosexuality



Ge -genitals; Sp – sexual preference; Si – sexual identity

M – masculinization; F – feminization

* - carryover across generations

Low concordance of monozygotic twins indicates that homosexuality (and other common gonad-trait discordances) require the combination of an inherited stronger-than-average sexually discordant epi-mark and a weaker-than-average sexually concordant epi-mark produced during early fetal development

Falsification and discard

Future, larger-scale genetic association studies will fail to identify genetic markers associated with most homosexuality

Future genome-wide epigenetic profiles will find differences between homosexuals and nonhomosexuals, but only at genes associated with androgen signaling in the later parts of the pathway (e.g., AR cofactors or miRNAs that regulate them) or be restricted to brain regions controlling sexual orientation, i.e., not affecting sexually dimorphic traits like genitalia or sexual identity.

