Arch Sex Behav
DOI 10.1007/s10508-017-1092-4

COMMENTARY

Understanding Homosexuality: Moving on from Patterns to Mechanisms

Sergey Gavrilets[1,2,3] · Urban Friberg[4] · William R. Rice[5]

Received: 20 September 2017 / Accepted: 26 September 2017

A correlation between male sexual preference (heterosexual or homosexual) and the number of older brothers (the fraternal birth order effect, FBOE) has been a subject of numerous studies since it was first identified by Blanchard and Sheridan (1992) and Blanchard and Bogaert (1996). The target article (Blanchard, 2017) builds on two and a half decades of work by Blanchard and coworkers to argue that "fraternal birth order is, by far, the most broadly established factor influencing sexual orientation in men." Although we agree that the evidence is strong that the FBOE contributes to male homosexuality, we argue that the predominant cause of homosexuality is something else. Genetic evidence suggests only a minor contribution of genetics, but there is strong indirect evidence for an epigenetic causation (Rice, Friberg, & Gavrilets, 2012). This new hypothesis has at least one major favorable attribute: it can be readily tested experimentally using current technology on human stem cells (Rice, Friberg, & Gavrilets, 2013).

There are several reasons why the FBOE cannot be a general explanation of homosexuality. First, it explains only a relatively small proportion of male homosexuality. The data analysis of Cantor, Blanchard, Paterson, and Bogaert (2002) concluded that the FBOE can explain one in seven homosexual men. Using different samples and methods, Blanchard and Bogaert (2004) got a higher estimate—about two in seven. Both of these estimates have wide confidence intervals that span values as low as 15% and no more than 48%. Clearly, homosexuality in men with no older brothers cannot be explained by the FBOE (unless their mother had previous miscarriages of male fetuses). Moreover, a number of studies done by researchers other than Blanchard and his colleagues (reviewed in LeVay, 2016) have not supported the FBOE. Blanchard and his colleague dismiss these studies on various methodological grounds. Furthermore, the FBOE does not explain the occurrence of cryptorchidism and hypospadias, traits that also relatively commonly show a gonad-trait discordance in males, as studies which have looked for an association between these traits and birth order have, if anything, found the reversed from expected pattern (reviewed in Pierik, Burdorf, Deddens, Juttmann, & Weber, 2004).

Second, the FBOE cannot explain female homosexuality. An association between female homosexuality and the number of older brother, as well as older sister, has been tested for repeatedly, but has never been found (reviewed in Blanchard, 2004).

Third, the FBOE is inconsistent with the low concordance of sexual preferences in twins who should be equally affected because they share both the genes and environment during fetal development. Estimates of proband concordance among twins (i.e., the probability that a twin is homosexual given that the other twin is homosexual) are low in both sexes: around 20% for monozygotic twins, with smaller percentages for dizygotic twins (Bailey, Dunne, & Martin, 2000; Långström, Rahman, Carlström, & Lichtenstein, 2010).

Fourth, the FBOE makes several predictions that have not yet been tested with data but appear to be counterintuitive. In

This comment refers to the article available at doi:10.1007/s10508-017-1007-4.

✉ Sergey Gavrilets
sergey@nimbios.org

[1] Department of Ecology and Evolutionary Biology, University of Tennessee, Knoxville, TN 37996, USA

[2] Department of Mathematics, University of Tennessee, Knoxville, TN, USA

[3] National Institute for Mathematical and Biological Synthesis, University of Tennessee, Knoxville, TN, USA

[4] IFM Biology, Linkoping University, Linkoping, Sweden

[5] Department of Ecology, Evolution and Marine Biology, University of California Santa Barbara, Santa Barbara, CA, USA

Published online: 06 October 2017

particular, the FBOE predicts (Bogaert, 2004): (1) higher frequency of homosexuals in more religious families (which are more likely to have a larger number of offspring), (2) higher frequency of homosexuals in more traditional non-Western societies where family sizes are large, (3) higher frequency of homosexuals in certain segments of the population that had a larger population birth rate (e.g., baby boomers), and (4) a general decrease in the frequency of homosexuals over the last couple of centuries in Western societies which experienced a dramatic reduction in the family size (e.g., Caldwell, 1997). We are not aware of data supporting these predictions.

Fifth, a correlational association cannot identify the causal mechanism producing this association, one also needs a mechanistic explanation. However, there is still no verified mechanistic explanation of the FBOE. The maternal immunization hypothesis (MIH) put forward by Blanchard and Bogaert (1996) suggests that the FBOE reflects the progressive immunization of some mothers to male specific (i.e., Y-linked) antigens by each succeeding male fetus and the concomitantly increasing effects of anti-male antibodies on sexual differentiation of the brain in each succeeding male fetus. According to this hypothesis, certain substances that occur primarily on the surfaces of male brain cells enter the mother's body. The mother's immune system recognizes these substances as foreign and produces antibodies to them. When the mother later becomes pregnant with another male fetus, her antibodies cross the placental barrier and enter the fetal brain altering the male-typical pattern of brain development and causing fitness-reducing sexual preferences.

Although this hypothesis is intuitively compelling, it has shortcomings. In particular, the MIH relies on several assumptions for which there is countervailing evidence (Whitehead, 2007). According to Whitehead (2007): (1) likely immune response prevalence is too low compared with calculated same-sex attraction prevalence resulting from the FBOE, (2) immune attack directed at testis would be more likely than brain attack but is not known, (3) the FBOE predicts unfavorable biology for late birth order males, but, in fact, the reverse is generally true, and neurological effects are very minor, and (4) aborted fetuses caused by likely maternal immune attack are predominantly girls rather than boys.

Moreover, from an evolutionary point of view, why would over 200 million years since the origin of mammals not be enough to evolve some modifiers preventing very costly negative immune reaction of the female body to such a routine and unavoidable event as pregnancy with a male fetus (50% of all pregnancies)? For example, there is plenty of evidence for MHC-related male choice (Chaix, Cao, & Donnelly, 2008; Millinski, 2006; Wedekind, Seebeck, Bettens, & Paepke, 1995), so that natural selection was an efficient way for increasing MHC diversity and offspring fitness viability. Bogaert and Skorska (2011) used hemolytic disease of the newborn (HDN) as a medical example of a maternal immune response underlying the FBO (15% of the US population is Rh-negative and at risk). However, the human population mixing at the scale observed now is an evolutionary new factor. In our evolutionary past, the HDN was likely much rarer than today, so the lack of genetic mechanisms preventing HDN is not surprising. Similarly, immune incompatibilities after organ transplants, which became possible due to advances in modern medicine, are not surprising at all. In both cases, natural selection would not be expected to have developed countervailing adaptations due to time limitations. In contrast, stable maintenance of immune incompatibility between mothers and 50% of their offspring causing strong fitness reductions would be paradoxical.

Given that the FBOE is not the predominant factor causing homosexuality, we need to make progress in identifying the major causative factor(s) producing this phenotype. Next, we consider several possibilities.

A major hypothesis in the last century was that men and women differed in the nature and quantities of sex hormones and that homosexual orientation was a result of an individual somehow acquiring a sex hormone profile of the opposite sex. However, in the 1970s and 1980s a succession of studies (e.g., Byne & Parsons, 1993; Downey, 1987; Jaffee, McCormack, & Vaitukaitis, 1980; Meyer-Bahlburg, 1984) found adult hormone profiles to be similar between homosexuals and heterosexuals in both sexes, indicating that sex-reversed adult sex hormone profiles were unlikely to be responsible for homosexuality in either sex. Transient sex-reverse androgen profiles during fetal development might still be a contributing factor, but below we indicate why this possibility is unlikely.

Are there major genes (with substantial effect sizes) that cause human homosexuality? Starting in the 1990s, several pedigree studies (Hamer, Hu, Magnuson, Hu, & Pattatucci, 1993; Ngun, Ghahramani, Sánchez, Bocklandt, & Vilain, 2011; Pattatucci & Hamer, 1995) found that both male and female homosexuality run in families and additional twin studies (Kirk, Bailey, Dunne, & Martin, 2000) indicated the male homosexuality is heritable.

A possible force for the maintenance of "gay genes" in populations is sexual conflict as first suggested by Camperio-Ciani, Corna, and Capiluppi (2004). Sexual conflict occurs if the interests of the sexes with regard to certain aspects of reproduction differ (Arnqvist & Rowe, 2005; Rice & Gavrilets, 2014). Sexual conflict is a special case of a more general intragenomic conflict (Rice, 1998; Rice & Holland, 1997). Ultimately, the origins of sexual conflict lie in the differences in the roles played by the sexes in the process of reproduction, which in turn lead to the differences between the sexes in the costs and benefits of mating and reproduction (Bateman, 1948; Parker, 1979; Trivers, 1972). Sexual conflict has been a burgeoning field in evolutionary biology for the past 20 years. The basic idea is that certain traits that increase a fitness component in one sex can simultaneously decrease it in the opposite sex. Numerous studies have shown that sexual conflict can occur over a number of traits, including mating rate (Holland & Rice, 1998; Rice, 1998; Rice & Holland, 1997), offspring size (Haig, 2000), parental care (Barta,

Houston, McNamara, & Szekely, 2002; Smith & Härdling, 2000), the use of sperm (Ball & Parker, 2003), and epigenetic control of development (Rice et al., 2012). Evolutionary consequences and effects of sexual conflict have also been investigated in detail. They include the evolution of male-beneficial traits that decrease female fitness, maintenance of genetic variation, rapid evolution of fertilization proteins and traits, and speciation (Gavrilets, 2014; Rice, 1998; Rice & Holland, 1997).

With regard to the maintenance of homosexuality, Gavrilets and Rice (2006) and Camperio-Ciani, Cermelli, and Zanzotto (2008) used modeling from population genetics to study theoretically the plausibility of different types of sexual conflict in the evolutionary maintenance of homosexuality. They also made a number of predictions which can be tested using empirical data to better understand genetic mechanisms of homosexuality. Rice, Gavrilets, and Friberg (2008) offered an explanation of homosexuality based on sexually antagonistic zygotic drive, which is functionally analogous to meiotic drive except that it operates due to competition among opposite-sex siblings rather than between competing gametes. A number of subsequent publications have significantly expanded both the theoretical and empirical bases of the claim that sexual conflict can explain homosexuality. There are several paths leading to such correlations and to a stable maintenance of homosexuality in the population. For example, a genetic allele that increases fertility of females may feminize their sons, increasing the probability they become homosexuals. In principle, such an allele can be autosomal or X-linked and it can have direct or maternally mediated fitness effects (Camperio-Ciani et al., 2008; Camperio-Ciani, Battaglia, & Zanzotto, 2014; Gavrilets & Rice, 2006). Supporting these theoretical expectations, Camperio-Ciani et al. (2014) provided a review of empirical data supporting the existence of correlations between male homosexuality and fertility on the maternal side of the lineage (see also Semenyna, Petterson, VanderLaan, & Vasey, 2017). Increased female fertility can be observed together with the FBOE (VanderLaan & Vasey, 2011).

However, the search for genes contributing to homosexuality, which started 25 years ago, has been largely unsuccessful. Although a recent large genome-wide association study (GWAS) by Sanders et al. (2015) has documented two chromosomal regions associated with male homosexuality (one X-linked, the other on autosome 8), which has resolved some conflicting results obtained from earlier attempts (Bailey et al., 1999; Hamer et al., 1993; Hu et al., 1995; Mustanski et al., 2005; Ramagopalan, Dyment, Handunneththi, Rice, & Ebers, 2010; Rice, Anderson, Risch, & Ebers, 1999), both these regions have a small effect sizes and low power in predicting homosexual versus heterosexual orientation. Collectively, GWAS thus indicate that there are no major genes contributing to male homosexuality. No comparable studies on female homosexuality exist.

Could male homosexuality have a genetic basis via polygenic inheritance (with many small effect loci) or genes with strong epistatic interactions? The fact that only two chromosomal regions were found to contribute to male homosexuality in the studies described above does not preclude a strong genetic basis for this phenotype if it is due to many small effect polygenes and/or genetic loci with strong epistasis. However, studies of monozygotic twins, which share nearly identical genotypes, found low concordance for male homosexuality (Bailey et al., 2000; Långström et al., 2010; see also above). This finding is inconsistent with a substantial genetic basis for male homosexuality no matter what the underlying genetic architecture. This finding is also inconsistent with a transient, in utero, disruption of fetal androgen signaling, because both twins would be expected to experience virtually identical exposure to potential hormone disruptors, androgen mimics, and maternal hormone anomalies, etc.

If genes are not responsible for the strong pedigree associations found for both male and female homosexuality, then what causes this reversed sexual preference trait to run in families? Previously, we used a wide diversity of empirical data, in combination with population genetic modeling, to motivate the hypothesis that epigenetic marks (epi-marks) that canalize sexual development sometimes fail to erase across generations and cause reversed sexual preference (Rice et al., 2012). In mammals, epigenetic marks are erased across generations when protamines replace histones on the paternal genome prior to nuclear syngamy, during the migration of the primordial germ cells to the developing gonads, and during the first few cell divisions when methyltransferases are in short supply (Hemberger, Dean, & Reik, 2009). Escape from transgenerational erasure can occur deterministically, as occurs in the case of imprinted genes, or stochastically when one or more erasure mechanisms fail on localized regions of the chromatin (Manikkam, Guerrero-Bosagna, Tracey, Haque, & Skinner, 2012). Epi-marks that canalize sexual development increase sensitivity to androgen signaling in XY fetuses and reduce it in XX fetuses. During human fetal development, strong androgen signaling leads to masculinization and weak androgen signaling leads to feminization, with estrogens and progesterones having far less influence until puberty. We used previously published studies of human null mutations to provide evidence that, in human fetuses, XY genotypes do, in fact, show increased sensitivity to androgen signaling and XX fetuses have reduced sensitivity. The main strength of our epi-mark hypothesis for homosexuality is that it makes a strong prediction for both male and female homosexuality that can be experimentally tested using human embryonic stem cells, and also pluripotent embryonic stem cells that retain the capacity to differentiate in neural and glial cells (e.g., human hair follicle stem cells) (Rice et al., 2013).

How could mutations that code for sex-specific epi-marks that sometimes carryover (unerased) across generations and cause

homosexuality at substantial frequency be favored by natural selection? One of the most counterintuitive results from our population genetic model of homosexuality via unerased sex-specific epi-marks was that the alleles that code for the epi-marks that cause homosexuality can be favored by natural selection. The epi-marks are always favored in the fetus in which they are produced because they canalize sexual development and protect the fetus from fitness-reducing intersexual phenotypes (caused by anomalous hormone profiles during fetal ontogeny, androgen disruptors, and androgen mimics, etc.). These epi-marks carryover at a low rates and cause gonad-trait discordances for sexual preferences in opposite-sex offspring, thereby reducing fitness in only some descendent offspring. By quantifying the cost and benefits of sex-specific epi-marks that sometimes carryover across generations and produce gonad-trait-discordances, we showed that mutations coding for such epi-marks have a net selective advantage across a wide span of parameter space. We have later developed this framework to explain gonad-trait discordance also for other traits, and as source of phenotypic variation in sexual traits in general (Rice, Friberg, & Gavrilets, 2016).

There are several known patterns associated with homosexuality, such as those observed in pedigree data, associations with matriline fecundity, and the FBOE. It is not impossible that some of these patterns arise because of different mechanisms, but more likely they all trace back to one and the same. The empirical evidence for an epigenetic causation of homosexuality, generated through selection for canalized sexual phenotypes, is still indirect. This hypothesis nevertheless provides a logical explanation that is closely connected to a plausible mechanism. This new hypothesis also has the favorable attribute that it can be readily tested experimentally, using current technology on human stem cells (Rice et al., 2013).

Acknowledgements We thank P. L. Vasey for useful comments and suggestions. This work was partially supported by the National Institute for Mathematical and Biological Synthesis through NSF Award EF-0830858, with additional support from the University of Tennessee, Knoxville (SG) and the Swedish Research Council (UF).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by the authors.

References

Arnqvist, G., & Rowe, L. (2005). *Sexual conflict*. Princeton, NJ: Princeton University Press.

Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. *Journal of Personality and Social Psychology, 78,* 524–536.

Bailey, J. M., Pillard, R. C., Dawood, K., Miller, M. B., Farrer, L. A., Trivedi, S., & Murphy, R. L. (1999). A family history study of male sexual orientation using three independent samples. *Behavior Genetics, 29,* 79–85.

Ball, M. A., & Parker, G. A. (2003). Sperm competition games: Sperm selection by females. *Journal of Theoretical Biology, 224,* 27–42.

Barta, Z. N., Houston, A. I., McNamara, J. M., & Szekely, T. (2002). Sexual conflict about parental care: The role of reserves. *American Naturalist, 159,* 687–705.

Bateman, A. J. (1948). Intrasexual selection in *Drosophila*. *Heredity, 2,* 349–368.

Blanchard, R. (2004). Quantitative and theoretical analyses of the relationship between older brothers and homosexuality in men. *Journal of Theoretical Biology, 230,* 173–187.

Blanchard, R. (2017). Fraternal birth order, family size, and male homosexuality: Meta-analysis of studies spanning 25 years. *Archives of Sexual Behavior*. doi:10.1007/s10508-017-1007-4.

Blanchard, R., & Bogaert, A. F. (1996). Homosexuality in men and number of older brothers. *American Journal of Psychiatry, 153,* 27–31.

Blanchard, R., & Bogaert, A. F. (2004). Proportion of homosexual men who owe their sexual orientation to fraternal birth order: An estimate based on two national probability samples. *American Journal of Human Biology, 16,* 151–157.

Blanchard, R., & Sheridan, P. M. (1992). Sibship size, sibling sex ratio, birth order, and parental age in homosexual and nonhomosexual gender dysphorics. *Journal of Nervous and Mental Disease, 180,* 40–47.

Bogaert, A. F. (2004). The prevalence of male homosexuality: The effect of fraternal birth order and variations in family size. *Journal of Theoretical Biology, 230,* 33–37.

Bogaert, A. F., & Skorska, M. (2011). Sexual orientation, fraternal birth order, and the maternal immune hypothesis: A review. *Frontiers in Neuroendocrinology, 32,* 247–254.

Byne, W., & Parsons, B. (1993). Human sexual orientation: The biological theories reappraised. *Archives of General Psychiatry, 50,* 228–239.

Caldwell, J. C. (1997). Reaching a stable global population: What we have learnt, and what we must do. *Health Transition Review, 7,* 37–42.

Camperio-Ciani, A., Battaglia, U., & Zanzotto, G. (2014). Human homosexuality: A paradigmatic arena for sexually antagonistic selection? *Cold Spring Harbor Perspective in Biology, 7,* a017657.

Camperio-Ciani, A., Cermelli, P., & Zanzotto, G. (2008). Sexually antagonistic selection in human male homosexuality. *PLoS ONE, 3,* e2282.

Camperio-Ciani, A., Corna, F., & Capiluppi, C. (2004). Evidence for maternally inherited factors favouring male homosexuality and promoting female fecundity. *Proceedings of the Royal Society London B, 271,* 2217–2221.

Cantor, J. M., Blanchard, R., Paterson, A. D., & Bogaert, A. F. (2002). How many gay men owe their sexual orientation to fraternal birth order? *Archives of Sexual Behavior, 31,* 63–71.

Chaix, R., Cao, C., & Donnelly, P. (2008). Is mate choice in humans MHC-dependent? *PLoS Genetics, 4,* e1000184.

Downey, J. (1987). Sex hormones in lesbian and heterosexual women. *Hormones and Behavior, 21,* 347–357.

Gavrilets, S. (2014). Is sexual conflict an engine of speciation? *Cold Spring Harbor Perspective in Biology, 6,* a017723.

Gavrilets, S., & Rice, W. R. (2006). Genetic models of homosexuality: Generating testable predictions. *Proceedings of the Royal Society London B, 273,* 3031–3038.

Haig, D. (2000). The kinship theory of genomic imprinting. *Annual Reviews in Ecology and Systematics, 31,* 9–32.

Hamer, D. H., Hu, S., Magnuson, V. L., Hu, N., & Pattatucci, A. M. (1993). A linkage between DNA markers on the X chromosome and male sexual orientation. *Science, 261,* 321–327.

Hemberger, M., Dean, W., & Reik, W. (2009). Epigenetic dynamics of stem cells and cell lineage commitment: Digging Waddington's canal. *Nature Reviews Molecular Cell Biology, 10,* 526–537.

Holland, B., & Rice, W. R. (1998). Chase-away sexual selection: Antagonistic seduction versus resistance. *Evolution, 52,* 1–7.

Hu, S., Pattatucci, A., Patterson, C., Li, L., Fulker, D., Cherny, S., et al. (1995). Linkage between sexual orientation and chromosome Xq28 in males but not females. *Nature Genetics, 11,* 248–256.

Jaffee, W. L., McCormack, M. M., & Vaitukaitis, J. L. (1980). Plasma hormones and the sexual preferences of men. *Psychoneuroendocrinology, 5,* 33–38.

Kirk, K. M., Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Measurement models for sexual orientation in a community twin sample. *Behavior Genetics, 30,* 345–356.

Långström, N., Rahman, Q., Carlström, E., & Lichtenstein, P. (2010). Genetic and environmental effects on same-sex sexual behavior: A population study of twins in Sweden. *Archives of Sexual Behavior, 39,* 75–80.

LeVay, S. (2016). *Gay, straight, and the reason why: The science of sexual orientation* (2nd ed.). Oxford, UK: Oxford University Press.

Manikkam, M., Guerrero-Bosagna, C., Tracey, R., Haque, M. M., & Skinner, M. K. (2012). Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures. *PLoS ONE, 7,* e3190.

Meyer-Bahlburg, H. F. L. (1984). Psychoendocrine research on sexual orientation: Current status and future options. *Progress in Brain Research, 61,* 375–398.

Milinski, M. (2006). The major histocompatibility complex, sexual selection, and mate choice. *Annual Review of Ecology and Systematics, 37,* 159–186.

Mustanski, B. S., DuPree, M. G., Nievergelt, C. M., Bocklandt, S., Schork, N. J., & Hamer, D. H. (2005). A genome wide scan of male sexual orientation. *Human Genetics, 116,* 272–278.

Ngun, T. C., Ghahramani, N., Sánchez, F. J., Bocklandt, S., & Vilain, E. (2011). The genetics of sex differences in brain and behavior. *Frontiers in Neuroendocrinology, 32,* 227–246.

Parker, G. A. (1979). Sexual selection and sexual conflict. In M. S. Blum & N. A. Blum (Eds.), *Sexual selection and reproductive competition in insects* (pp. 123–166). New York, NY: Academic Press.

Pattatucci, A. M. L., & Hamer, D. H. (1995). Development and familiality of sexual orientation in females. *Behavior Genetics, 25,* 407–420.

Pierik, F. H., Burdorf, A., Deddens, J. A., Juttmann, R. E., & Weber, R. F. A. (2004). Maternal and paternal risk factors for cryptorchidism and hypospadias: A case-control study in newborn boys. *Environmental and Health Perspectives, 112,* 1570–1576.

Ramagopalan, S. V., Dyment, D. A., Handunneththi, L., Rice, G. P., & Ebers, G. C. (2010). A genome-wide scan of male sexual orientation. *Journal of Human Genetics, 55,* 131–132.

Rice, G., Anderson, C., Risch, N., & Ebers, G. (1999). Male homosexuality: Absence of linkage to microsatellite markers at Xq28. *Science, 284,* 665–667.

Rice, W. R. (1998). Intergenomic conflict, interlocus antagonistic coevolution, and the evolution of reproductive isolation. In D. J. Howard & S. H. Berlocher (Eds.), *Endless forms: Species and speciation* (pp. 261–270). New York, NY: Oxford University Press.

Rice, W. R., Friberg, U., & Gavrilets, S. (2012). Homosexuality as a consequence of epigenetically canalized sexual development. *Quarterly Reviews in Biology, 87,* 343–368.

Rice, W. R., Friberg, U., & Gavrilets, S. (2013). Homosexuality via canalized sexual development: A testing protocol for a new epigenetic model. *BioEssays, 35,* 343–368.

Rice, W. R., Friberg, U., & Gavrilets, S. (2016). Sexually antagonistic epigenetic marks that canalize sexually dimorphic development. *Molecular Ecology, 25,* 1812–1822.

Rice, W. R., & Gavrilets, S. (2014). *The genetics and biology of sexual conflict*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Rice, W. R., Gavrilets, S., & Friberg, U. (2008). Sexually antagonistic 'zygotic drive' of the sex chromosomes. *PLoS Genetics, 4,* e1000313.

Rice, W. R., & Holland, B. (1997). The enemies within: Intergenomic conflict, interlocus contest evolution (ICE), and intraspecific Red Queen. *Behavioral Ecology and Sociobiology, 41,* 1–10.

Sanders, A. R., Martin, E. R., Beecham, G. W., Guo, S., Dawood, K., Rieger, G., et al. (2015). Genome-wide scan demonstrates significant linkage for male sexual orientation. *Psychological Medicine, 45,* 1379–1388.

Semenyna, S. W., Petterson, L. J., VanderLaan, D. P., & Vasey, P. L. (2017). A comparison of the reproductive output among the relatives of Samoan androphilic *fa'afafine* and gynephilic men. *Archives of Sexual Behavior, 46,* 87–93.

Smith, H. G., & Härdling, R. (2000). Clutch size evolution under sexual conflict enhances the stability of mating systems. *Proceedings of the Royal Society London B, 267,* 2163–2170.

Trivers, R. L. (1972). Parental investment and sexual selection. In B. Campbell (Ed.), *Sexual selection and the descent of Man 1871–1971* (pp. 136–179). Chicago, IL: Aldine Publishing.

VanderLaan, D. P., & Vasey, P. L. (2011). Male sexual orientation in Independent Samoa: Evidence for fraternal birth order and maternal fecundity effects. *Archives of Sexual Behavior*, *40*, 495–503.

Wedekind, C., Seebeck, T., Bettens, F., & Paepke, A. J. (1995). MHC-dependent mate preferences in humans. *Proceedings Biological Sciences, 22,* 245–249.

Whitehead, N. E. (2007). An antiboy antibody? Re-examination of the maternal immune hypothesis. *Journal of Biological Science, 39,* 905–921.