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Evolutionary Perspective of Human Papilloma Virus Infection in Humans

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Abstract

The Human Papilloma Virus (HPV) strains (16 and 18 mainly) have been proved to be the major cause of cancers of cervix, vulva, penis, Oropharyngeal tissues and many others. HPV infection spreads mainly through sexual intercourse. There are very limited non-sexual modes of HPV transmission available. Sexual intimacy, which includes kissing, is a major mode of transmission in case of HPV whereas in the case of other sexually transmitted infections like HIV and HBV non-sexual factors like contaminated blood transfusions contribute significantly in the spread of the virus to the other host. According to recent research, the HPV virus has been found to be associated with oral and breast cancers which have been linked with the rampant trend of oral sex among the western youth. The virus has adopted to colonize the oral cavity thus creating a new opportunity to spread through passionate kissing which has been confirmed by genotyping. Intense selection pressure can select virus to manipulate the host sexual behavior in a way that facilitates transmission. The selection pressure for such manipulations is very strong in the countries having conservative societies like India, Srilanka, Nepal, Bangladesh and others where sexuality still remains a taboo. People in these countries generally disapprove love marriage, premarital sex and having multiple sex partners. Majority of the population avoids more than one sex partner post-marriage in their entire lifetime. This is a very serious constraint for the virus to get into new hosts. DNA viruses like high risk HPV strains can produce substantial number of variants owing to factors like large population sizes, long infection time and hypermutation of the epitopes which can lead to significant evolution of virus within the host. Evolutionary Medicine can help us to understand infectious diseases better and thus take a step closure to their cure.

Keywords: HPV infection; Oral cancer; Breast cancer; PCR

Introduction

Every infectious agent is programmed with two fundamental imperatives of survival and reproduction. The exploration of infectious diseases with such perspective can offer great insights for the better understanding of the sexually transmitted infections. Parasites often alter the behavior of their host to facilitate transmission to newer hosts [1]. One of the most fascinating and recent example comes from malaria causing protozoan *Plasmodium falciparum.* This parasite makes the infected human host more attractive for the mosquitoes to enhance its chances of transmission by frequent bites [2]. *Toxoplasma gondii* manipulates mate choice in the female rats by enhancing the sexual attractiveness of the infected males [3]. Viruses are no more an exception when it comes to manipulation of the host for their own advantage. One of the most cited example is that of the Rabies virus which infects the neurons in the limbic cortical areas of brain of the host and thus modulates the aggressive behavior for better transmission [4]. The chances of host sexual behavior manipulation in case of sexually transmitted infections caused by viruses are very high due to the intense selection pressure present in certain specific ecological niches. The proposed hypothesis is intended to express the possibility of manipulation of such sexual behavior by viruses and microbes that are transmitted sexually in Human Subjects and HPV seems to be the candidate with the fairest chances of such manipulation.

HPV infection, Human Cancers and Etiology

HPV is considered the major cause of cervical cancer among the women all over the world. It is detected in 98% of the Cervical Cancer tissues as well as the pre-cancerous lesions. HPV has also been confirmed as the major causative agent of other cancers like Anal, Vaginal, Penile, Vulvar and Oropharnygeal [5].

Human Papillomavirus belongs to the papillomaviridae family. It mainly infects two types of tissue 1) Cutaneous and 2) Mucosal [6,7]. The cutaneous HPV mainly infects the skin and is responsible for the skin melanoma. The mucosal variant of the Virus is associated with the infection of mucosa of Cervix, GIT, and genital regions. HPV is a DNA virus. It has non-capsulated icosahedral capsid and a double stranded circular DNA [6,7]. The genome consists of mainly three regions 1) Earlier or E region 2) L or later region 3) Promoter or enhancer region that enhance the expression of the E and the L genes. The E region has mainly 7 genes and sometimes it is 8 in rare HPV stains [8-11]. The genes are E1, E2, E3, E4, E5, E6, E7 and E8. The different genes regulated different functions from viral replication to the formation of the viral assembly [8-11]. E6 is associated with the deregulation of cell division controlling gene called P53 and E7 is associated with other Cancer protective gene called Rb gene or Retinoblastoma gene [8-11]. The protein products of these two genes are mainly associated with HPV induced cancer. The L1 and the L2 genes are linked with formation of the virus particles [8-11]. The Virus infects the basal cells of the epithelium. These basal cells infected with HPV later divide and their daughter cells migrate to the upper layer of the tissue and undergo differentiation. Differentiation of the cells infected with HPV leads to the beginning of productive phase of the viral life cycle [8-11]. This is done by the virus after hijacking the cellular DNA synthesis mechanisms. The expression of E6 and E7 pushes the differentiating cells into the S Phase by altering cell cycle regulatory proteins leading to viral genome amplification in the cells [8-11]. Proteins like L1 and L2 of the late phase helps in encapsulating the newly formed Viral genomes.

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The thousands of virions formed during the entire process are shed from the uppermost layer of the epithelium [8-11].

HPV and Oral Cancer

International Agency of Research of Cancer (IARC) in 2011 has declared that there is significant proof to show that HPV-16 is causally associated with oral cancer cases [12]. Almost more than 90% of the HPV-positive oropharyngeal cancers are found to be infected with the HPV 16 subtype [13,14]. Earlier infection with HPV 16 is associated with a nine-fold increased risk of oropharyngeal cancer, specifically for squamous cell carcinomas of the base of the tongue, tonsil, and epiglottis [15]. Epidemiological data of last 10 years from the countries like United States, Finland, Sweden, the Netherlands, the United Kingdom, and Scotland showed increase of OSCC, tonsillar cancer, and base of tongue cancer cases [16-21]. Changes in sexual patterns, such as early debut of oral sex, increased oral sex or increasing numbers of oral or vaginal sex partners and even opened mouth kissing are considered the possible causes for the rise in HPV positive oral cancers in these countries [22]. Persistent HPV infection of the oral cavity may lead to genetic damage and altered immune function and thus consequently leading to cancer. The HPV positive Cancer was found among significantly younger patients compared to the one which are negative to HPV. The evidence for the expression E6 and E7 has further proved the role of HPV in the oral cancers [23]. The HPV positive tumors were found to have a different histological and genetic profile which further confirms the causative role of HPV in the cancer [24].

HPV and Breast Cancer

Breast cancer is one of the leading causes of death among women all over the world. It is the second most common cancer after lung cancer in the western world [25]. There are no clear etiologic factors of breast cancer determined even after decades of research. Recently the cases of breast cancer among the younger women lacking the conventional risk factors for the disease has tempted the scientific community to explore alternative causative factors like infections. MMTV virus has been linked with breast cancer since long 60 years [25]. The other two causally linked viruses are EBV and Human Papilloma Virus. HPV is a strong candidate for the causative infectious link for the breast cancer because of two major reasons: 1) HPV has been proved to be major causative agent of human cancers like Cervix, penis, vagina, and many others. 2) HPV has been found to immortalize breast cells *in vitro* cell cultures. Scientists across the world have found HPV DNA in the breast cancer tissues [5].

Year	Author	Country	No of the HPV Positive Cases (% of positive cases)	HPV types	Techniques used for the detection
1992	Di Lonardo et al. [26]	Italy	7/70 (10)	HPV 16	PCR/ISH
1999	Henning et al. [27]	Norway	19/41 (43)	HPV 16	PCR/ISH
1999	Yu et al. [28]	China	19/72 (26)	HPV 33 and HPV 1	PCR/Southern Blot
2001	Liu et al. [29]	China	6/17 (35)	HPV 16,18 & 33	PCR/Dot Blot Hybridization
2002	Li et al. [30]	China	19/28 (68)	HPV16 & 18	PCR
2004	Damian et al. [31]	Brazil	25/101 (25)	HPV 16 & 18	PCR
2004	Widschwendter et al. [32]	Australia	7/11 (64)	HPV 16	PCR
2005	De Villiers et al. [33]	USA	25/29 (86)	HPV 16 & 6	PCR
2005	Kan et al. [34]	Australia	24 (48)	HPV16 & 18	PCR
2005	Tsai et al. [35]	Taiwan	8/62 (13)	HPV 16,18 & 33	PCR
2006	Kroupis et al. [36]	Greece	17/107 (16)	HPV 16,59,58,73 and 82	PCR
2006	Gumus et al. [37]	Turkey	37/50 (74)	HPV 18 & 33	PCR
2007	Choi et al. [38]	Korea	8/123 (7)	HPV 16,18 & 33	PCR
2008	Akil et al. [39]	Syria	69/113 (61)	HPV 16,18,31,33 and 35	PCR
2008	Khan et al. [40]	Japan	26/124 (21)	HPV 16,6,18 and 33	PCR
2009	He et al. [41]		20/24 (60)	HPV 16	PCR
2009	De leon et al. [42]	Mexico	15/51 (29)	HPV 16 &18	PCR
2009	Mendizabul et al. [43]	Mexico	3/67 (4)	HPV 16,18 and 33	PCR
2009	Heng et al. [44]	Australia	8/26 (20)	HPV 18	PCR
2010	Aceto et al. [45]	Italy	3/5 (60)	HPV 16 & 18	PCR
2011	Aguayo et al. [46]	Chile	4/46 (9)	HPV 16	PCR
2011	Antonsson et al. [47]	Australia	27/50 (50)	HPV 6 & 7	PCR in situ
2011	Silva and Silva [48]	Brazil	12/90 (13)	HPV 16 & 18	PCR/ISH
2012	Baltzell et al. [49]	USA	4/70 (6)	HPV 16	PCR in situ/ISH
2012	Joshi & Buchring [50]		3/29 (16)		PCR
2013	Saurez et al. [51]	Argentina	16/61 (26%)	HPV11 & 16	PCR

Table 1: Authors who have detected HPV DNA in cancer and in the normal breast tissue.

Studies from 1999 to 2013 about HPV relation in breast cancer showed that prevalence varies between 4% (3/67) in Mexico to 86% (25/29) in the USA (Table 1) [26-51]. These variations are based in different geographic regions and are mainly because of susceptibility of the population to the various detection methods of HPV types or to the primer type of PCR used (Table 1) [26-51].

PCR: polymerase chain reaction; ISH: *in situ* hybridization

The most common HPV types detected in the HPV positive breast cancer tissue samples are high risk strains like HPV16, HPV18 and HPV33. Like HPV positive oral squamous cell carcinomas the patients with HPV positive breast cell carcinomas were significantly younger in age compared to HPV negative breast cancer patients [25]. There are various theories on the transmission of the virus to the breast tissue. One of the potential mechanisms suggested is through oral-genital contact or direct contact with the genitals and the breast other than the hematological spread [52]. Some authors have also suggested vertical transmission during the breast feeding from the infant with oral HPV infection. HPV has been also found in the breast milk in some rare cases [53]. The oral HPV infection of the partner between the 6th and 12th postpartum months was linked with the breast cancer too [54]. In many studies high risk HPV DNA was also detected in normal tissue and the nipples of the breast [33,35,37,41,44].

There has been also many other studies where investigators have failed to find any HPV species in the breast cancer tissue samples [55-64].

There has been number of studies in the last decade globally that points towards high risk HPV strains as the causative agents for breast cancer. There is a possibility that high risk HPV strains might induce some initial mutations which may lead to alteration of one of the cell proliferation barriers as well as the first step towards carcinogenesis. In order to confirm the role of HPV in breast cancer biomarkers of HPV and its oncogenic process E6 and E7 expression, P53 and Rb methylation, HPV mRNA expression, Viral Load in the tissues, Telomerase activity and others must be studied through modern tools like Gene expression arrays. Koilocytosis is the signature pathology of the HPV at the cellular level and thus it must be considered in all the breast cancer studies.

Darwinian view of HPV infection in Humans

The high risk Human Papilloma Virus [HPV] strains [16 and 18 mainly] have been proved to be the major cause of cancers of cervix, vulva, penis and other reproductive organs [65]. Persistent infection is one of the most important factors that can lead to cancer in the long term. Evolutionary principles can help us to understand evolved unique traits of these pathogens and selection forces that shape them. The ability of HPV to infect and colonize different organ sites provides with an adaptive advantage to maximize the chances and frequency of spreading to newer hosts as well as reproducing independently at multiple sites. In majority of the cases the infection of these different tissues is innocuous but in some cases persistent infection may cause mutations in the cells and thus initiating carcinogenesis process. Persistent or the long term infection is one of the most common evolved traits of the sexually transmitted Viruses. Sexually transmitted viruses must be persistent within the host as the opportunities for transmission are relatively thin and infrequent compared to other modes of transmission. These viruses are only transmitted either through sex or juicy or passionate kissing. HPV infection spreads mainly through sexual intercourse [65]. There are very limited non-sexual modes of HPV transmission available. Sexual intimacy, which includes open mouth kissing, is a major mode of transmission in case of HPV. HPV high risk strain infection has been recently found to play a major role in oral cancers which are directly associated with the rising trend of oral sex among the western youth [66]. The risk of developing oral HPV infection was found to increase with increase in number of lifetime oral or vaginal sex partners. It has also been reported that not only oral sex, but also open-mouthed kissing, was associated to the development of oral HPV infection [22,66]. The virus has adapted to colonize in the oral cavity, thus has created a new opportunity to spread through juicy and open mouth kissing in case of partners having oral infection. The Virus can go a step further and can actually make people kiss more passionately with higher frequency to improve the chances of infecting new hosts to a great extent. The virus will adapt to colonize almost every site that may give it a selective advantage to spread to large number of new hosts which is evident from the HPV induced cancers of genitals in humans like that of vagina, vulva, anus and penis [65]. Recently high risk strains of HPV 16, 18 and 33 have also been detected in normal breast as well as the Cancer tissues across the world [67]. In many cases the HPV detected in the breast cancer tissue is among the women of younger age from countries like USA, Australia and Greece which have rising trend of multiple sex partners, Oral Sex and one night stand or Casual sex [68-70]. The HPV positive breast cancer patients in Canada and Syria were also found to be significantly younger compared to the women with HPV negative breast cancer [68-71]. Infection at younger age will give ample opportunity to the virus to infect large number of new hosts in the entire lifetime of the infected girl or women and thus may also lead to cancer of the infected organ in long run. The colonization of Breast tissue especially the outer surface and the nipple area among the sexually active young girls and women make lot of evolutionary sense. Breasts are one of the most intimately involved sites during sexual act and thus can help in spread of virus to very large number of new hosts especially when both of the couple has multiple sex partners. In many studies the women with breast cancer had earlier cervical infection of HPV and the HPV strain detected in the breast cancer tissue samples were the same that infected their cervical or genital region [32]. It is very likely that after cunnilingus the male partners infect the breast nipples and surrounding area via hand and most probably through oral route with the same HPV strain that has infected the female cervix or genitals. Open mouthed kissing after cunnilingus may cause infection of oral cavity in women with the same HPV strain that has infected her genitals. The colonization of the breast nipples and surrounding area will lead to oral infection of the male counterparts and they can further infect some of their other female sex partners leading to a whole vicious cycle of infection benefiting significantly to the virus. It is very likely that virus may also manipulate the host sexual behavior in a way that facilitates transmission in regions where the chances of transmission are very thin due to some cultural constraints. The chances of such manipulations of sexual behavior are very high in the countries having conservative approach towards sexuality. In majority of the South Asian countries, mainly in India, Nepal, Bangladesh and others, sexuality still remains a taboo. The natives in such societies generally disapprove love marriage, premarital sex and having multiple sex partners unlike western countries. Majority of the population hardly prefer more than one sex partners post-marriage in their entire life. Nations with majority of Muslim population across the world, including those in South Asia, follow an ancient trend of male and female circumcision which has been proved to be highly effective in blocking the transmission of HPV and other sexually transmitted

infections [72]. The pathogens in such case will have very scarce chance of infecting a new host even in the entire lifetime of its current host and it will eventually die if it fails to infect a new one. This type of cultural constraints create a very strong selection pressure on the virus to evolve with a trait that can manipulate sexual behavior of the host to increase its rate of transmission since the available modes for transmission narrow down in such conditions. As a manifestation of such manipulations it is very likely to find increased levels of testosterone in the infected men and that of estrogen in case of women. Infection of the brain may also lead to change in the sexual patterns of the host. The manipulation need not always arise out of neuronal infection in CNS as higher replication in target peripheral tissues along with the modulation of neuro-immunal pathways and further communication via hormonal signaling to CNS may also result in behavioral changes [73,74]. The major advantage of increased sex hormone level in host is immunosuppression as it has been recently found that ovulating women are at greater risk of acquiring HPV and other sexually transmitted infections due to sudden dip in the immunity caused by higher level of serum estradiol that allows spermatozoa to survive the threat of an immune response and to fertilize an egg successfully [75]. Parasites are also capable enough to sense the physiological changes in the host and direct those changes to enhance their reproductive fitness [76]. DNA based viruses like HPV may also produce substantial number of variants owing to factors like large population sizes, long infection time and hypermutation of the epitopes that can lead to significant evolution of the virus within the host [76]. The HPV 16 which is a high risk strain known to cause cancer of cervix, genitals and extra genitals has recently been linked to prostate cancer and lung Cancer [77,78]. Considering the versatility of the virus to colonize diverse tissues in Human body it will not be exorbitant to speculate that it can also colonize human brain and manipulate the neuronal regions regulating sexual behavior like amygdala, hypothalamus and others for its own evolutionary advantage. Another major advantage to the virus on Colonizing brain is the protection from the immune surveillance of the host and an opportunity for persistent infection due its immune privileged site status.

Documented Studies Supporting Proposed Hypothesis

Host manipulation by viruses in rodents and primates

There are many examples in case of rodent and primate infections where viruses manipulate their host behavior by infecting the neurons in limbic system, hypothalamus and other regions of the brain. Viruses transmitted during the sexual act which often includes biting in many species are under very intense selective pressure to alter the host sexual behavior as the opportunities of transmission are quite less due to restricted availability of non-sexual modes. Borna Diseases virus induces aggression in rats by infecting the neurons in vomeronasal regions, olfactory bulbs and limbic cortical areas [79,80]. Herpes Simplex Virus induces the same effect in mice as that of BDV by regulating 5-HT and DA synthesis pathways in mice [81]. Higher aggression and wounding are often correlated with higher SIV infections in primates. The proximate mechanisms for such effect are infection of glial cells in basal ganglia and certain neurons in thalamus region of the brain. Feline immunodeficiency virus which infects cats manipulates their host in much similar way as SIV does in primates. Infections in the areas of brain like hippocampus, hypothalamus, thalamus, olfactory bulb, amygdala, frontal cortex and septum have been speculated to be responsible for higher aggressive and sexual behavior in rats infected with BDV [82-84]. Elevated serum testosterone levels and consequently enhanced aggressive behavior have been detected in mice infected with tick-born encephalitis virus [85]. Aggressive Norway rats infected with Hantavirus have been documented with lower 5-HIAA levels along with higher testosterone serum concentration [86].

Manipulation of the sexual behavior by viruses in humans

Host behavior manipulation in case of sexually transmitted diseases is one such phenomenon that makes lot of sense in the light of evolution. This field is still in its nascent phase when it comes to such manipulations in case of humans as scientists across the world have just started coming with some convincing illustrations like that done by the virus of *genital herpes*. Herpes virus has adapted to colonize oral cavity for rapid transmission through Juicy and passionate kisses or the one that includes exchange of saliva. Most importantly changing sexual behaviors are changing transmission dynamics in ways that will shape certain pathogens for faster transmission with culture playing pivotal role in the regulation of such transmission processes. This has particularly happened in the case for transmission of herpes viruses in response to recent increases in oral-genital sex in western culture. Other than this ganglion infection in genital herpes is speculated to alter the sensory input to sex organs leading to enhanced libido and thus higher probability of virus transmission [73]. Scientists from University of California, Berkeley have documented higher levels of testosterone among the HIV positive patients during their primary stages of infection in South Africa [87]. Elevated serum testosterone above normal standards may induce higher libido and thus can lead to higher mating frequency thereby increase the chances of transmission to other host. There are two major obvious rationales for this type of manipulations.

1. Evolutionary success of sexually transmitted pathogens depends on mating frequency of the host rather than its population density. Most of the STDs have been evolved to persistence as chances of host mating with different partners are quite less in small span of time. The hosts with the highest mating success are also at the highest risk of getting sexually transmitted infections [88]. Thus there is very high selection pressure on the pathogens to adapt in a way that facilitate their transmission by altering mating frequency.

2. RNA viruses like HIV have very high mutation rate per replication and thus there are more mutational variants available within the host for the evolution of desired trait [89].

The bizarre manipulations of the *Toxoplasma gondii*

Toxoplasma gondii is one of the most extensively studied parasites for the host behavior manipulation hypothesis. *Toxoplasma gondii* infection in both mice and rats reverses the rodents' natural aversion to the smell of cat urine and causes them to instead "develop an actual attraction to the pheromones" [90]. This behavioral change is thought to be beneficial for the parasite as it can engage in sexual recombination only in the Cat intestines [90]. The manipulation also enhances the transmission of the parasite through the trophic route. *Toxoplasma gondii* does not stop here as it has been recently found to manipulate the mate choice among the female rats. Male rats infected with *Toxoplasma gondii* become more attractive for the uninfected female rats [3]. This leads to further transmission of the parasite from infected male to uninfected female and later to their progenies [91]. The proximate mechanisms behind the manipulation elucidated so far are associated with the higher levels of Testosterone in the infected males caused by enhanced expression of steroidogenic enzymes and

LHR receptors in testes [91,92]. Testosterone is also known to affect the fear response among the rats by binding to certain receptors in the limbic system that regulate this emotion [93]. *Toxoplasma gondii* manipulation of intermediate host behavior could be due to the parasite localizing in specific brain regions and the most likely brain regions are those associated with regulation of fear response [94]. Amygdala in brain is involved in fear processing and recent work provides a potential process for fatal feline attraction mediated by pathway that activates the amygdala. Modulation of the sexual arousal pathways in the posterodorsal amygdala has also been reported. There are immense possibilities that the parasite may hijack this sexual attraction mechanism in order to override the rat's innate aversion to cat odor [94]. The specificity of these manipulations points towards the targeted physiological manipulation rather than accidental or pathological manifestations of infection.

The parasitic protozoan *Toxoplasma gondii* infects about one-third of the population of developed countries and hence can be a good model to study the manipulation hypothesis in humans [95]. *Toxoplasma*-infected subjects differ from uninfected controls in the personality profile estimated with two versions of Cattells 16PF, Cloningers TCI and Big Five questionnaires [95]. Most of these personality defect progresses with the increase in the infection time, suggesting that *Toxoplasma* influences human personality rather than human personality influencing the chances of infection [95]. *Toxoplasma gondii* infection increases the reaction time of infected subjects, which can explain the large number of traffic accidents found among the infected subjects reported in three retrospective and one very large prospective case-control study [95]. Recent studies have found that the male with the infection have higher testosterone levels and thus were found more attractive by the females when compared with the males without the infection. The exact proximate mechanisms behind the effect among humans are under investigation [95]. Raised or disrupted dopamine levels have been reported in both rodent and human *Toxoplasma gondii* infection and within human patients with schizophrenia [96-99]. Elevated levels of Dopamine have also been reported in the patients of obsessive compulsive disorder (OCD), bipolar disorder and amongst those with suicide attempts [100-103]. *Toxoplasma gondii* was recently found to encode a protein with high homology and showing similar catalytic properties to the tyrosine hydroxylases found in mammals [104]. This *Toxoplasma gondii* ortholog synthesizes L-DOPA, precursor to dopamine, as well as tyrosine,and has been demonstrated to result in increased dopamine levels associated with *Toxoplasma gondii* cysts in the rodent brain [99]. In a very recent study done of *Toxoplasma* infection in mice, it was found that the parasites infects the dentritic immune cells and manipulate them to secrete neurotransmitter called GABA a signal substance that, amongst other effects, inhibits the sensation of fear and anxiety. Disturbances of the GABA system are seen in people with depression, schizophrenia, bipolar diseases, anxiety syndrome and other mental diseases. Further investigations on the manipulative effects of *Toxoplasma gondii* infection on the GABA system will help to crack the toxoplasmosis and mental illness puzzle [105].

Study on the manipulation induced by latent *Toxoplasma* infection among the humans is still in its infancy. Experimental data from a study done on significantly higher number of human hosts is required to arrive at any concrete conclusion. Further investigation in this direction will certainly open up new avenues for behavioral manipulations induced by parasites in humans as a host.

The curious case of *Candida albicans* yeast

Candida albicans which is one of the most common infections among the sexually active women has evolved significantly [106]. It has adapted to specially colonize vagina and these vaginal strains have also adapted to sexual transmission, specifically female-to-male transmission. The fungus can spread to the host's male partner by colonizing his glans penis via vaginal intercourse or his oral cavity via cunnilingus [106,107]. This adaption of sexual transmissibility has been also supported with evidence from Genetic studies on change in allelic frequency for the same [107]. The most significant and highest level of adaptation achieved by this fungus is with respect to manipulation of sexual behavior in the host. *Candida albicans* infections have been linked with following five major aspects of human sexual behavior:

1. Early age of first intercourse,
2. Casual sex with previous unknown partners in the past month,
3. Vaginal sex during menstruation,
4. Oral sex [fellatio]
5. Receptive anal sex.

Candida albicans has also evolved to cross the blood brain barrier and colonize sites in Human Brain [108]. The most bizarre adaptation is the ability of this fungus to identify various regions of Brain and its capacity to adhere differently to different neuronal tissues. This recent adaptation of recognizing various neuronal tissues has been confirmed with autopsy of macaque brains.

In an *ex vivo* adhesion assay of primate Macacamulata in which tissues from frontal lobes and striatum [caudate, putamen, and portions of the globuspallidus were used, *Candida albicans* adhered to gray matter at about six times the level of its adhesion to white matter. The fungus was able to bind to different cell types within the cortex, basal ganglia, and white matter [109]. Thus similar studies in case of the HPV infection might also help us to investigate manipulation of sexual behavior with respect to proximate mechanisms.

Colonization of brain by HPV in Humans

HPV has been also successful in colonizing Human Brain as there is ample evidence on HPV as the causative agent for Retinoblastoma in Kids [110]. Colonization of the Human Brain in case of adults gives ample opportunity for hypothesized behavioral manipulations induced by Virus directly or indirectly due to immune responses which may be of adaptive advantage to the virus. Adherence of the virus to specific areas like amygdala, Hypothalamus, Limbic system and other areas of brain that regulate Sexual behavior and similar traits might help to understand the level of adaptation by the virus.

Factors that may Contradict the Hypothesis

Sexual signaling in animals and insects

Females in various species avoid males infected with parasites and parasite-free males are often found to advertise their status via different phenotypic traits which is a well-documented phenomenon in mainstream science [111]. This process selects for heritable resistance and reduces direct exposure of the female to parasites [112]. Parasites that coevolve with the host are likely to overcome this obstacle. Recently researchers from Stanford and Nangyang Technological University documented a case of parasitic manipulation of host mate choice. As per the report *Toxoplasma gondii*, a sexually transmitted infection

of brown rats, enhances sexual attractiveness of infected males [77]. Similarly insect virus Hz-2v alters mating behavior and pheromone production in *Helicoverpazea* moths. Virus-infected females were found to produce five to seven times more pheromone than control females and attracted twice as many males as did control females in flight tunnel experiments [113]. Thus under some evolutionary niches, parasites can indeed manipulate host sexual signaling to enhance their reproductive success.

Counter adaptations by the host against parasitic manipulation

Reproduction is the crucible of Evolution even above survival. We all know because of short life span and high mutation rate the process of evolution is very rapid among the pathogens whereas it is not possible for us to keep up with their pace of evolution. In case of Humans it takes very intense selection pressures and many generations for evolution of a new trait. Parasites that are transmitted through sexual routes like that of HPV and HIV certainly have very high selection pressure to manipulate their host sexually because of very limited routes of transmission as if they fail to do so they will die with the host. Evolution of Persistence and benignity are another such trait shared by pathogens of STDs which gives them more chances of transmission during the entire lifetime of host and to enhance their reproductive success [113]. There is no such intense selection pressure on the Humans to come up with counter adaptive strategies as the advantage of sex is far higher than cost of the infection and anyhow the mortality associated with such infections are mainly in post-reproductive phase where selection pressure is too weak to help.

Presence of other infectious agents within the host

Hosts at a time may be infected with more than one parasite or multiple parasites. Manipulative strategy of one parasite might be dangerous for the reproductive success of other within the same host and in that case the counter manipulative response by the rest of the parasites may weaken the actual manipulation induced by sexually transmitted pathogens**.** Sometimes opposite can happen as the host might be infected with multiple STDs like HPV, HIV, and Hepatitis B etc., and in that case sexual behavior manipulation by one virus might actually give an adaptive advantage to others and thus can make it less costly affair for rest of them.

Adaptive manipulation versus accidental effects

The observed manipulated behavior in the host may not always be directly induced by the parasite. Parasitic manipulation can be directly induced by the secretion of the bioactive compounds or they may be manifestation of the immune response of the host against the infection giving an evolutionary advantage to the parasite. Sometimes chemicals like Cytokines are secreted by the host as an immune response which does have a strong effect on various neuronal tissues leading to change in host behavior. Parasites can actually mimic this type of immune response by directly secreting cytokines and induce similar change in host behavior to get an evolutionary advantage. Different parasites may induce different immune responses which can elicit different behavior in the host [114,115].

Several examples of pathogens affecting the proximate mechanisms were reported by Klein (2003) that mediate the expression of social behaviors in vertebrates [aggressive, reproductive and parental behaviors], in ways that may increase parasitic transmission [116].

Testing of the hypothesis by methods below

1. *Ex vivo* adhesion assay of Human Brain cells with respect to Human Papilloma Virus, HIV and other sexually transmitted Virus like Hepatitis B might give an important insight and evidence whether these pathogens have evolved to an extent that they can recognize different regions in the brain and bind differently to them.

2. HPV after being proved to be the main causative agent for cervical cancer has also been linked to various other important cancers like oropharnygeal, tongue, tonsillar, breast, skin and most recently with prostate cancer. I speculate that in future it may be found in the brain cancer tissues also. We must look for the evidences of HPV DNA and that of some other sexually transmitted viruses like Herpes Simplex, Hepatitis B, Epstein Barr Virus and HIV in Brain tumor samples of the patients after their death. The same kind of study needs to be done among those patients who died of cancers caused by HPV. We must look for the HPV DNA in those regions in the brain that regulate sexual behavior.

3. Genetic studies that may offer evidence on change in allelic frequencies on the proposed adaptations and the one which are prevalent might stand as a strong support for the hypothesis and prove it to be an ongoing process. The genetic basis of a virus induced host behavior manipulation has been recently determined in a gypsy moth caterpillar and it really seems to be a giant leap in study of parasitic manipulations [117].

4. Proteomics can rapidly provide a comprehensive view of the expression of entire genomes, Proteomics would serve as an excellent tool to study the host [and sometimes the parasite] genomes in action during manipulative processes. Although at the moment all the studies using proteomics to identify the mechanisms of parasitic manipulation are still in progress, preliminary results reveal a bright future for such an approach.

5. Phylogenetic studies can also be done as methods for tracing evolutionary phylogenies have powerful new applications that use genetic data to trace the history of pathogens across millions of years, within outbreaks continuing for long years, and even within individuals.

Conclusion

Evolutionary or Darwinian Medicine, a nascent research area in Medicine can significantly contribute in understanding of the sexually transmitted diseases. Evolutionary methods can help to analyze host -pathogen co-evolution that shapes extreme traits whose costs can be substantial to the host. It is equally important to determine the exact proximate causes of host behavior manipulations for better understanding of Sexually transmitted diseases and their treatment. It is also necessary to apply interdisciplinary approach to answer the challenging questions offered by host manipulation studies. The community of Evolutionary Ecologists, Biologists, Medical Scientists and Epidemiologists must come together to take this field forward. The knowledge derived from such research may significantly contribute to the public health and can help us to take a step closer in the constant evolutionary battle with the pathogen. If pathogens like HPV, HIV, Hepatitis B and *Candida albicans* affects sex hormone levels; this might be the proximate means of behavior manipulation. It doesn't matter whether this effect began accidentally. This is how evolution works. An accidental effect is seized by natural selection and then refined to make it work better. The advantages of understanding diseases from the evolutionary perspective are enormous and this will help further

theory of Evolution to achieve its true worth in Medical Science for better understanding of diseases and their treatment.

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References

1. Thomas F, Adamo S, Moore J (2005) Parasitic manipulation: where are we and where should we go? Behav Processes 68: 185-199.
2. Lacroix R, Mukabana WR, Gouagna LC, Koella JC (2005) Malaria infection increases attractiveness of humans to mosquitoes. PLoS Biol 3: e298.
3. Dass SA, Vasudevan A, Dutta D, Soh LJ, Sapolsky RM, et al. (2011) Protozoan parasite Toxoplasma gondii manipulates mate choice in rats by enhancing attractiveness of males. PLoS One 6: e27229.
4. Dietzschold B, Morimoto K, Hooper DC (2001) Mechanisms of virus-induced neuronal damage and the clearance of viruses from the CNS. Curr Top Microbiol Immunol 253: 145-155.
5. Villa LL (2006) Biology of genital human papillomavirus. Chapter 1, International Journal of Gynecology and Obstetrics 94: S3-S7.
6. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV (2002) The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 55: 244-265.
7. Steenbergen RD, de Wilde J, Wilting SM, Brink AA, Snijders PJ, et al. (2005) HPV-mediated transformation of the anogenital tract. J Clin Virol 32: S25-S33.
8. Lizano M, Berumen J, García-Carrancá A (2009) HPV-related carcinogenesis: basic concepts, viral types and variants. Arch Med Res 40: 428-434.
9. Cardoso JC, Calonje E (2011) Cutaneous manifestations of human papillomaviruses: a review. Acta Dermatovenerol Alp Panonica Adriat 20: 145-154.
10. Lazarczyk M, Cassonnet P, Pons C, Jacob Y, Favre M (2009) The EVER proteins as a natural barrier against papillomaviruses: a new insight into the pathogenesis of human papillomavirus infections. Microbiol Mol Biol Rev 73: 348-370.
11. Doorbar J (2005) The papillomavirus life cycle. J Clin Virol 32 Suppl 1: S7-15.
12. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (2012) Biological Agents Volume 100B, A Review of Human Carcinogens. LYON, France 100B: 278-280.
13. Dahlstrand HM, Dalianis T (2005) Presence and influence of human papillomaviruses (HPV) in Tonsillar cancer. Adv Cancer Res 93: 59-89.
14. World Health Organization (2007) IARC monographs on the evaluation of carcinogenic risk to humans. Volume 90. Human papillomaviruses. International Agency for Research on Cancer, Lyon, France.
15. Sturgis EM, Cinciripini PM (2007) Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer 110: 1429-1435.
16. Braakhuis BJ, Visser O, Leemans CR (2009) Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: Increasing incidence, but not in young adults. Oral Oncol 45: e85-89.
17. Conway DI, Stockton DL, Warnakulasuriya KA, Ogden G, Macpherson LM (2006) Incidence of oral and oropharyngeal cancer in United Kingdom (1990-1999) -- recent trends and regional variation. Oral Oncol 42: 586-592.
18. Robinson KL, Macfarlane GJ (2003) Oropharyngeal cancer incidence and mortality in Scotland: are rates still increasing? Oral Oncol 39: 31-36.
19. Hammarstedt L, Dahlstrand H, Lindquist D, Onelöv L, Ryott M, et al. (2007) The incidence of tonsillar cancer in Sweden is increasing. Acta Otolaryngol 127: 988-992.
20. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML (2008) Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 26: 612-619.
21. Syrjänen S (2004) HPV infections and tonsillar carcinoma. J Clin Pathol 57: 449-455.
22. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, et al. (2007) Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 356: 1944-1956.
23. Lindquist D, Romanitan M, Hammarstedt L, Näsman A, Dahlstrand H, et al. (2007) Human papillomavirus is a favourable prognostic factor in tonsillar cancer and its oncogenic role is supported by the expression of E6 and E7. Mol Oncol 1: 350-355.
24. Gillespie MB, Rubinchik S, Hoel B, Sutkowski N (2009) Human papillomavirus and oropharyngeal cancer: what you need to know in 2009. Curr Treat Options Oncol 10: 296-307.
25. Amarante MK, Watanabe MA (2009) The possible involvement of virus in breast cancer. J Cancer Res Clin Oncol 135: 329-337.
26. Di Lonardo A, Venuti A, Marcante ML (1992) Human papillomavirus in breast cancer. Breast Cancer Res Treat 21: 95-100.
27. Hennig EM, Suo Z, Thoresen S, Holm R, Kvinnsland S, et al. (1999) Human papillomavirus 16 in breast cancer of women treated for high grade cervical intraepithelial neoplasia (CIN III). Breast Cancer Res Treat 53: 121-135.
28. Yu Y, Morimoto T, Sasa M, Okazaki K, Harada Y, et al. (1999) HPV33 DNA in premalignant and malignant breast lesions in Chinese and Japanese populations. Anticancer Res 19: 5057-5061.
29. Liu Y, Klimberg VS, Andrews NR, Hicks CR, Peng H, et al. (2001) Human papillomavirus DNA is present in a subset of unselected breast cancers. J Hum Virol 4: 329-334.
30. Li T, Lu ZM, Guo M, Wu QJ, Chen KN, et al. (2002) p53 codon 72 polymorphism (C/G) and the risk of human papillomavirus-associated carcinomas in China. Cancer 95: 2571-2576.
31. Damin AP, Karam R, Zettler CG, Caleffi M, Alexandre CO (2004) Evidence for an association of human papillomavirus and breast carcinomas. Breast Cancer Res Treat 84: 131-137.
32. Widschwendter A, Brunhuber T, Wiedemair A, Mueller-Holzner E, Marth C (2004) Detection of human papillomavirus DNA in breast cancer of patients with cervical cancer history. J Clin Virol 31: 292-297.
33. de Villiers EM, Sandstrom RE, zur Hausen H, Buck CE (2005) Presence of papillomavirus sequences in condylomatous lesions of the mamillae and in invasive carcinoma of the breast. Breast Cancer Res 7: R1-11.
34. Kan CY, Iacopetta BJ, Lawson JS, Whitaker NJ (2005) Identification of human papillomavirus DNA gene sequences in human breast cancer. Br J Cancer 93: 946-948.
35. Tsai JH, Tsai CH, Cheng MH, Lin SJ, Xu FL, et al. (2005) Association of viral factors with non-familial breast cancer in Taiwan by comparison with non-cancerous, fibroadenoma, and thyroid tumor tissues. J Med Virol 75: 276-281.
36. Kroupis C, Markou A, Vourlidis N, Dionyssiou-Asteriou A, Lianidou ES (2006) Presence of high-risk human papillomavirus sequences in breast cancer tissues and association with histopathological characteristics. Clin Biochem 39: 727-731.
37. Gumus M, Yumuk PF, Salepci T, Aliustaoglu M, Dane F, et al. (2006) HPV DNA frequency and subset analysis in human breast cancer patients' normal and tumoral tissue samples. J Exp Clin Cancer Res 25: 515-521.
38. Choi YL, Cho EY, Kim JH, Nam SJ, Oh YL, et al. (2007) Detection of human papillomavirus DNA by DNA chip in breast carcinomas of Korean women. Tumour Biol 28: 327-332.
39. Akil N, Yasmeen A, Kassab A, Ghabreau L, Darnel AD, et al. (2008) High-risk human papillomavirus infections in breast cancer in Syrian women and their association with Id-1 expression: a tissue microarray study. Br J Cancer 99: 404-407.
40. Khan NA, Castillo A, Koriyama C, Kijima Y, Umekita Y, et al. (2008) Human papillomavirus detected in female breast carcinomas in Japan. Br J Cancer 99: 408-414.
41. He Q, Zhang SQ, Chu YL, Jia XL, Wang XL (2009) The correlations between HPV16 infection and expressions of c-erbB-2 and bcl-2 in breast carcinoma. Mol Biol Rep 36: 807-812.
42. de León DC, Montiel DP, Nemcova J, Mykyskova I, Turcios E, et al. (2009) Human papillomavirus (HPV) in breast tumors: prevalence in a group of Mexican patients. BMC Cancer 9: 26.
43. Mendizabal-Ruiz AP, Morales JA, Ramírez-Jirano LJ, Padilla-Rosas M, Morán-

Moguel MC, et al. (2009) Low frequency of human papillomavirus DNA in breast cancer tissue. Breast Cancer Res Treat 114: 189-194.

44. Heng B, Glenn WK, Ye Y, Tran B, Delprado W, et al. (2009) Human papilloma virus is associated with breast cancer. Br J Cancer 101: 1345-1350.

45. Aceto GM, Solano AR, Neuman MI, Veschi S, Morgano A, et al. (2010) High-risk human papilloma virus infection, tumor pathophenotypes, and BRCA1/2 and TP53 status in juvenile breast cancer. Breast Cancer Res Treat 122: 671-683.

46. Aguayo F, Khan N, Koriyama C, González C, Ampuero S, et al. (2011) Human papillomavirus and Epstein-Barr virus infections in breast cancer from chile. Infect Agent Cancer 6: 7.

47. Antonsson A, Spurr TP, Chen AC, Francis GD, McMillan NA, et al. (2011) High prevalence of human papillomaviruses in fresh frozen breast cancer samples. J Med Virol 83: 2157-2163.

48. Silva RG Jr, da Silva BB (2011) No evidence for an association of human papillomavirus and breast carcinoma. Breast Cancer Res Treat 125: 261-264.

49. Baltzell K, Buehring GC, Krishnamurthy S, Kuerer H, Shen HM, et al. (2012) Limited evidence of human papillomavirus in [corrected] breast tissue using molecular in situ methods. Cancer 118: 1212-1220.

50. Joshi D, Buehring GC (2012) Are viruses associated with human breast cancer? Scrutinizing the molecular evidence. Breast Cancer Res Treat 135: 1-15.

51. Pereira Suarez AL, Lorenzetti MA, Gonzalez Lucano R, Cohen M, Gass H, et al. (2013) Presence of human papilloma virus in a series of breast carcinoma from Argentina. PLoS One 8: e61613.

52. Simões PW, Medeiros LR, Simões Pires PD, Edelweiss MI, Rosa DD, et al. (2012) Prevalence of human papillomavirus in breast cancer: a systematic review. Int J Gynecol Cancer 22: 343-347.

53. Yoshida K, Furumoto H, Abe A, Kato T, Nishimura M, et al. (2011) The possibility of vertical transmission of human papillomavirus through maternal milk. J Obstet Gynaecol 31: 503-506.

54. Sarkola M, Rintala M, Grénman S, Syrjänen S (2008) Human papillomavirus DNA detected in breast milk. Pediatr Infect Dis J 27: 557-558.

55. Bratthauer GL, Tavassoli FA, O'Leary TJ (1992) Etiology of breast carcinoma: no apparent role for papillomavirus types 6/11/16/18. Pathol Res Pract 188: 384-386.

56. Wrede D, Luqmani YA, Coombes RC, Vousden KH (1992) Absence of HPV 16 and 18 DNA in breast cancer. Br J Cancer 65: 891-894.

57. Czerwenka K, Heuss F, Hosmann JW, Manavi M, Lu Y, et al. (1996) Human papilloma virus DNA: a factor in the pathogenesis of mammary Paget's disease? Breast Cancer Res Treat 41: 51-57.

58. Gopalkrishna V, Singh UR, Sodhani P, Sharma JK, Hedau ST, et al. (1996) Absence of human papillomavirus DNA in breast cancer as revealed by polymerase chain reaction. Breast Cancer Res Treat 39: 197-202.

59. Lindel K, Forster A, Altermatt HJ, Greiner R, Gruber G (2007) Breast cancer and human papillomavirus (HPV) infection: no evidence of a viral etiology in a group of Swiss women. Breast 16: 172-177.

60. de Cremoux P, Thioux M, Lebigot I, Sigal-Zafrani B, Salmon R, et al. (2008) No evidence of human papillomavirus DNA sequences in invasive breast carcinoma. Breast Cancer Res Treat 109: 55-58.

61. Subhawong AP, Subhawong T, Nassar H, Kouprina N, Begum S, et al. (2009) Most basal-like breast carcinomas demonstrate the same Rb-/p16+ immune phenotype as the HPV-related poorly differentiated squamous cell carcinomas which they resemble morphologically. Am J Surg Pathol 33: 163-175.

62. Hachana M, Ziadi S, Amara K, Toumi I, Korbi S, et al. (2010) No evidence of human papillomavirus DNA in breast carcinoma in Tunisian patients. Breast 19: 541-544.

63. Chang P, Wang T, Yao Q, Lv Y, Zhang J, et al. (2012) Absence of human papilloma virus in patients with breast cancer in north-west China. Med Oncol 29: 521-525.

64. Hedau S, Kumar U, Hussain S, Shukla S, Pande S, et al. (2011) Breast cancer and human papillomavirus infection: no evidence of HPV etiology of breast cancer in Indian women. BMC Cancer 11: 27.

65. Giuliano AR, Tortolero-Luna G, Ferrer E, Burchell AN, de Sanjose S, et al. (2008) Epidemiology of human papillomavirus infection in men, cancers other than cervical and benign conditions. Vaccine 26: K17-K28.

66. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML (2009) Oral sexual behaviors associated with prevalent oral human papillomavirus infection. J Infect Dis 199: 1263-1269.

67. Lawson JS, Kan CY, Iacopetta BJ, Whitaker NJ (2006) Are some breast cancers sexually transmitted? Br J Cancer 95: 1708.

68. Yasmeen A, Bismar TA, Kandouz M, Foulkes WD, Desprez PY, et al. (2007) E6/E7 of HPV type 16 promotes cell invasion and metastasis of human breast cancer cells. Cell Cycle 6: 2038-2042.

69. Yasmeen A, Ricciardi R, Kassab A, Bismar TA, Al Moustafa A-E (2007) High-risk HPVs in human breast cancer and normal mammary tissues. Breast 16: 445.

70. Akil N, Kassab A, Yasmeen A, Darnel AD, Bismar TA, et al. (2008) Human breast cancer and sexual activities. Br J Cancer 98: 508-509.

71. Schmitt DP, Shackelford TK (2008) Big Five traits related to short-term mating: From personality to promiscuity across 46 nations. Evolutionary Psychology 6: 246-282.

72. Rizvi SA, Naqvi SA, Hussain M, Hasan AS (1999) Religious circumcision: a Muslim view. BJU Int 83 Suppl 1: 13-16.

73. Klein SL, Nelson RJ (2010) Social Behavior and Parasites. In: Breed MD, Moore J, Encyclopedia of Animal Behavior, Volume 3, Oxford: Academic Press, 216-225.

74. Adamo SA (2002) Modulating the modulators: parasites, neuromodulators and host behavioral change. Brain Behav Evol 60: 370-377.

75. Relloso M, Aragoneses-Fenoll L, Lasarte S, Bourgeois C, Romera G, et al. (2012) Estradiol impairs the Th17 immune response against Candida albicans. J Leukoc Biol 91: 159-165.

76. Ewald PW (2004) Evolution of virulence. Infect Dis Clin North Am 18: 1-15.

77. Whitaker NJ, Glenn WK, Sahrudin A, Orde MM, Delprado W, et al. (2013) Human papillomavirus and Epstein Barr virus in prostate cancer: Koilocytes indicate potential oncogenic influences of human papillomavirus in prostate cancer. Prostate 73: 236-241.

78. Aguayo F, Castillo A, Koriyama C, Higashi M, Itoh T, et al. (2007) Human papillomavirus-16 is integrated in lung carcinomas: a study in Chile. Br J Cancer 97: 85-91.

79. Solbrig MV, Fallon JH, Lipkin WI (1995) Behavioral disturbances and pharmacology of Borna disease. Curr Top Microbiol Immunol 190: 93-101.

80. Solbrig MV, Koob GF, Joyce JN, Lipkin WI (1996) A neural substrate of hyperactivity in borna disease: changes in brain dopamine receptors. Virology 222: 332-338.

81. Lycke E, Roos BE (1974) Influence of changes in brain monoamine metabolism on behaviour of herpes simplex-infected mice. J Neurol Sci 22: 277-289.

82. Da Cunha A, Rausch DM, Eiden LE (1995) An early increase in somatostatin mRNA expression in the frontal cortex of rhesus monkeys infected with simian immunodeficiency virus. Proc Natl Acad Sci U S A 92: 1371-1375.

83. Nerrienet E, Amouretti X, Müller-Trutwin MC, Poaty-Mavoungou V, Bedjebaga I, et al. (1998) Phylogenetic analysis of SIV and STLV type I in mandrills (Mandrillus sphinx): indications that intracolony transmissions are predominantly the result of male-to-male aggressive contacts. AIDS Res Hum Retroviruses 14: 785-796.

84. Sopper S, Koutsilieri E, Scheller C, Czub S, Riederer P, et al. (2002) Macaque animal model for HIV-induced neurological disease. J Neural Transm 109: 747-766.

85. Moshkin M, Gerlinskaya L, Morozova O, Bakhvalova V, Evsikov V (2002) Behaviour, chemosignals and endocrine functions in male mice infected with tick-borne encephalitis virus. Psychoneuroendocrinology 27: 603-608.

86. Easterbrook JD, Kaplan JB, Glass GE, Pletnikov MV, Klein SL (2007) Elevated testosterone and reduced 5-HIAA concentrations are associated with wounding and hantavirus infection in male Norway rats. Horm Behav 52: 474-481.

87. Philip Starks (2000) AIDS2000: 13th International AIDS Conference, Durban South Africa.

88. Thrall PH, Antonovics J, Dobson AP (2000) Sexually transmitted diseases in

polygynous mating systems: prevalence and impact on reproductive success. Proc Biol Sci 267: 1555-1563.

89. Preston BD, Poiesz BJ, Loeb LA (1998) Fidelity of HIV-1 reverse transcriptase. Science 242: 1168-1171.

90. Vyas A, Kim SK, Giacomini N, Boothroyd JC, Sapolsky RM (2007) Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors. Proc Natl Acad Sci U S A 104: 6442-6447.

91. Vyas A (2013) Parasite-augmented mate choice and reduction in innate fear in rats infected by Toxoplasma gondii. J Exp Biol 216: 120-126.

92. Lim A, Kumar V, Hari Dass SA, Vyas A (2013) Toxoplasma gondii infection enhances testicular steroidogenesis in rats. Mol Ecol 22: 102-110.

93. Cooke BM (2006) Steroid-dependent plasticity in the medial amygdala. Neuroscience 138: 997-1005.

94. House PK, Vyas A, Sapolsky R (2011) Predator cat odors activate sexual arousal pathways in brains of Toxoplasma gondii infected rats. PLoS One 6: e23277.

95. Flegr J (2013) Influence of latent Toxoplasma infection on human personality, physiology and morphology: pros and cons of the Toxoplasma-human model in studying the manipulation hypothesis. J Exp Biol 216: 127-133.

96. Howes OD, Kapur S (2009) The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull 35: 549-562.

97. Stibbs HH (1985) Changes in brain concentrations of catecholamines and indoleamines in Toxoplasma gondii infected mice. Ann Trop Med Parasitol 79: 153-157.

98. Yolken RH, Dickerson FB, Fuller Torrey E (2009) Toxoplasma and schizophrenia. Parasite Immunol 31: 706-715.

99. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, et al. (2011) The neurotropic parasite Toxoplasma gondii increases dopamine metabolism. PLoS One 6: e23866.

100. Berk M, Dodd S, Kauer-Sant'anna M, Malhi GS, Bourin M, et al. (2007) Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder. Acta Psychiatr Scand Suppl : 41-49.

101. Denys D, Zohar J, Westenberg HG (2004) The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. J Clin Psychiatry 65 Suppl 14: 11-17.

102. Diehl DJ, Gershon S (1992) The role of dopamine in mood disorders. Compr Psychiatry 33: 115-120.

103. Roy A, Karoum F, Pollack S (1992) Marked reduction in indexes of dopamine metabolism among patients with depression who attempt suicide. Arch Gen Psychiatry 49: 447-450.

104. Gaskell EA, Smith JE, Pinney JW, Westhead DR, McConkey GA (2009) A unique dual activity amino acid hydroxylase in Toxoplasma gondii. PLoS One 4: e4801.

105. Fuks JM, Arrighi RB, Weidner JM, Kumar Mendu S, Jin Z, et al. (2012) GABAergic signaling is linked to a hypermigratory phenotype in dendritic cells infected by Toxoplasma gondii. PLoS Pathog 8: e1003051.

106. Li J, Fan SR, Liu XP, Li DM, Nie ZH, et al. (2008) Biased genotype distributions of Candida albicans strains associated with vulvovaginal candidosis and candidal balanoposthitis in China. Clin Infect Dis 47: 1119-1125.

107. Schmid J, Rotman M, Reed B, Pierson CL, Soll DR (1993) Genetic similarity of Candida albicans strains from vaginitis patients and their partners. J Clin Microbiol 31: 39-46.

108. Jong AY, Stins MF, Huang SH, Chen SH, Kim KS (2001) Traversal of Candida albicans across human blood-brain barrier in vitro. Infect Immun 69: 4536-4544.

109. Denaro FJ, López-Ribot JL, Chaffin WL (1995) Adhesion of Candida albicans to brain tissue of Macaca mulata in an ex vivo assay. Infect Immun 63: 3438-3441.

110. Orjuela M, Castaneda VP, Ridaura C, Lecona E, Leal C, et al. (2000) Presence of Human Papilloma Virus in Tumor Tissue from Children with Retinoblastoma: An Alternative Mechanism for Tumor Development. Clin Cancer Res 6: 4010-4016.

111. Knell RJ, Webberley KM (2004) Sexually transmitted diseases of insects: distribution, evolution, ecology and host behaviour. Biol Rev Camb Philos Soc 79: 557-581.

112. Hamilton WD, Zuk M (1982) Heritable true fitness and bright birds: a role for parasites? Science 218: 384-387.

113. Burand JP, Tan W, Kim W, Nojima S, Roelofs W (2005) Infection with the insect virus Hz-2v alters mating behavior and pheromone production in female Helicoverpa zea moths. J Insect Sci 5: 6.

114. Kindt TJ, Goldsby RA, Osborne BA, Kuby J (2011) Immunology. Sixth edition, W. H. Freeman Publishers.

115. Adamo SA (1998) The specificity of behavioral fever in the cricket Acheta domesticus. J Parasitol 84: 529-533.

116. Klein SL (2003) Parasite manipulation of the proximate mechanisms that mediate social behavior in vertebrates. Physiol Behav 79: 441-449.

117. Hoover K, Grove M, Gardner M, Hughes DP, McNeil J, et al. (2011) A gene for an extended phenotype. Science 333: 1401.