Joint Graduate Seminar Dec 2015
Department of Microbiology
Faculty of Medicine
The Chinese University of Hong Kong

Virus's Control Over Host's Behavior

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Year : Year 2
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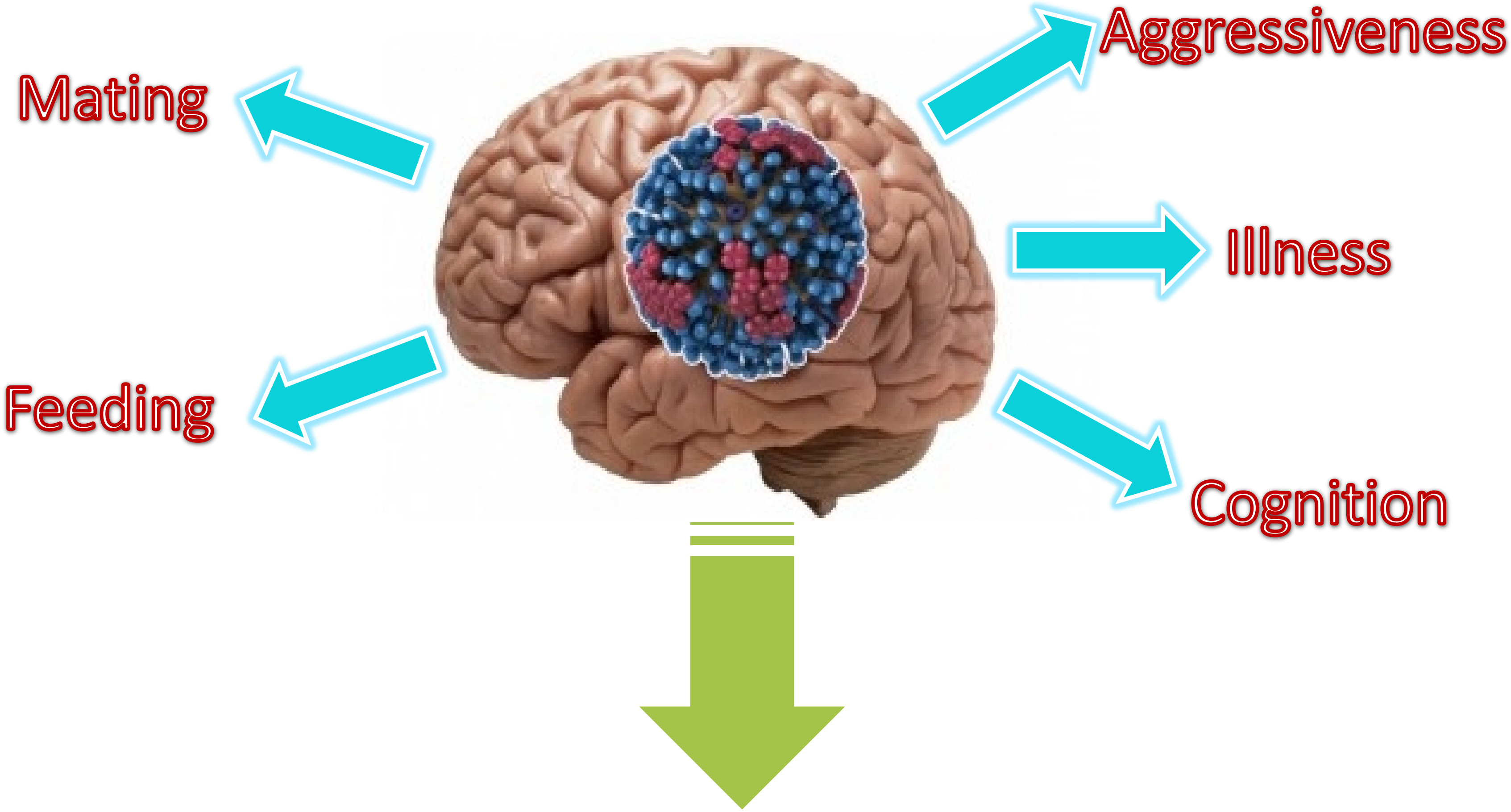
Introduction

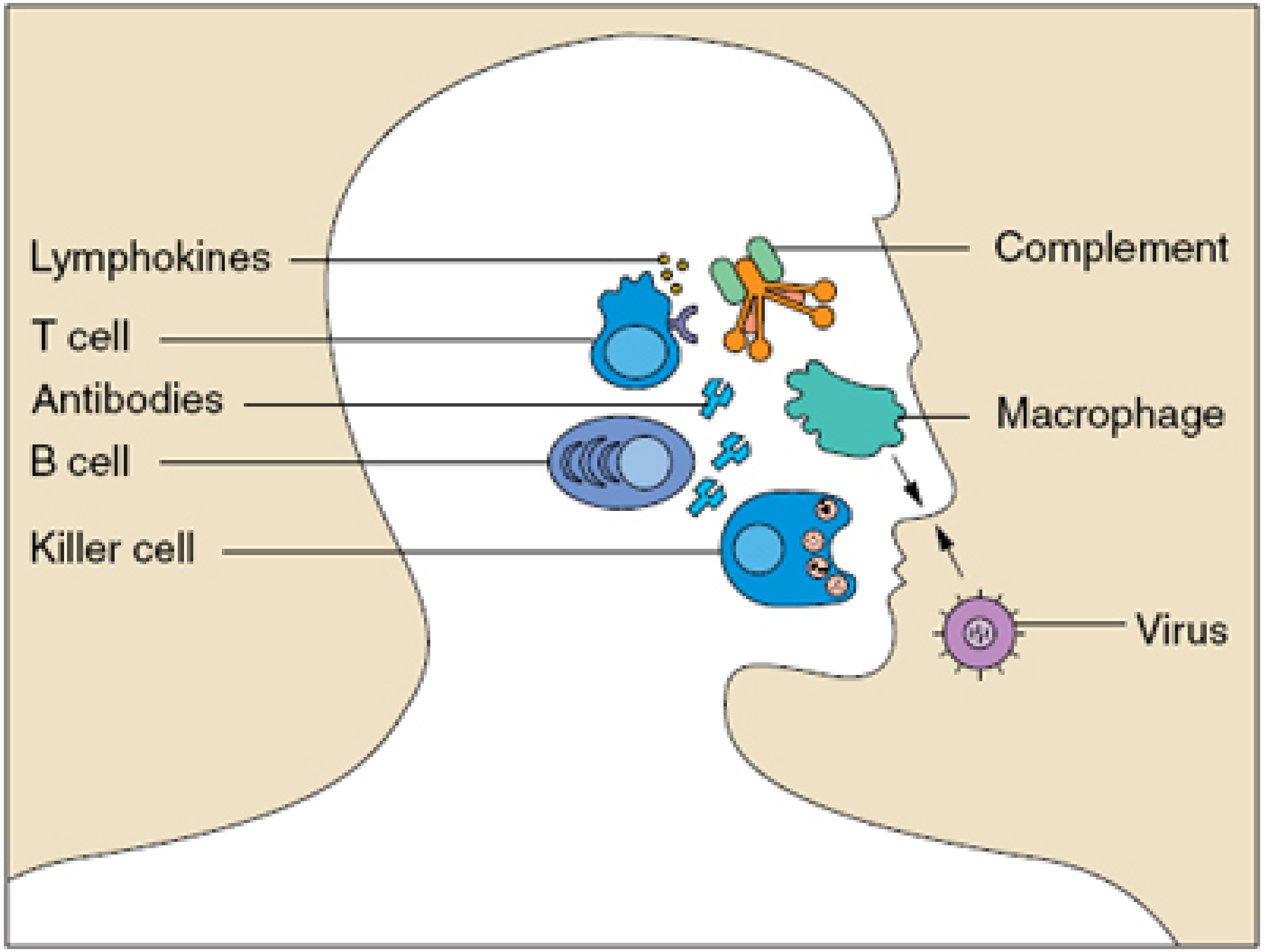


Purposes:

e.g. Replication, Transmission, etc.

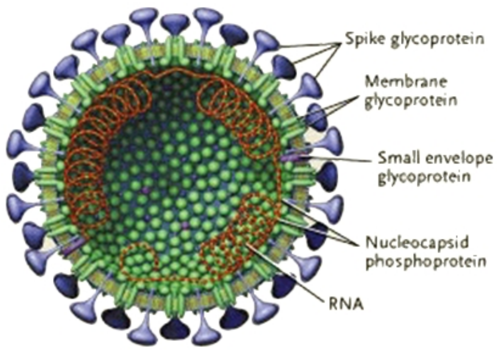
(Modified from nationalgeographic.com)

Illness

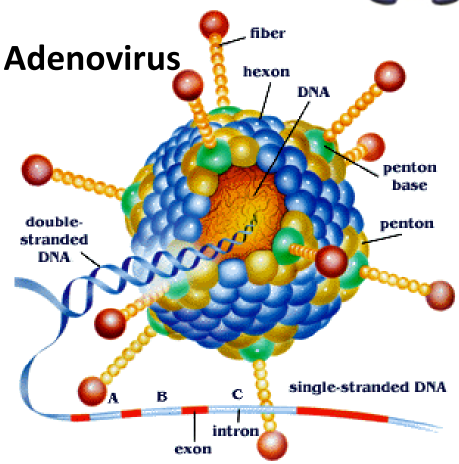


(Adapted from www.vaccines.gov)

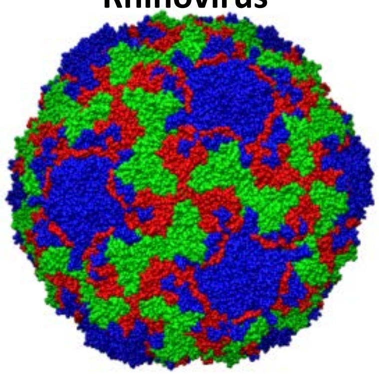
Coronavirus

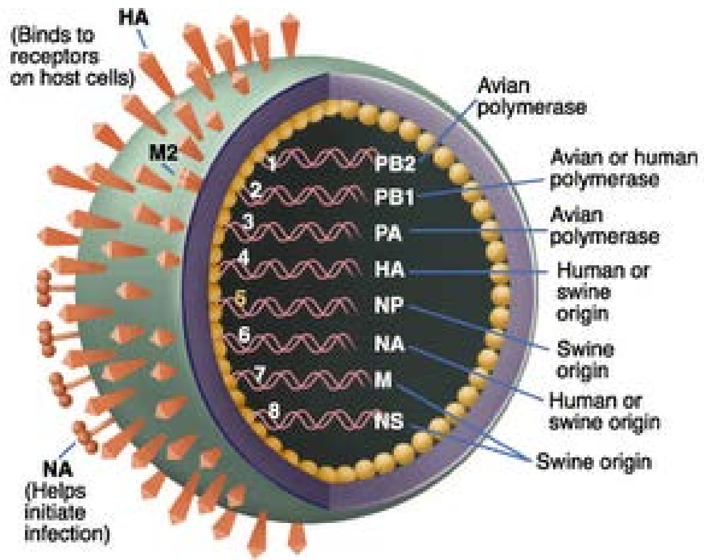


Adenovirus



Rhinovirus



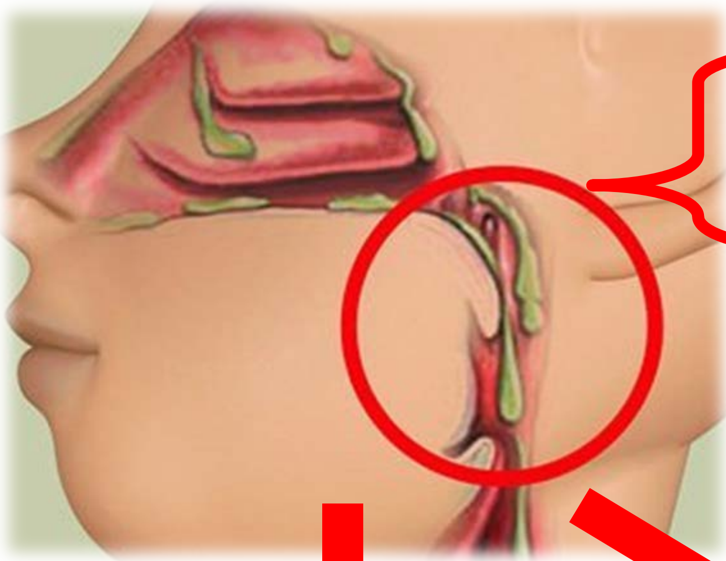


Common Cold Viruses

(e.g. rhionvirus, adenovirus, coronavirus)

Influenza Virus

- Cellular damages
- Mucus production
- Inflammation
- Protective reflex originally
- Many droplets
- Virus-laden aerosols

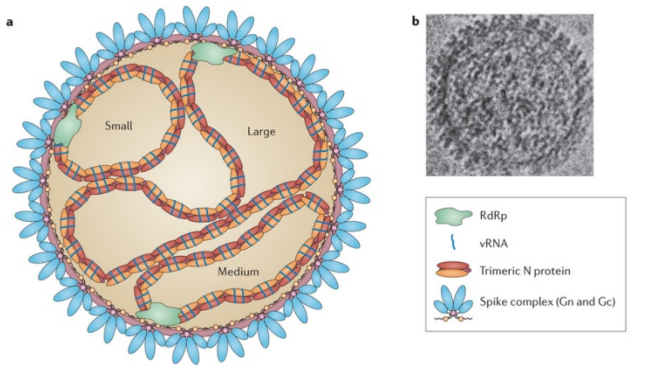


Trigeminal nerve   Vagus nerve

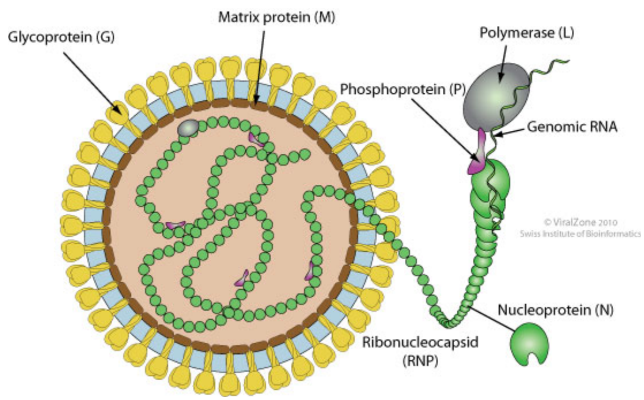
Sneezing

Coughing

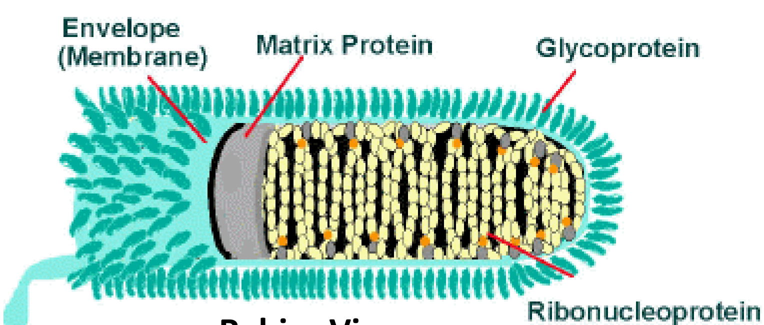
Aggressiveness



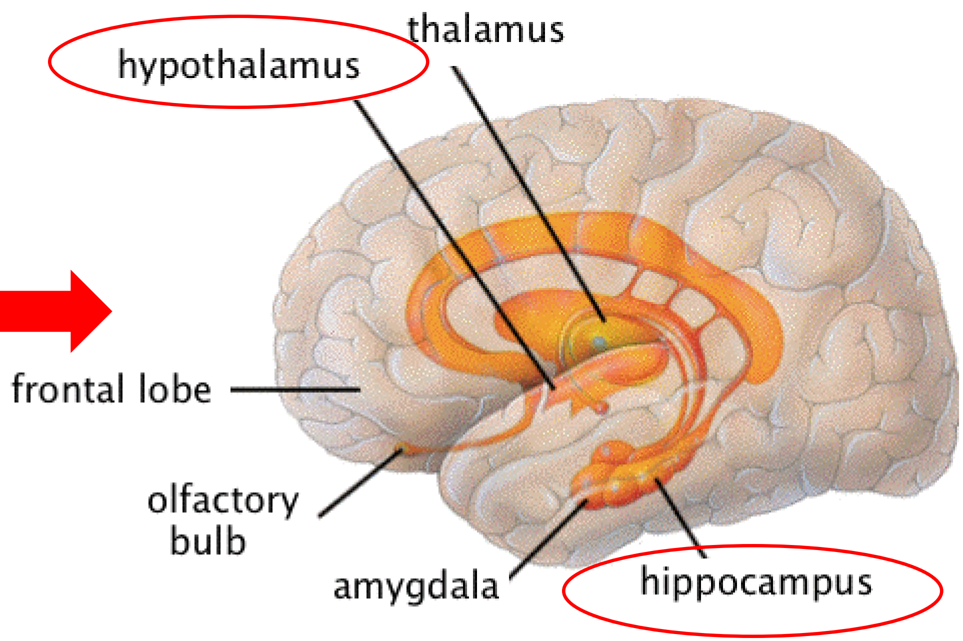
Hantaviruses



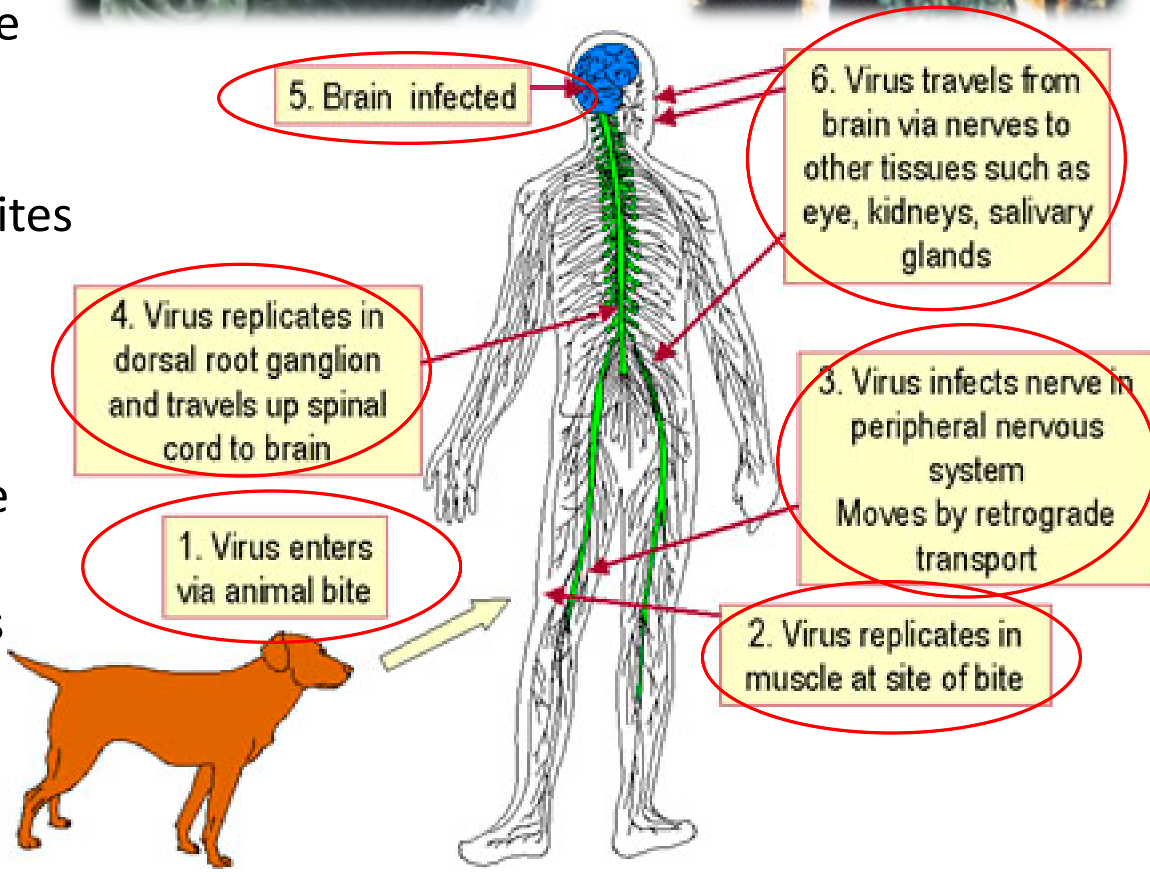
Borna Disease Virus



Rabies Virus



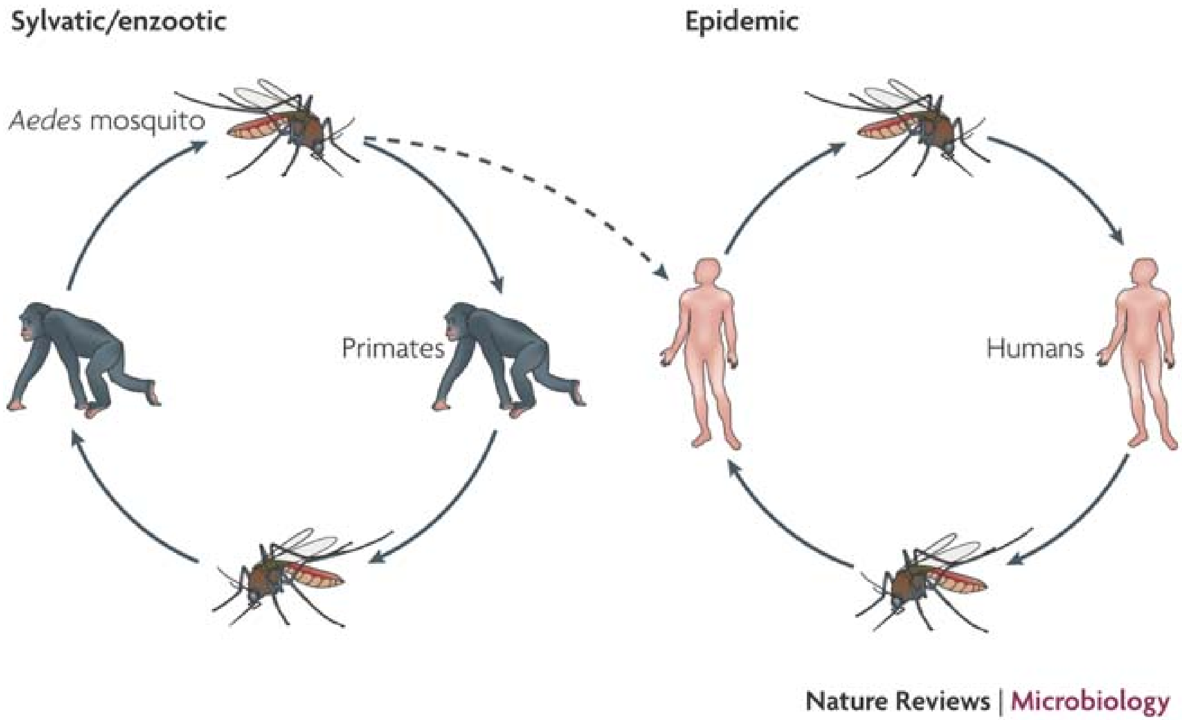
- Rabies as example
- Single-stranded,
  -ve standed RNA virus
- Rhabdovirus
- Fatal zoonotic
  neuroinvassive disease
- Three stages :
  1) First stage –
     replicating in bite sites
  2) Second stage –
     furious rabies,
     hyperreactivity,
     irritable, restless,
     violently aggressive
  3) Third stage –
     throat/jaw muscles
     paralysis, drooling,
     death



Feeding

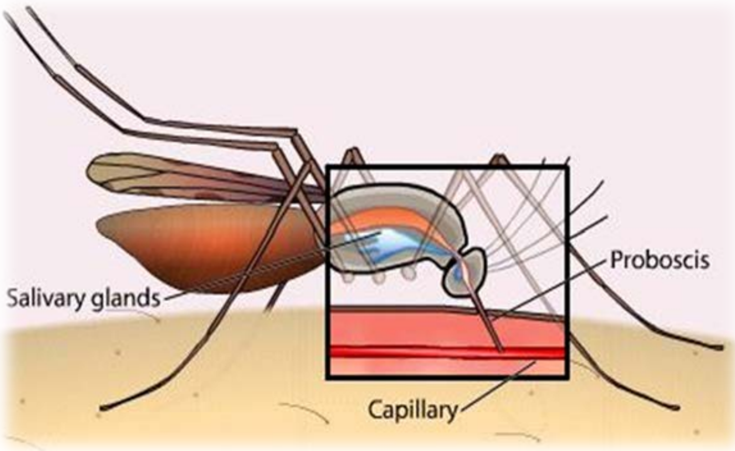
Arbovirus

- Arthropod vectors
- e.g. Dengue Virus, Yellow Fever Virus
- Only as passengers?
- Also as hosts
- Changed host-seeking, blood-feeding processes

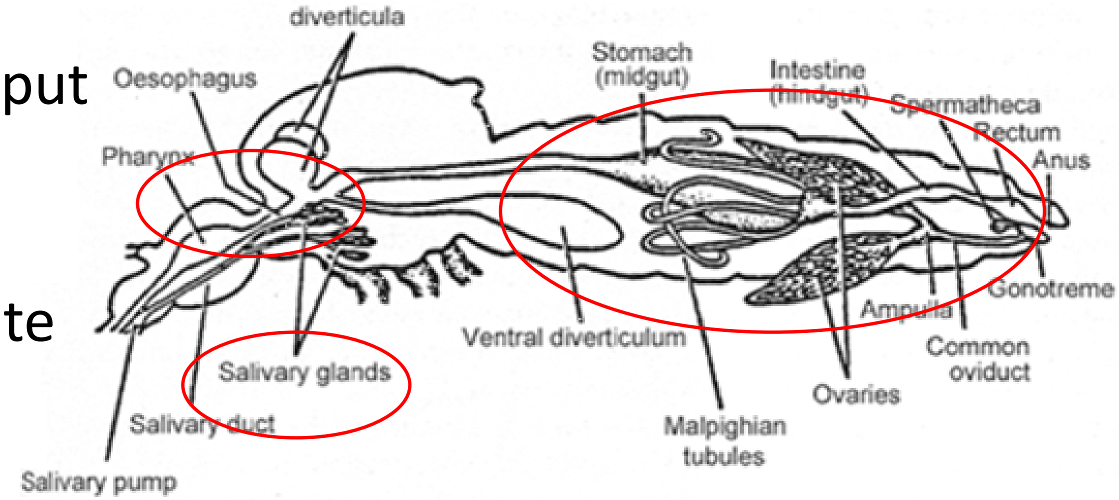


- Flying around longer
- Longer time for full feeding
- Feeding regulation organs:
  - Central nervous system
  - Peripheral sensory organs
  - Abdominal organs
  - Salivary glands

  All heavily infected
- Blood source detection ability enhanced
- Less efficient ingestion
- More biting
- Increased saliva output



Increased biting rate for better viral transmission



Plant viruses

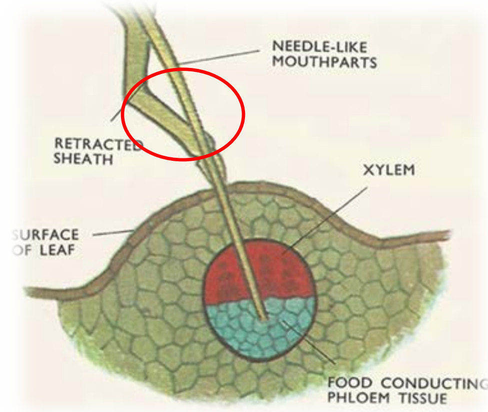
- e.g. *Tomato Spotted Wilt Virus* (TSWV)
- Insects only as vectors?
- Inserts also as hosts
- Feeding patterns altered

Thrips

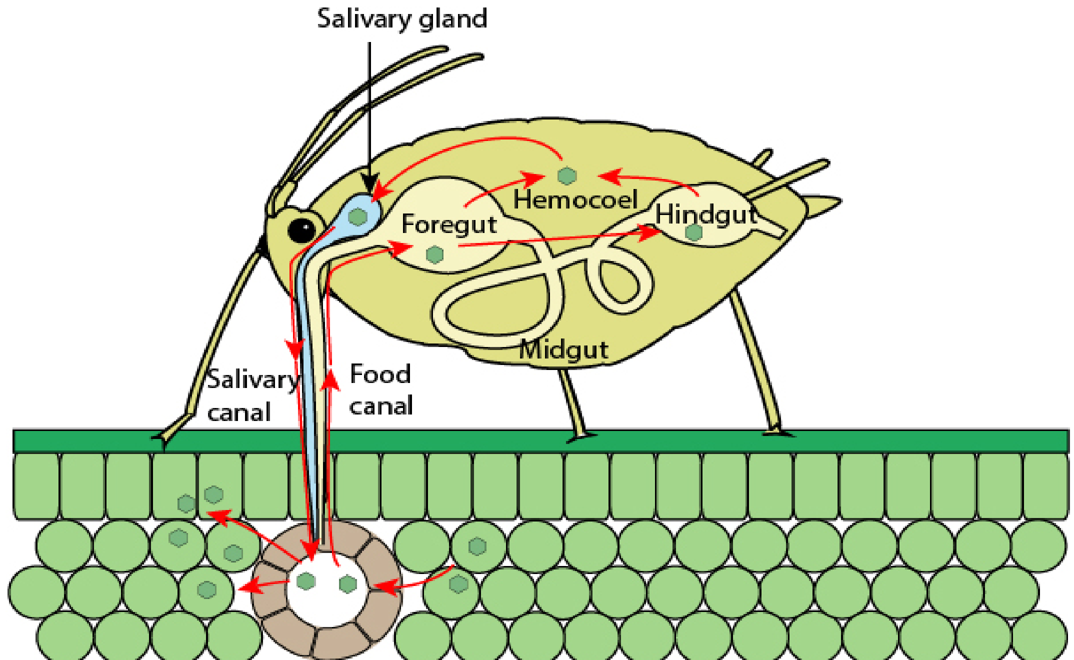
Aphid

- Tiny insets feeding on plants
- Probing through plant epidermis with stylets
- Sucking out cellular contents
- Feeding up to three times more
- Causing almost three times more probes
- Virus – laden saliva

Increased feeding for better viral transmission



Plant virus circulative route in insect

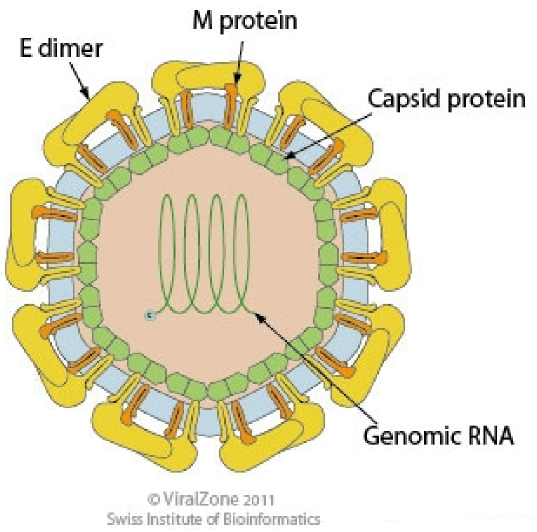


(Adapted from viralzone.expasy.org/all_by_protein/3738.html

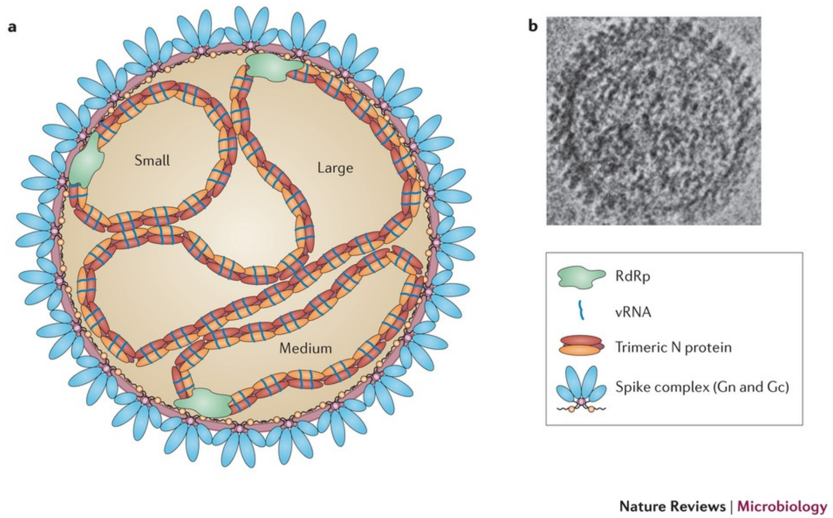
Mating

Rats & Mice

- Libido dialed up
- Mating processes changed
- Viral infections



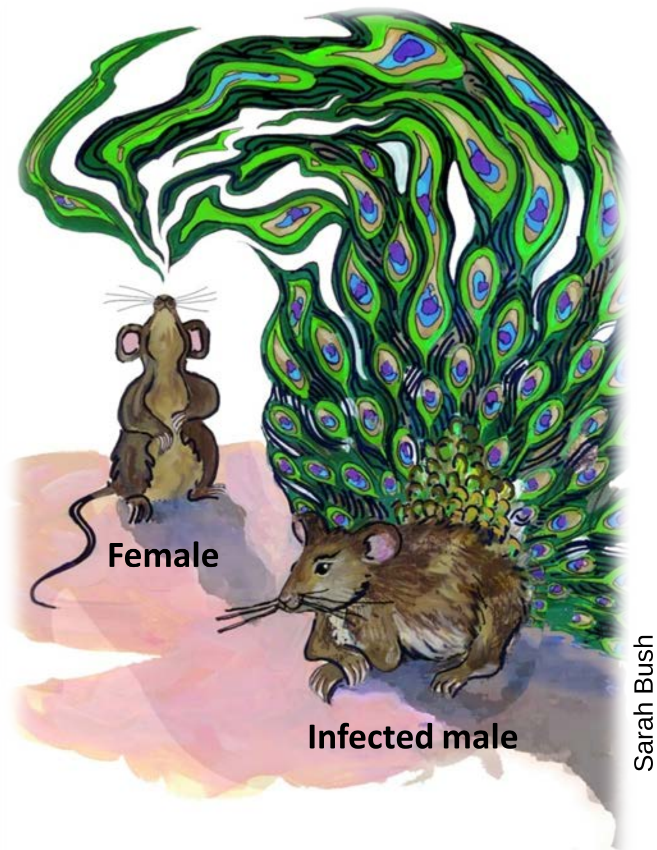
Flaviviruses

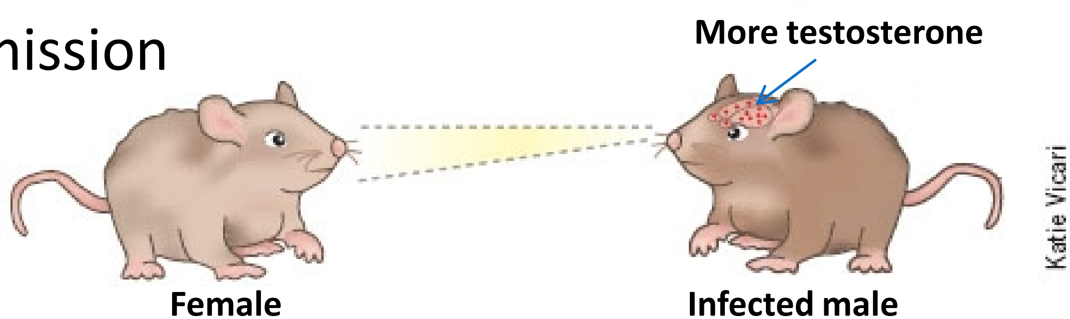


Hantaviruses

- Hosts' neuroendocrine mechanisms highjacked
- Infected males' enhanced odour attractiveness for oestrus females
- Elevated testosterone level
- More sexually active

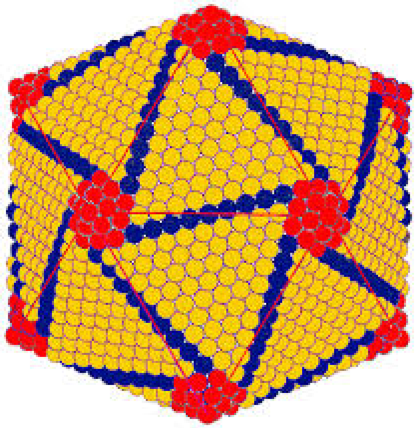
More frequent close contact for better viral transmission





Field Crickets

- *Gryllus texensis*
- Iridovirus - large icosahedral, cytoplasmic, double-stranded DNA viruses
- Courtship songs
- Cricket iridovirus IIV-6 (CrIV)

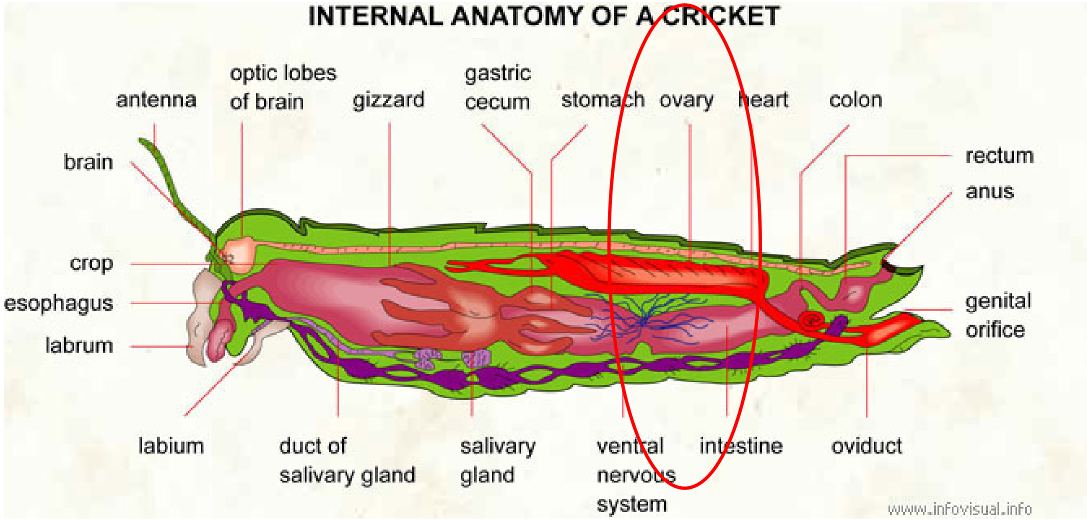


Iridovirus

- Infected male
  - at least twice as fast to start singing
  - Enhanced sex drives
  - Sterile:
    1) testis cells not infected
    2) sperm cells little or no motility

- Infected females
  - Sterile:
    1) Cannot produce eggs
    2) Ovaries replaced by fat body

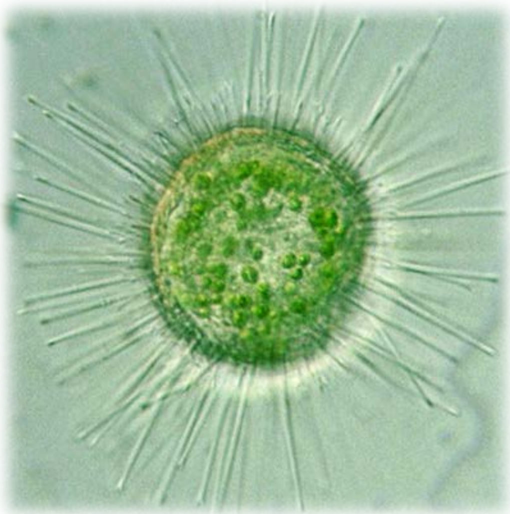
More time and energy for mating and virion generations



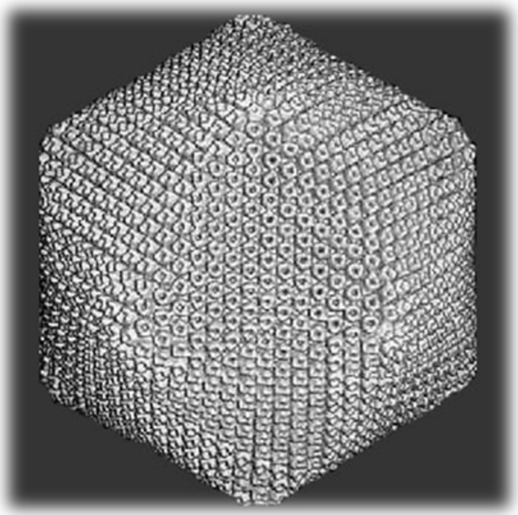
Cognition

Acanthocystis Turfacea Chlorella virus-1

- Commonly-found, giant, double-stranded DNA virus
- Infecting freshwater green algae
- Virus's DNA in humans' oropharyngeal regions
- Over 40% randomly selected individuals



Acanthocystis Turfacea



Chlorella virus

PNAS PNAS PNAS PNAS

Chlorovirus ATCV-1 is part of the human oropharyngeal virome and is associated with changes in cognitive functions in humans and mice

Robert H. Yolken[a,1], Lorraine Jones-Brando[a], David D. Dunigan[b], Geetha Kannan[c], Faith Dickerson[d], Emily Severance[a], Sarven Sabunciyan[a], C. Conover Talbot Jr.[e], Emese Prandovszky[a], James R. Gurnon[b], Irina V. Agarkova[b], Flora Leister[a], Kristin L. Gressitt[a], Ou Chen[a], Bryan Deuber[a], Fangrui Ma[b], Mikhail V. Pletnikov[c], and James L. Van Etten[b,1]

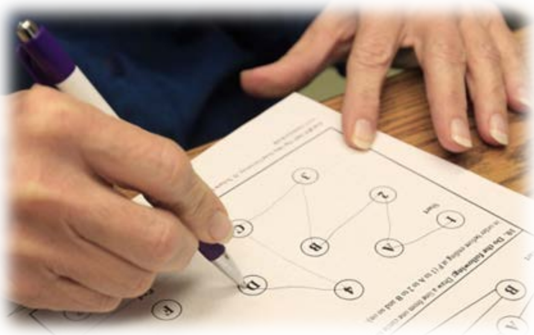
[a]Stanley Division of Developmental Neurovirology, Department of Pediatrics, [c]Department of Psychiatry and Behavioral Sciences, and [e]Institute for Basic Biomedical Sciences, Johns Hopkins School of Medicine, Baltimore, MD 21205; [b]Nebraska Center for Virology and Department of Plant Pathology, University of Nebraska, Lincoln, NE 68583-0900; and [d]Department of Psychology, Sheppard Pratt Health System, Baltimore, MD 21205

Contributed by James L. Van Etten, October 3, 2014 (sent for review August 9, 2014; reviewed by Joram Feldon and Allan V. Kalueff)

Chloroviruses (family *Phycodnaviridae*) are large DNA viruses known to infect certain eukaryotic green algae and have not been previously shown to infect humans or to be part of the human virome. We unexpectedly found sequences homologous to the chlorovirus *Acanthocystis turfacea* chlorella virus 1 (ATCV-1) in a metagenomic analysis of DNA extracted from human oropharyngeal samples. These samples were obtained by throat swabs of adults without a psychiatric disorder or serious physical illness who were participating in a study that included measures of cognitive functioning. The presence of ATCV-1 DNA was confirmed by quantitative PCR with ATCV-1 DNA being documented in oropharyngeal samples obtained from 40 (43.5%) of 92 individuals. The presence of ATCV-1 DNA was not associated with demographic variables but was associated with a modest but statistically significant decrease in the performance on cognitive assessments of visual processing and visual motor speed. We further explored the effects of ATCV-1 in a mouse model. The inoculation of ATCV-1 into the intestinal tract of 9–11-wk-old mice resulted in a subsequent decrease in

In the process of analyzing whole genome sequences obtained from unfractionated samples of the oropharynx from healthy individuals participating in a study that involved the assessment of cognitive functioning, we unexpectedly discovered a substantial number of sequence reads very similar to virus *Acanthocystis turfacea* chlorella virus 1 (ATCV-1), a member of the genus *Chlorovirus* (family *Phycodnaviridae*). This family of algae-infecting viruses is common in aqueous environments but not previously thought to infect humans or animals or to inhabit human mucosal surfaces (13). Viruses that cross kingdoms are rare; however, some plant viruses can replicate in both their plant host as well as an invertebrate vector. However, there is one report indicating a possible algal-infecting virus associated with humans. In this report, cervicovaginal secretion samples contained virus-like particles, and these samples inhibited the propagation of certain algal cultures, consistent with the presence of a virus capable of infecting algae (14).

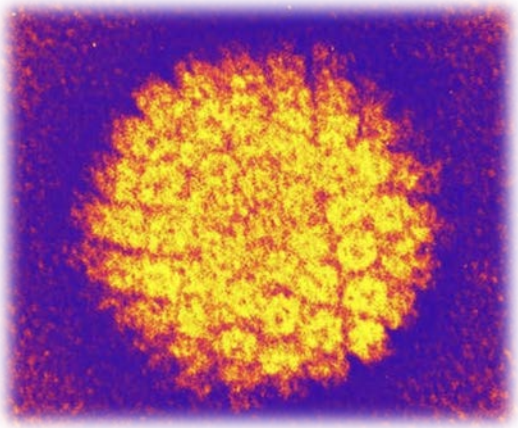
- Poorer performances in cognitive and motor skill tests
- 10% worse in spatial orientation
- Lower speed, accuracy and attention of visual processing
- Infected mice, similar deficits
- Not associated with sex, income, education level, race, place of birth, or cigarette smoking



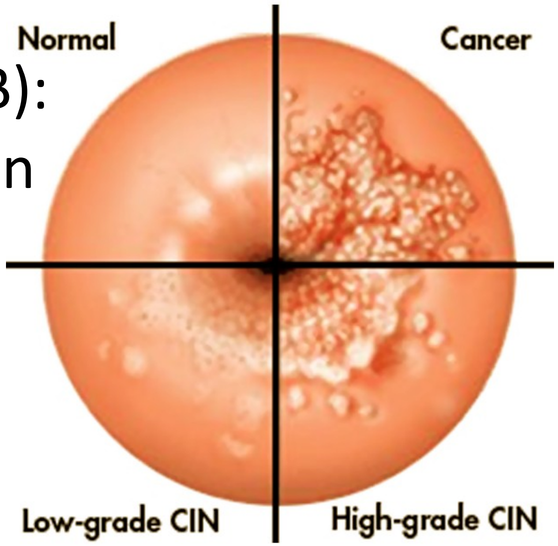
1) Altered hippocampal multiple gene expression
2) Changed dopamine recognition ability

Human Papillomavirus

- Small, non-enveloped,
  double-stranded DNA tumor virus
- e.g. cervical cancers, anal cancers, etc.
- Joint studies:
  the University of Pennsylvania &
  the University of Amsterdam
- Focal cortical dysplasia type IIB (FCDIIB):
  - sporadic developmental malformation
  - cerebral cortex
  - pediatric epilepsy
  - cognitive decline



HPV



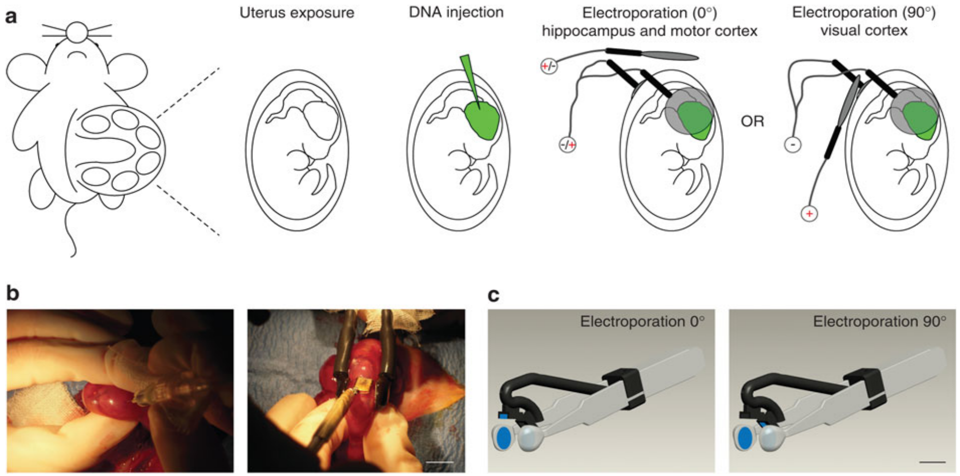
Detection of Human Papillomavirus in Human Focal Cortical Dysplasia Type IIB

Julie Chen, BA,[1] Victoria Tsai, MS,[1] Whitney E. Parker, BA,[1] Eleonora Aronica, MD, PhD,[2,3] Marianna Baybis, MS,[1] and Peter B. Crino, MD, PhD[1,4]

Objective: Focal cortical dysplasia type IIB (FCDIIB) is a sporadic developmental malformation of the cerebral cortex highly associated with pediatric epilepsy. Balloon cells (BCs) in FCDIIB exhibit constitutive activation of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway. Recently, the high-risk human papillomavirus type 16 oncoprotein E6 was identified as a potent activator of mTORC1 signaling. Here, we test the hypothesis that HPV16 E6 is present in human FCDIIB specimens.
Methods: HPV16 E6 protein expression was assayed by immunohistochemistry in FCDIIB specimens (n = 50) and control brain specimens (n = 36). HPV16 E6 DNA was assayed by polymerase chain reaction (PCR) and in situ hybridization; HPV16 E6 mRNA was assayed by reverse transcriptase PCR. HPV16 E6 was transfected into fetal mouse brains by in utero electroporation to test the effects of E6 on cortical development.
Results: HPV16 E6 protein was robustly expressed in all FCDIIB specimens in BCs, but not in regions without BCs or in control tissue specimens including normal brain, lymphoblasts, and fibroblasts, cortical tubers, and U87 glioma cells. E6 expression in FCDIIB colocalized with phosphoactivated S6 protein, a known mTORC1 substrate. HPV16 E6 DNA and mRNA were detected in representative specimens of FCDIIB but not control cortex, and were confirmed by sequencing. Transfection of E6 into fetal mouse brains caused a focal cortical malformation in association with enhanced mTORC1 signaling.
Interpretation: Our results indicate a new association between HPV16 E6 and FCDIIB and demonstrate for the first time HPV16 E6 in the human brain. We propose a novel etiology for FCDIIB based on HPV16 E6 expression during fetal brain development.

ANN NEUROL 2012;72:881–892

- Immunohistochemistry + PCR + in situ hybridization
- HPV16 oncogenic protein E6 & capsid protein L1 in FCDIIB balloon cells
- All 50 FCDIIB cases involved
- Other normal samples all not detected
- Animal tests:
  - E6 expression in fetal mouse brains
  - In utero electroporation
  - Similar developmental malformations



(Adapted from dal Maschio M., 2012)

- The University of California
- Opponent views
- Repeated experiments in 14 FCDIIB samples
- No HPV detected
- Contaminations or unknown cross-reactions with neuroglial proteins?

- The first team
- Serious defenses
- FCDIIB brain tissue specimens
- Obtained under sterile surgical conditions
- Aerosol controls

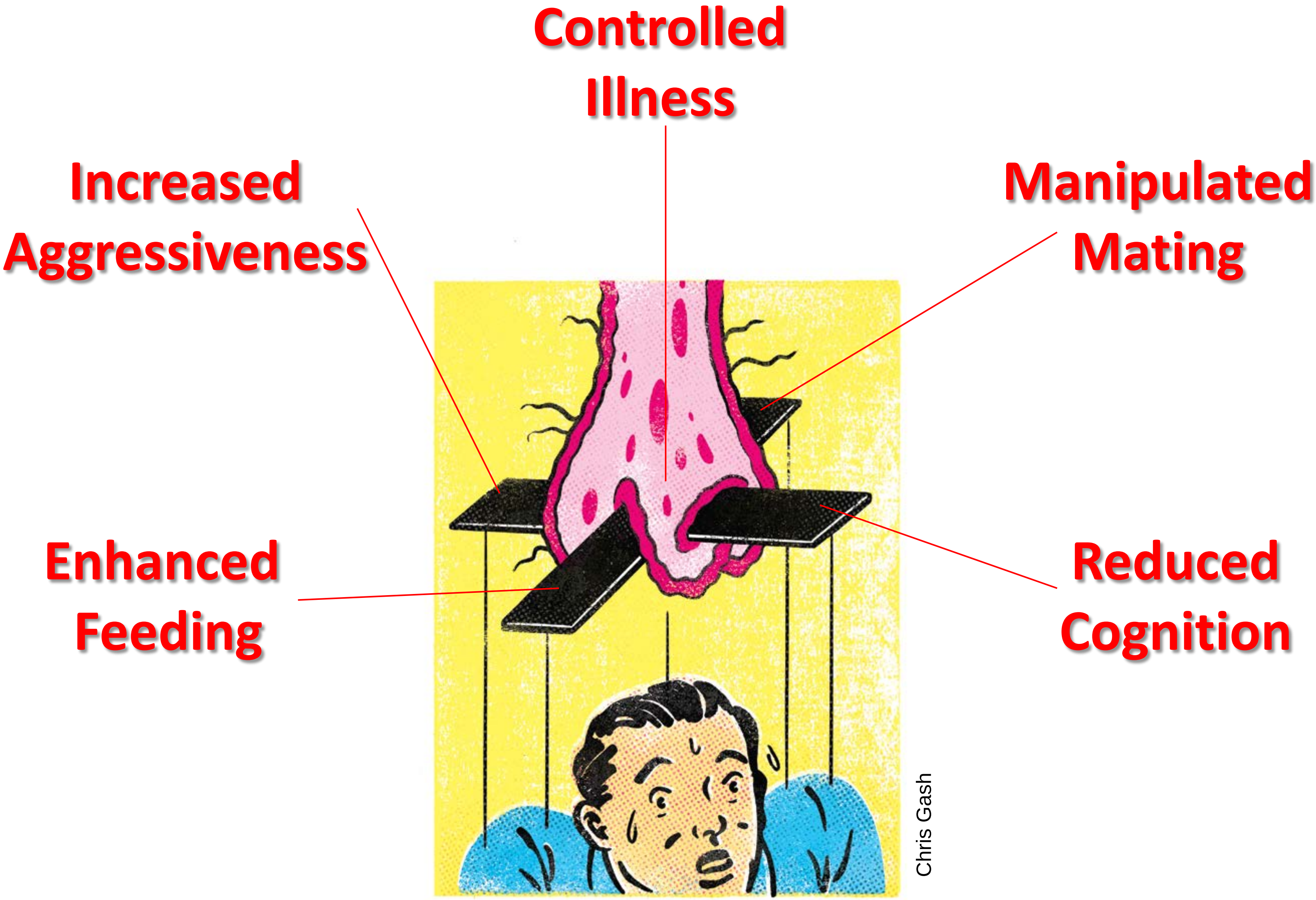
Failure to Detect Human Papillomavirus in Focal Cortical Dysplasia Type IIb

Kevin A. Shapiro, MD, PhD,[1] Declan McGuone, MB, BCh,[2]
Vikram Deshpande, MB, BS,[2] Peter M. Sadow, MD, PhD,[2]
Anat Stemmer-Rachamimov, MD,[2] and Kevin J. Staley, MD[3]

Objective: Recent studies have reported evidence of human papillomavirus 16 (HPV-16) in a very high proportion of pathological specimens of focal cortical dysplasia type IIb, but not in control specimens, motivating the proposal that viral infection during fetal development may play a causal role in the pathogenesis of focal cortical dysplasias. However, the significance of the association between HPV infection and focal cortical dysplasia type IIb, and its reproducibility across surgical centers, remain unclear. Here we sought evidence for HPV-16 in an independent cohort of surgical specimens.
Methods: We identified 14 specimens of focal cortical dysplasia type IIb from a single surgical center between 1995 and 2013. Multiple methods were used to establish presence or absence of HPV, including DNA polymerase chain reaction, conventional in situ hybridization, chromogenic in situ hybridization, and immunohistochemistry for p16.
Results: We found no conclusive evidence of HPV in any of the specimens. All but 1 of the cases were negative by >1 method.
Interpretation: These results raise questions about the prevalence of HPV infection in focal cortical dysplasias and about its potential importance as a causative agent.

ANN NEUROL 2015;78:63–67

Summary


Controlled
Illness
Increased
Aggressiveness
Manipulated
Mating
Enhanced
Feeding
Reduced
Cognition
Chris Gash

Acknowledgement

- Prof. Paul Chan
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- Emily Tsui
- Dennis Hu
- Kelton Cheung
- Thomas Hung
- Kirsty Kwok

and all my dear fellow labmates

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Thank You

Q&A