

Xenotropic Murine Leukemia Virus-Related Virus (XMRV)

Disease Agent:

- Xenotropic murine leukemia virus-related virus (XMRV)

Disease Agent Characteristics:

- Family: *Retroviridae*; Subfamily: *Orthoretrovirinae*; Genus: *Gammaretrovirus*; Species: Xenotropic murine leukemia virus-related virus (XMRV)
- Virion morphology and size: Virions have a complex construction and consist of an envelope, a nucleocapsid, and a nucleoid. Virions are spherical to pleomorphic measuring 80-100 nm in diameter. Virions have a buoyant density in sucrose of 1.15-1.17 g cm⁻³.
- Nucleic acid: The genome is a dimer of linear, positive-sense, single-stranded RNA, 8300 nucleotides long.
- Physicochemical properties: As enveloped retroviruses, the virions should be susceptible to heat, detergents and many disinfectants such as 1% sodium hypochlorite, 2% glutaraldehyde, formaldehyde and ethanol.

Disease Name:

- No confirmed disease associations

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical; transmission from transfusion has not been documented in humans, although pathogenic retroviruses (i.e., HIV and HTLV) are clearly transfusion transmitted.
- Public perception and/or regulatory concern regarding blood safety: Moderate based on the characteristics of other retroviruses and investigations that have linked some disease states to human infection with this agent. Concern has been publicly expressed regarding transfusion transmission of XMRV following publication of data associating it with chronic fatigue syndrome (CFS).
- Public concern regarding disease agent: Low based at least partly on lack of familiarity with a virus that is potentially linked to human disease; however, may be higher in groups with diseases associated with XMRV.

Background:

- A diverse range of mammalian species are susceptible to infection by gammaretroviruses. These retroviruses have genomes that contain only *gag*, *pro*, *pol*, and *env* genes. They include murine leukemia virus, feline leukemia virus, koala retrovirus, and gibbon ape leukemia virus that cause leukemia and other syndromes in their host species.
- Evidence of human infection with gammaretroviruses was lacking until 2006 when genomes of a previously undescribed gammaretrovirus, XMRV, were detected in a cohort of US men with localized prostate cancer undergoing radical prostatectomy. The hypothesis was that these men harbored a homozygous mutation of the *RNASEL* gene (R462Q) that

impaired the function of the ribonuclease L antiviral enzyme rendering patients unusually susceptible to the oncogenic potential of the virus. However, a subsequent study found XMRV DNA or proteins in 6% and 23%, respectively, of malignant prostate cancers irrespective of the RNase polymorphism. Studies in 833 Irish and German subjects with prostate cancer, including 139 with the RNase L mutations, found XMRV in only one patient. Correspondingly, no antibodies were detected among 146 patients from these cohorts.

- In 2009, a statistical association of XMRV infection in CFS patients was reported from a single US center. Peripheral blood mononuclear cells (PBMC) from 67% of CFS patients contained the proviral DNA of XMRV compared to 3.7% of healthy controls. These patients did not have the RNase L polymorphism. Secondary infections in tissue culture could be established from PBMC, B and T cells and plasma of patients. The study concluded, "(T)hese findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS."
- 186 CFS patients from a UK cohort who had been described as being "unwell for a median of 4 years" were screened for XMRV provirus and the closely related murine leukemia virus (MLV) from whole blood preparations. Neither XMRV nor MLV sequences were detected from any of the CFS cases.
- Another UK study tested 170 CFS patients from two cohorts (one with long-term established CFS and the other with samples collected 1.5-4 years after a CFS diagnosis) and 395 controls including 157 blood donors. DNA was extracted from PBMC and tested by RT-PCR targeting two envelope regions (sensitivity of 16 copies). No XMRV sequences were identified from 142 CFS cases and 157 controls tested. However, 26 of 565 (4.6%) samples had XMRV neutralizing antibody activity but only one of the 26 was from a CFS patient. Four samples were XMRV specific but most of the remaining antibody reactivity was due to cross-reactivity with other viruses. The authors note that "XMRV infection may occur in the general population, although with currently uncertain outcomes."
- In a Dutch cohort, PBMC cryopreserved in 1991-1992 from 32 CFS patients and 43 healthy controls tested by RT-PCR targeting the *integrase* gene and/or a nested PCR assay targeting the *gag* gene and having a sensitivity of 10 XMRV sequence copies per 10⁵ PBMC failed to detect XMRV sequences in any sample.
- Reasons for the discordant findings are not clear but may include differences in the cohorts studied or selection of patients from cohorts for testing, variable assay procedures, differences in prevalence in different geographic areas, varying properties of XMRV or other factors.

Common Human Exposure Routes:

- Unknown

Likelihood of Secondary Transmission:

- Unknown

At-Risk Populations:

- Unknown

Vector and Reservoir Involved:

- Unknown

Blood Phase:

- The first published XMRV-CFS study found culturable virus in plasma and PBMC.

Survival/Persistence in Blood Products:

- Unknown

Transmission by Blood Transfusion:

- Unknown

Cases/Frequency in Population:

- In one CFS study, 3.7% of healthy controls harbored viral DNA sequences in PBMC; however, the expression pattern of viral genes in the infected controls appeared to differ from those among the CFS population so the relevance of the observation must be explored. Preliminary data from another study using developmental serological methods in a small sample of US blood donors found a seroprevalence of ~0.1%.
- The population prevalence of XMRV infection is unknown and rates may vary in different regions.

Incubation Period:

- Unknown

Likelihood of Clinical Disease:

- Unknown

Primary Disease Symptoms:

- If causal relationships are confirmed, symptoms will be those of the associated diseases.
 - Many prostate cancers are asymptomatic, but symptoms of urinary obstruction and metastatic spread occur with advancing disease.
 - CFS (also called, more descriptively, myalgic encephalomyelitis) is characterized by new onset, unexplained, persistent or recurrent fatigue, diffuse post-exertional malaise and/or fatigue, myalgia, sleep dysfunction, and neurological/cognitive impairment with immune, autonomic and/or neuroendocrine manifestations of 6 months duration or longer (3 months in children). Symptoms are not caused by ongoing exertion, are not relieved by rest, and result in a substantial reduction of previous levels of occupational, educational, social, or personal activities. Co-morbid conditions, such as fibromyalgia syndrome and irritable bowel syndrome may overlap with CFS. The clinical case definition includes a list of exclusionary conditions.

Severity of Clinical Disease:

- The original cohort of prostate cancer patients harboring the homozygous mutation in the RNase L gene had localized prostate cancer. The strength of this association will require more investigation.
- CFS produces very significant disability with substantial disruption of activities of daily living among those meeting strict case definitions.

Mortality:

- Unknown, but XMRV has been associated with a more aggressive form of prostate cancer in one study that awaits confirmation.

Chronic Carriage:

- Chronicity is a feature of the *Retroviridae* family.

Treatment Available/Efficacious:

- Unknown

Agent-Specific Screening Question(s):

- No specific question is in use for blood donors and is not indicated because transfusion transmission has not been demonstrated.
- No XMRV-specific question is feasible in the absence of any established risk factors for XMRV infection and the experimental nature and limited availability of diagnostic tests.
- No sensitive or specific question is feasible for CFS.
 - If the high apparent prevalence of XMRV infection reported in healthy control subjects in the original CFS study is confirmed, and given the high prevalence of chronic fatigue in the population, donor history screening would not be expected to be effective.
 - The rate at which potential donors carrying a criteria-based diagnosis of CFS would present to donor centers is unknown, but probably low in light of the associated disability.

Laboratory Test(s) Available:

- No FDA-licensed blood donor-screening test exists.
- Standards for the diagnosis of XMRV infection have not been established.
- Research assays include RT-PCR, cell culture, flow cytometry-based immunoassay, chemiluminescent immunoassay and immunohistochemical analyses.

Currently Recommended Donor Deferral Period:

- No FDA Guidance or AABB Standard exists regarding XMRV infection.
 - Pending the availability of further data, prudent practice would be indefinite deferral of donors who have received a diagnosis of XMRV infection.
- Current practice per FDA Guidance and AABB Standards is to accept donors who are healthy at the time of donation.

- CFS advocacy organizations and the National Cancer Institute have historically discouraged blood donation by CFS patients.
- Blood collection facilities should follow established SOPs regarding donors with cancer.

Impact on Blood Availability:

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

Impact on Blood Safety:

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

Leukoreduction Efficacy:

- The initial studies in CFS suggest there is plasma viremia, so leukoreduction is unlikely to be completely effective.

Pathogen Reduction Efficacy for Plasma Derivatives:

No specific data are available but presumed to be robust as the agent is an enveloped virus that should be sensitive to many measures used in the fractionation process.

Other Prevention Measures:

- Unknown

Suggested Reading:

- Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NKG, Lerner AM, Bested AC, Flor-Henry P, Joshi P, Powles, ACP, Sherkey JA, van de Sande, MI. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *J Chron Fatigue Syndr.* 2003;11:7-115.
- Coffin JM and Stoye JP. Perspectives: a new virus for old diseases? *Science.* 2009;326:530-1.
- Dong B, Kim S, Hong S, Das Gupta J, Malathi K, Klein EA, Ganem D, Derisi JL, Chow SA, Silverman RH. An infectious retrovirus susceptible to an IFN antiviral pathway from human prostate tumors. *Proc Natl Acad Sci U S A.* 2007;104:1655-60.
- Erlwein O, Kaye S, McClure MO, Weber J, Wills G, Collier D, Wessely S, Cleare A. Failure to detect the novel retrovirus XMRV in chronic fatigue syndrome. *PLoS ONE.* 5(1):e8519. doi:10.1371/journal.pone.0008519.
- Fischer N, Hellwinkel O, Schulz C, Chun FK, Huland H, Aepfelbacher M, Schlomm T. Prevalence of human gammaretrovirus XMRV in sporadic prostate cancer. *J Clin Virol.* 2008;43:277-83.
- Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, and the International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med.* 1994; 121:953-9.
- Groom HCT, Boucherit VC, Makinson K, Randal E, Baptista S, Hagan S, Gow GW, Mattes FM, Breuer J, Kerr JR, Stoye JP, Bishop KN. Absence of xenotropic murine leukaemia virus-related virus in UK patients with chronic fatigue syndrome. *Retrovirology.* 2010; 7:10 doi:10.1186/1742-4690-7-10.
- Hohn O, Krause H, Barbarotto P, Niederstadt L, Beimforde N, Denner J, Miller K, Kurth R, Bannert N. Lack of evidence for xenotropic murine leukemia virus-related virus (XMRV) in German prostate cancer patients. *Retrovirology.* 2009;6:92.
- Hong S, Klein EA, Das Gupta J, Hanke K, Weight CJ, Nguyen C, Gaughan C, Kim KA, Bannert N, Kirchhoff F, Munch J, Silverman RH. Fibrils of prostatic acid phosphatase fragments boost infections with XMRV (xenotropic murine leukemia virus-related virus), a human retrovirus associated with prostate cancer. *J Virol.* 2009;83:6995-7003.
- Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlander N, Altekruse SF, Feuer EJ, Huang L, Mariotto A, Miller BA, Lewis DR, Eisner MP, Stinchcomb DG, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2006*, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2006/. Accessed November 5, 2009.
- Lombardi VC, Ruscetti FW, Das Gupta J, Pfof MA, Hagen KS, Peterson DL, Ruscetti SK, Bagni RK, Petrow-Sadowski C, Gold B, Dean M, Silverman RH, Mikovits JA. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science.* 2009;326:585-589.
- Qui X, P Swanson, Luk K-C, Das Gupta J, Onlamoon N, Silverman R, Villanger F, Devare S, Schochetman G, Hackett, J Jr. XMRV: examination of viral kinetics, tissue tropism, and serological markers of infection. The 17th Conference on Retroviruses and Opportunistic Infections (CROI 2010). At <http://www.retroconference.org/2010/Abstracts/39393.htm>. Accessed 3 March 2010.
- Reeves WC, Jones, JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, Morrissey M, Devlin R. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. *Popul Health Metr.* 2007;5:5.
- Schlaberg R, Choe DJ, Brown KR, Thaker HM, Singh IR. XMRV is present in malignant prostatic epithelium and is associated with prostate cancer, especially high-grade tumors. *Proc Natl Acad Sci U S A.* 2009;106:16351-6.
- Silverman RH. A scientific journey through the 2-5A/RNase L system. *Cytokine Growth Factor Rev.* 2007;18:381-8.
- Smith WR, Noonan C, Buchwald D. Mortality in a cohort of chronically fatigued patients. *Psychol Med.* 2006;36:1301-6.
- The Universal Virus Database, v3. <http://www.ncbi.nlm.nih.gov/ICTVdb/ICTVdb/> Accessed November 4, 2009.
- Urisman A, Molinaro RJ, Fischer N, Plummer SJ, Casey G, Klein EA, Malathi K, Magi-Galluzzi C, Tubbs RR, Ganem D, Silverman RH, DeRisi JL. Identification of a novel gamma-retrovirus in prostate tumors of patients homozygous for R462Q *RNASEL* variant. *PLoS Pathog.* 2006;2:e25.
- van Kuppeveld FJM, de Jong AS, Lanke KH, Verhaegh GW, Melchers WJG, Swanink CMA, Bleijenberg G, Netea MG, Galama JMD, van der Meer JWM. Prevalence of xenotropic murine leukaemia virus-related virus in patients with chronic fatigue syndrome in the Netherlands: retrospective analysis of samples from an established cohort. *BMJ* 2010;340:c1018. doi:10.1136/bmj.c1018.