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:**
- Evidence of association, but not causation, has been reported for XMRV infection with the following conditions:
  - Prostate cancer
  - Chronic Fatigue Syndrome (CFS)

**Priority Level:**
- **Scientific/Epidemiologic evidence regarding blood safety:** Theoretical; although pathogenic retroviruses (i.e., HIV and HTLV) are clearly transfusion transmitted, such transmission of XMRV has been neither demonstrated nor alleged. There is no data suggesting an association of prostate cancer or CFS with transfusion.
- **Public perception and/or regulatory concern regarding blood safety:** Moderate based on the characteristics of other retroviruses and the early stage of investigations of the clinical associations of human infection with this agent. Concern has been publicly expressed regarding transfusion transmission of XMRV following publication of data associating it with CFS.
- **Public concern regarding disease agent:** Low at least partly based on lack of familiarity with a virus only very recently associated with any prevalent human disease; however, may be higher in groups with diseases associated with XMRV.

**Background:**
- A diverse range of mammalian species is susceptible to infection by gammaretroviruses. These are simple retroviruses whose genomes encode 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.

**Survival/Persistence in Blood Products:**
- 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 a familial aggregation of an aggressive form of prostate cancer. The hypothesis was that these men, who harbored a homozygous mutation of the antiviral enzyme RNase L, were unusually susceptible to the oncogenic potential of the virus. However, in a subsequent study, XMRV DNA or proteins were found in 6 and 23%, respectively, of malignant prostates irrespective of the RNase polymorphism. Studies in a German cohort did not detect XMRV infection in nearly 600 prostate cancer samples.
- In 2009, a statistical association of XMRV infection with CFS was reported. Peripheral blood mononuclear cells (PBMC) from 67% of stringently defined CFS patients contained the proviral DNA of XMRV compared to 3.7% of healthy controls. These patients did not have the RNase L polymorphism mentioned above. Secondary infections in tissue culture could be established from PBMCs, B and T cells and plasma of patients. The study concluded, “These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS.”
- Whether the association of XMRV infection with these syndromes is causal or is confounded by factors like geographic variability of the prevalence of the virus or the presence of unusual susceptibility to viral infection in the clinical cohorts studied is unknown. Published studies lack a complete description about selection of the CFS patient and control cohorts.

**Common Human Exposure Routes:**
- Unknown

**Likelihood of Secondary Transmission:**
- Unknown

**At-Risk Populations:**
- Unknown

**Vector and Reservoir Involved:**
- Unknown

**Blood Phase:**
- A perspective accompanying the original CFS study concluded “(G)iven that infectious virus is present in plasma and in blood cells, blood-borne transmission is a possibility.”

**Transmission by Blood Transfusion:**
- Unknown
Cases/Frequency in Population:
- In the CFS study referred to above, 3.7% of healthy controls harbored viral DNA sequences in PBMCs; 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.

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 encephalitis) is characterized by persistent or recurrent fatigue, diffuse musculoskeletal pain, sleep disturbances, and subjective cognitive impairment of 6 months duration or longer. 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. Alterations of immune, neuroendocrine, and autonomic function may be associated with this syndrome, but none is diagnostic. There is considerable overlap between this condition, fibromyalgia, and some affective disorders.

Severity of Clinical Disease:
- The original cohort of prostate cancer patients harboring the homozygous mutation in the RNase L gene had aggressive 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 sensitive or specific question is feasible.
  - The high apparent prevalence of infection reported in healthy control subjects and the high prevalence of chronic fatigue in the population are expected to make donor history screening unreliable.
  - The rate at which potential donors carrying a criteria-based diagnosis of CFS 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 PCR, cell culture, flow cytometry-based immunoassay, and immunohistochemical analyses.

Currently Recommended Donor Deferral Period:
- No FDA Guidance or AABB Standard exists for blood donors.
- Current practice is to accept donors who are healthy at the time of donation.
- Pending the availability of further data, prudent practice would be indefinite deferral of donors who have received a diagnosis of XMRV infection.

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:


