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Mikovits; Judy A. ; et al. **December 22, 2011**

STRAINS OF XENOTROPIC MURINE LEUKEMIA-RELATED VIRUS AND METHODS FOR DETECTION THEREOF

Abstract

Provided are novel strains of Xenotropic Murine Leukemia Virus-Related Virus (***XMRV***), or polynucleotides or polypeptides thereof. Identified herein are nucleic acid changes or amino acid changes identified in ***XMRV*** strains isolated from subjects. Also provided are methods of detecting such ***XMRV*** strains based at least in part on the identified nucleic acid changes or amino acid changes.

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Goverment Interests

cytokine or chemokine signature indicative of an immune response in a subject in vivo; and (vi) formation of anti-***XMRV*** antibodies according to an in vivo humoral immune response in a subject.

5. An isolated Xenotropic Murine Leukemia Virus-Related Virus (***XMRV***) Gag-Pol polypeptide comprising: (i) an amino acid sequence according to SEQ ID NO: 161 and one or more amino acid sequence changes selected from the group consisting of K31G, K31R, V36I, a 7 amino acid deletion from aa126-146, a 7 amino acid deletion from aa132-152, G59S, V60I, P105L, S27P, K31R, S62P; K65N, K65N and a downstream reading frame change according to SEQ ID NO: 105, and H76R, or a detectable fragment thereof; (ii) an amino acid sequence having at least about 95% sequence identity to a sequence of (i) and having an ***XMRV*** associated function or activity; or (iii) a functional fragment of a sequence of (i) or (ii) and having an ***XMRV*** associated function or activity.

6. The isolated ***XMRV*** Gag-Pol polypeptide of claim 5, wherein the ***XMRV*** associated function or activity is selected from the group consisting of: (i) a peptidase A2 domain at amino acid position 559-629, a reverse transcriptase domain at amino acid position 739-930, an RNase H domain at amino acid position 1172-1318, an integrase catalytic domain at amino acid position 1442-1600, a CCHC-type domain at amino acid position 500-517, a coiled coil at amino acid position 436-476, a PTAP/PSAP motif at amino acid position 109-112, a LYPX(n)L motif at amino acid position 128-132, a PPXY motif at amino acid position 161-164, a Pro-rich region at amino acid position 71-191, or Pro-rich region at amino acid position 71-168, a protease active site at amino acid position 564, a magnesium metal binding catalytic site for reverse transcriptase activity at amino acid positions 807, 881, or 882, a magnesium metal binding site for RNase H activity at amino acid positions 1181, 1219, 1240, or 1310, a magnesium metal binding catalytic site for integrase activity at amino acid positions 1453 or 1512, and a cleavage site by viral protease p14 at amino acid positions 129-130, 213-214, 476-477, 532-533, 657-658, or 1328-1329; (ii) an ability for the Gag-Pol polypeptide to be cleaved to a matrix protein p15, a RNA-binding phosphoprotein p12, a capsid protein p30, a nucleocapsid protein p10, a protease p14, a reverse transcriptase/ribonuclease H, and an integrase p46; (iii) matrix protein p15 activity, RNA-binding phosphoprotein p12 activity, capsid protein p30 activity, nucleocapsid protein p10 activity, protease p14 activity, reverse transcriptase/ribonuclease H activity, or integrase p46 activity; (iv) stimulation of a cytokine or chemokine signature indicative of an immune response in a subject in vivo; and (v) formation of anti-***XMRV*** antibodies according to an in vivo humoral immune response in a subject.

7. A method of detecting a strain of Xenotropic Murine Leukemia Virus-Related Virus (***XMRV***) in a sample comprising detecting presence, absence, or quantity of the ***XMRV*** polynucleotide or polypeptide of any one of claims 1-6, or an immune response of a subject thereto, in the sample.

8. The method of claim 7, wherein: the sample is selected from the group consisting of a blood sample, a serum sample, a plasma sample, a cerebrospinal fluid sample, and a solid tissue sample; or the sample comprises cells selected from the group consisting of fibroblasts, endothelial cells, peripheral blood mononuclear cells, and haematopoietic cells, or a combination thereof.

9. The method of any one of claims 7-8, wherein detecting presence, absence, or quantity of an ***XMRV*** strain in a sample comprises: contacting the sample and at least one probe that binds to at least one ***XMRV*** strain polypeptide, or detectable fragment thereof, under conditions sufficient for formation of a complex comprising the at least one probe and the least one polypeptide or fragment if present in the sample; and detecting presence, absence or quantity of the complex comprising the at least one probe and the at least one polypeptide or fragment.

10. The method of claim 9, wherein one or more of the following is satisfied: (i) the at least one probe is a polyclonal antibody, a monoclonal antibody, an Fab fragment an antibody, an antigen-binding fragment of an antibody, an aptamer, or an avimer, optionally selected from the group consisting of an anti gp 55

14. The method of claim 14, wherein one or more of the following is satisfied: (i) the at least one nucleobase polymer comprises a sequence that hybridizes to a nucleic acid sequence comprising at least about 10 contiguous nucleotides of an ***XMRV*** polynucleotide comprising at least one of the nucleic acid sequence changes, or complement thereof; (ii) the conditions sufficient for hybridization to occur consists of high stringency hybridization conditions; (iii) the nucleobase polymer comprises DNA, RNA, or a nucleic acid analogue; (iv) the nucleobase polymer further comprises a label selected from the group consisting of a radioisotope, a chromogen, a chromophore, a fluorophore, a fluorogen, an enzyme, a quantum dot and a resonance light scattering particle, and detecting presence, absence or quantity of the hybridization complex comprises detecting presence, absence or quantity of the label; or (v) detecting presence, absence or quantity of the hybridization complex comprises a hybridization assay selected from the group consisting of a Southern hybridization assay, a Northern hybridization assay, a dot-blot hybridization assay, a slot-blot hybridization assay, a Polymerase Chain Reaction (PCR) assay and a flow cytometry assay, optionally, the PCR assay comprising a quantitative real time polymerase chain reaction assay.

15. The method of any one of claims 7-14, further comprising: correlating the presence, absence, or quantity of the ***XMRV*** strain with an ***XMRV***-related disease or condition; wherein the sample is a sample of a subject.

16. The method of claim 15, wherein the subject has, is suspected of having, or is at risk for developing an ***XMRV***-related disease or condition; or the subject exhibits signs or symptoms of an ***XMRV***-related disease or condition.

17. The method of any one of claims 15-16, wherein the ***XMRV***-related disease or condition is selected from the group consisting of prostate cancer, Chronic Fatigue Syndrome, autism, autism spectrum disorders, Gulf War Syndrome, Multiple Sclerosis, Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, Niemann-Pick Type C Disease, fibromyalgia, chronic Lyme disease, non-epileptic seizures, thymoma, myelodysplasia, Immune Thrombocytopenic Purpura, Mantle Cell Lymphoma, and Chronic Lymphocytic Leukemia lymphoma.

18. The method of any one of claims 15-17, further comprising (i) selecting or modifying a treatment on the basis of detection of the presence, absence, or quantity of an ***XMRV*** strain in a sample of the subject; or (ii) administering to the subject a therapeutically effective amount of an anti-viral compound if an ***XMRV*** strain is detected.

Description

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. Provisional Application Ser. No. 61/321,147, filed Apr. 6, 2010; and U.S. Provisional Application Ser. No. 61/358,734, filed Jun. 25, 2010; each of which is incorporated herein in its entirety.

MATERIAL INCORPORATED-BY-REFERENCE

[0003] The Sequence Listing, which is a part of the present disclosure, includes a computer readable form comprising nucleotide or amino acid sequences of the present invention. The subject matter of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0010] The ***XMRV*** genome encodes, in 5'-to-3' order, the 3' long terminal repeat (LTR); a short, apparently non-coding sequence comprising a splice site acceptor ("SA"); the Gag gene; the Pro-Pol gene, comprising a splice donor site ("SD"), the extreme 3'-end of which overlaps with the 5'-end of the Env gene; the Env gene; another short non-coding sequence; the 3'-end LTR; and a poly-A tail (see e.g., FIG. 1).

[0011] ***XMRV*** sequences published to date show little sequence diversity. The full-length sequences of ***XMRV*** genomes isolated from infected individuals available in GenBank have 99.4% nucleotide identity (see Knouf et al. 2009 J Virol 84(14), 7353-7356; Lombardi et al. 2009 Science 326(5952), 585-589; Urisman et al. 2006 PLoS Pathog 2(3), e25).

SUMMARY OF THE INVENTION

[0012] Among the various aspects of the present invention is the provision of a novel ***XMRV*** polypeptide and polynucleotide sequences as well as method for detecting such.

[0013] One aspect provides an isolated ***XMRV*** polynucleotide. In some embodiments, the ***XMRV*** polynucleotide has a nucleic acid sequence according to SEQ ID NO: 1 and one or more nucleotide sequence changes selected from the group consisting of C80T, G90A, A96G, A97G, G111A, A137-157 deletion, T173C, G180A, G183A, C197T, C247T, C257T, C308T, C308G, C319T, C320T, T326C, A329G, C715T, T791G, A804G, T816Del, A856G, A665Del, T691G, G790A, T791G, T796C, G807Del, A840G, A873G, A875G, C903T, T963G, C5810Del, A6101T, G6154T, G7421A, A7459C, and an insertion at nucleotide position 7322 having a sequence of SEQ ID NO: 179. In some embodiments, the ***XMRV*** polynucleotide is a detectable fragment thereof (e.g., at least about 10 or more contiguous nucleic acids containing at least one of the above nucleotide sequence changes). In some embodiments, the ***XMRV*** polynucleotide has a nucleic acid sequence having at least about 95% sequence identity to a sequence described above. In some embodiments, the ***XMRV*** polynucleotide has a nucleic acid sequence having at least about 95% sequence identity to a sequence described above and having an ***XMRV*** associated function or activity. In some embodiments, the ***XMRV*** polynucleotide is a functional fragment of a sequence described above having an ***XMRV*** associated function or activity.

[0014] In some embodiments, the ***XMRV*** associated function or activity is encoding of an RNA active gammaretrovirus core encapsidation signal. In some embodiments, the ***XMRV*** associated function or activity is formation of ***XMRV*** virion particles. In some embodiments, the ***XMRV*** associated function or activity is stimulation of a cytokine or chemokine signature indicative of an immune response in a subject in vivo. In some embodiments, the ***XMRV*** associated function or activity is formation of anti-***XMRV*** antibodies according to an in vivo humoral immune response in a subject. In some embodiments, the ***XMRV*** associated function or activity is similar, same, or greater ex vivo fitness compared to an ***XMRV*** control or strain according to a growth competition assay. In some embodiments, the ***XMRV*** associated function or activity is ability to infect a cell in a modified Derse assay. In some embodiments, the ***XMRV*** associated function or activity is reverse transcriptase activity. In some embodiments, the ***XMRV*** associated function or activity is an ability to immortalize or modify a phenotype of a primary cell or cell culture. In some embodiments, the ***XMRV*** associated function or activity is an ability to induce cell syncytia or cell death on exposure or infection of cultured primary cells or co-cultured indicator cells. In some embodiments, the ***XMRV*** associated function or activity is an ability to form plaques in cell culture on exposure or infection. In some embodiments, the ***XMRV*** associated function or activity is similar, same, or lower tissue culture infective dose (TCID.sub.5o) compared to an ***XMRV*** control or strain. In various embodiments, the ***XMRV*** associated function or activity can be a combination of any of the above.

least about 95% sequence identity to a sequence described above having an *XMRV* associated function or activity. In some embodiments, the isolated *XMRV* Gag-Pol polypeptide is a functional fragment of a sequence described above having an *XMRV* associated function or activity.

[0019] In some embodiments, the *XMRV* associated function or activity is a peptidase A2 domain at amino acid position 559-629. In some embodiments, the *XMRV* associated function or activity is a reverse transcriptase domain at amino acid position 739-930. In some embodiments, the *XMRV* associated function or activity is an RNase H domain at amino acid position 1172-1318. In some embodiments, the *XMRV* associated function or activity is an integrase catalytic domain at amino acid position 1442-1600. In some embodiments, the *XMRV* associated function or activity is a CCHC-type domain at amino acid position 500-517. In some embodiments, the *XMRV* associated function or activity is a coiled coil at amino acid position 436-476. In some embodiments, the *XMRV* associated function or activity is a PTAP/PSAP motif at amino acid position 109-112. In some embodiments, the *XMRV* associated function or activity is a LYPX(n)L motif at amino acid position 128-132. In some embodiments, the *XMRV* associated function or activity is a PPXY motif at amino acid position 161-164. In some embodiments, the *XMRV* associated function or activity is a Pro-rich region at amino acid position 71-191. In some embodiments, the *XMRV* associated function or activity is or Pro-rich region at amino acid position 71-168. In some embodiments, the *XMRV* associated function or activity is a protease active site at amino acid position 564. In some embodiments, the *XMRV* associated function or activity is a magnesium metal binding catalytic site for reverse transcriptase activity at amino acid positions 807, 881, or 882. In some embodiments, the *XMRV* associated function or activity is a magnesium metal binding site for RNase H activity at amino acid positions 1181, 1219, 1240, or 1310. In some embodiments, the *XMRV* associated function or activity is a magnesium metal binding catalytic site for integrase activity at amino acid positions 1453 or 1512. In some embodiments, the *XMRV* associated function or activity is a cleavage site by viral protease p14 at amino acid positions 129-130, 213-214, 476-477, 532-533, 657-658, or 1328-1329. In some embodiments, the *XMRV* associated function or activity is an ability for the Gag-Pol polypeptide to be cleaved to a matrix protein p15, a RNA-binding phosphoprotein p12, a capsid protein p30, a nucleocapsid protein p10, a protease p14, a reverse transcriptase/ribonuclease H, and an integrase p46. In some embodiments, the *XMRV* associated function or activity is matrix protein p15 activity. In some embodiments, the *XMRV* associated function or activity is RNA-binding phosphoprotein p12 activity. In some embodiments, the *XMRV* associated function or activity is capsid protein p30 activity. In some embodiments, the *XMRV* associated function or activity is nucleocapsid protein p10 activity. In some embodiments, the *XMRV* associated function or activity is protease p14 activity. In some embodiments, the *XMRV* associated function or activity is reverse transcriptase/ribonuclease H activity. In some embodiments, the *XMRV* associated function or activity is integrase p46 activity. In some embodiments, the *XMRV* associated function or activity is stimulation of a cytokine or chemokine signature indicative of an immune response in a subject in vivo. In some embodiments, the *XMRV* associated function or activity is formation of anti-*XMRV* antibodies according to an in vivo humoral immune response in a subject. In various embodiments, the *XMRV* associated function or activity can be a combination of any of the above.

[0020] Another aspect provides a method of detecting a strain of *XMRV* in a sample, In some embodiments, the method includes detecting presence, absence, or quantity of an *XMRV* polynucleotide or polypeptide described above, or an immune response of a subject (e.g., production of an anti-*XMRV* antibody) thereto, in the sample.

[0021] In some embodiments, the sample is selected from a blood sample, a serum sample, a plasma sample, a cerebrospinal fluid sample, or a solid tissue sample. In some embodiments, the sample includes fibroblasts, endothelial cells, peripheral blood mononuclear cells, or haematopoietic cells, or a combination thereof.

above.

[0026] In some embodiments, detecting presence, absence, or quantity of an ***XMRV*** strain in a sample includes a nucleic acid-based assay. In some embodiments, nucleic acid-based detection includes contacting the sample and at least one nucleobase polymer under conditions sufficient for hybridization to occur between the at least one nucleobase polymer and a polynucleotide of a ***XMRV*** strain, or complement thereof, if present in the sample; and detecting presence, absence or quantity of a hybridization complex comprising the nucleobase polymer and the ***XMRV*** polynucleotide, or complement thereof wherein the at least one nucleobase polymer comprises a sequence that hybridizes to a nucleic acid sequence comprising at least about 10 contiguous nucleotides of a polynucleotide of an ***XMRV*** strain, or complement thereof.

[0027] In some embodiments of nucleic acid-based detection, the at least one nucleobase polymer comprises a sequence that hybridizes to a nucleic acid sequence comprising at least about 10 contiguous nucleotides of an ***XMRV*** polynucleotide comprising at least one of the nucleic acid sequence changes, or complement thereof. In some embodiments of nucleic acid-based detection, the conditions sufficient for hybridization to occur consists of high stringency hybridization conditions. In some embodiments of nucleic acid-based detection, the nucleobase polymer comprises DNA, RNA, or a nucleic acid analogue. In some embodiments of nucleic acid-based detection, the nucleobase polymer further comprises a label selected from the group consisting of a radioisotope, a chromogen, a chromophore, a fluorophore, a fluorogen, an enzyme, a quantum dot and a resonance light scattering particle, and detecting presence, absence or quantity of the hybridization complex comprises detecting presence, absence or quantity of the label. In some embodiments, nucleic acid-based detection includes a hybridization assay selected from the group consisting of a Southern hybridization assay, a Northern hybridization assay, a dot-blot hybridization assay, a slot-blot hybridization assay, a Polymerase Chain Reaction (PCR) assay and a flow cytometry assay. In some embodiments, nucleic acid-based detection includes a quantitative real time polymerase chain reaction assay.

[0028] In some embodiments, methods include correlating the presence, absence, or quantity of the ***XMRV*** strain with an ***XMRV***-related disease or condition; wherein the sample is a sample of a subject. In some embodiments, the subject has, is suspected of having, or is at risk for developing an ***XMRV***-related disease or condition. In some embodiments, the subject exhibits signs or symptoms of an ***XMRV***-related disease or condition. In some embodiments, the ***XMRV***-related disease or condition is selected from the group consisting of prostate cancer, Chronic Fatigue Syndrome, autism, autism spectrum disorders, Gulf War Syndrome, Multiple Sclerosis, Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, Niemann-Pick Type C Disease, fibromyalgia, chronic Lyme disease, non-epileptic seizures, thymoma, myelodysplasia, Immune Thrombocytopenic Purpura, Mantle Cell Lymphoma, and Chronic Lymphocytic Leukemia lymphoma.

[0029] In some embodiments, methods include selecting or modifying a treatment on the basis of detection of the presence, absence, or quantity of an ***XMRV*** strain in a sample of the subject. In some embodiments, methods include administering to the subject a therapeutically effective amount of an anti-viral compound if an ***XMRV*** strain is detected.

[0030] Other objects and features will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] Those of skill in the art will understand that the drawings, described below, are for illustrative purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

ENV, as counted with reference to VP62 (SEQ ID NO:1).

[0047] FIG. 15 is a sequence alignment of eight polynucleotide sequences isolated from ***XMRV***-infected subjects, and the VP62 reference sequence. The sequenced region corresponds to bases 7183-7504 in ENV, as counted with reference to VP62 (SEQ ID NO:1).

[0048] FIG. 16 is a sequence alignment of forty polynucleotide sequences isolated from ***XMRV***-infected subjects, and the VP62 reference sequence. The sequenced region corresponds to bases 665-1018 in GAG, as counted with reference to VP62 (SEQ ID NO:1).

[0049] FIG. 17 is a sequence alignment of five polypeptide sequences isolated from ***XMRV***-infected subjects, and the VP62 reference sequence along with sequences for VP42 (SEQ ID NO: 164) and VP35 (SEQ ID NO: 163). The sequenced region corresponds to bases 5792-6281 in ENV, as counted with reference to VP62 (SEQ ID NO:1).

[0050] FIG. 18 is a sequence alignment of eight polypeptide sequences isolated from ***XMRV***-infected subjects, and the VP62 reference sequence. The sequenced region corresponds to bases 7183-7504 in ENV, as counted with reference to VP62 (SEQ ID NO:1).

[0051] FIG. 19 is a sequence alignment of forty polypeptide sequences isolated from ***XMRV***-infected subjects, and the VP62 reference sequence. The sequenced region corresponds to bases 665-1018 in GAG, as counted with reference to VP62 (SEQ ID NO:1).

[0052] FIG. 20 phylogenetic tree showing the relationships between ***XMRV*** sequences and murine xenotropic retroviruses.

[0053] FIG. 21 is a cartoon diagram of sequences showing that SU sequences of viruses transmitted from the plasma of UK ME/CFS patients to LNCaP cells share homology with ***XMRV*** and not with polytropic MLV.

[0054] FIG. 22 is a cartoon diagram of sequences showing that clones from one subject have sequences that are more similar to polytropic MLV sequences than to VP62 sequences.

DETAILED DESCRIPTION OF THE INVENTION

[0055] The present disclosure is based, at least in part, on the observation that Xenotropic Murine Leukemia Virus-Related Virus (***XMRV***) exhibits significant sequence heterogeneity between clinical isolates; and that subjects infected with ***XMRV*** exhibit varying clinical symptoms.

[0056] ***XMRV*** Strains

[0057] One aspect of the present disclosure provides isolated ***XMRV*** nucleic acid or polypeptide sequences. The present inventors have discovered multiple strains of ***XMRV*** isolates existing in nature, in the same or different subjects. The present inventors have also discovered that various ***XMRV*** strains can be categorized into distinctive subgroups. The present disclosure describes at least two distinct groups, identified herein as X-***XMRV*** and P-***XMRV***. The P-***XMRV*** group can include a modified P-***XMRV***, referred to herein as mP-***XMRV***. Various groups can be distinguished or defined by characteristic differences in their polynucleotide or polypeptide sequences (see e.g., TABLES 1-4 and FIGS. 5-11, 14-19). It has also been discovered that infection by multiple ***XMRV*** groups can occur in a single subject. For example, it is reported herein that a single individual can be infected with both P- and X-***XMRV*** at the same time (see e.g., FIGS. 10-11).

GAAAAGTCTCTGACCTCGTTGTCTGAGGTGGTCCTACAGAACCGGAGGGGAT TAGTCTA (SEQ ID NO: 179); or a functional fragment thereof.

[0064] As a further example, a polynucleotide of an ***XMRV*** strain can have an ***XMRV*** associated function or activity and at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a sequence according to SEQ ID NO: 1 and having one or more (e.g., at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten, or more) nucleotide changes selected from C80T, G90A, A96G, A97G, G111A, A137-157 deletion, T173C, G180A, G183A, C197T, C247T, C257T, C308T, C308G, C319T, C320T, T326C, A329G, C715T, T791G, A804G, T816Del, A856G, A665Del, T691G, G790A (potential hypermethylation site), T791G, T796C, G807Del, A840G, A873G, A875G, C903T, T963G, C5810Del, A6101T, G6154T, G7421A, A7459C, and an insertion at nucleotide position 7322 having a sequence of GAAAAGTCTCTGACCTCGTTGTCTGAGGTGGTCCTACAGAACCGGAGGGGAT TAGTCTA (SEQ ID NO: 179); or a functional fragment thereof.

[0065] A polynucleotide of an ***XMRV*** strain can be a functional fragment of a polynucleotide sequence disclosed herein. A functional fragment of an ***XMRV*** polynucleotide sequence can be an upstream or downstream truncated ***XMRV*** sequence, where the polynucleotide retains an ***XMRV*** associated function or activity, as described further herein, or the polynucleotide encodes a polypeptide having an ***XMRV*** associated function or activity, as described further herein. Polynucleotide or polypeptide function or activity of an ***XMRV*** strain can be as discussed further herein.

[0066] A detectable polynucleotide fragment of an ***XMRV*** strain disclosed herein can comprise at least about 10 contiguous nucleotides of a polynucleotide sequence described herein. For example, detectable polynucleotide fragment of an ***XMRV*** strain disclosed herein can comprise at least about 15, at least about 20, at least about 25, at least about 50, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, at least about 600, at least about 650, at least about 700, at least about 750, at least about 800, at least about 850, at least about 900, at least about 950, or at least about 1000, or more, contiguous nucleotides of a polynucleotide sequence described herein. A detectable polynucleotide fragment can have at least one (e.g., at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten, or more) nucleic acid change described herein.

[0067] Polypeptide Sequences of an ***XMRV*** Strain.

[0068] Envelope.

[0069] An ***XMRV*** strain can have a polypeptide sequence according to reference VP62 Envelope polypeptide (SEQ ID NO: 160) and one or more of the following amino acid sequence changes: H116L, G134Stop, an insertion between amino acid positions 517-518 having a sequence of GLDLEKSLTSLSHVVLQNRR (SEQ ID NO: 180), E535K, D549A, and R568G, or a functional fragment thereof. For example, an Envelope polypeptide of an ***XMRV*** strain can have at least two, at least three, at least four, at least five, or at least six, or more, of amino acid changes described herein.

[0070] A polypeptide of an ***XMRV*** strain can have an ***XMRV*** associated function or activity and at least about 80% sequence identity to a polypeptide sequence according to reference VP62 Envelope polypeptide SEQ ID NO: 160 and one or more (e.g., at least two, at least three, at least four, at least five, or at least six, or more) of the following amino acid sequence changes: H116L, G134Stop, an insertion between amino acid positions 517-518 having a sequence of GLDLEKSLTSLSHVVLQNRR (SEQ ID NO: 180), E535K, D549A, and R568G, or a functional fragment thereof.

[0078] A detectable polypeptide fragment of an ***XMRV*** strain disclosed herein can comprise at least about 4 contiguous amino acids of a polypeptide sequence described herein. For example, detectable polypeptide fragment of an ***XMRV*** strain disclosed herein can comprise at least about 6, at least about 8, at least about 10, at least about 15, at least about 20, at least about 30, at least about 40, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, or at least about 100, or more, contiguous amino acids of a polypeptide sequence described herein. A detectable polypeptide fragment can have at least one (e.g., at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten, or more) amino acid change described herein.

[0079] The present inventors have discovered that there is variation in the ***XMRV*** viral RNA that is expressed in peripheral blood mononuclear cells (PBMCs). Findings described herein show more sequence diversity between ***XMRV*** viral polynucleic acids than has been previously reported. Described herein are at least two subgroups of ***XMRV***: subgroup X and subgroup P. The X subgroup of ***XMRV*** (X-***XMRV***) is shown herein to be closely related to known ***XMRV*** sequences and X-MLVs, but does have some nucleotide substitutions relative to known reference sequences, such as VP62 (SEQ ID NO: 1). The P subgroup of ***XMRV*** (P-***XMRV***) is shown herein to be closely related to P-MLVs and Pm-MLVs and has been discovered to have several specific differences. For example, in MA sequences, P-***XMRV*** differs from known ***XMRV*** sequences at a number of nucleotides, although it is highly conserved with other ***XMRV*** sequences at the amino acid level. As another example, in SU sequences, P-***XMRV*** cannot be detected by PCR primers based on X-***XMRV***-type sequences, further suggesting that P-***XMRV*** SU sequences are different from X-***XMRV*** sequences.

[0080] ***XMRV*** has a 24-nt deletion in the glycoGag region of its genome, relative to any other known exogenous MuLV. This 24-nt deletion encompasses a stop codon that is 53 amino acids downstream from the alternative translational start site. While no other MuLV is known to share the same 24-nt deletion as ***XMRV,*** a shorter deletion of nine nucleotides internal to the 24-nt deletion is present in the genomes of several non-ecotropic MuLV proviruses. In cultured cells, the glycoGag region is not essential for viral replication, and lesions in this same region have been associated with variations in pathogenic properties in vivo. For example, an alteration in ten nucleotides affecting five residues in the N-terminal peptide of glycoGag was found to be responsible for a 100-fold difference in the frequency of neuroinvasion observed between CasFrKP and CasFrKP41 MuLV strains.

[0081] Table 1 identifies variation in ***XMRV*** sequences, and shows which amino acid residue/positions characterize both X- and P-***XMRV*** groups (see e.g., Examples 4-8).

TABLE-US-00001 TABLE 1 Nucleotide changes identified in clinical isolates of ***XMRV,*** with reference to sequence numbering of VP62, Accession number DQ399707.1 (SEQ ID NO: 1) and Accession number EF185282.1 (SEQ ID NO: 162). Location in Location in SEQ ID NO: 1 SEQ ID NO: 162 Groups AA change C80T C75T mP G90A G85A mP A96G A91G mP K31G A97G A92G X, mP, P K31R G111A G106A P V36I A137-157 deletion A132-152 deletion mP 7 amino acid deletion* T173C T168C P G180A G175A P G59S #G183A #G178A X, mP, P V60I C197T C192T P C247T C242T P C257T C252T P C308T C303T P C308G C303G mP C319T C314T mP P105L C320T C315T mP, P T326C T321C mP, P A329G A324G X, mP, P Amino acid changes determined with respect to alignment SEQ ID NO: 162. *Due to direct repeat in this region (ATGGCC), deletion could be from 126-146 or from 132-152. #place where VP42, EK1 and EK2 have same substitutions relative to the other published.

[0082] Lys31Arg is present in VP35 (SEQ ID NO: 163) while VP42 (SEQ ID NO: 164) has Lysine at

GAG666-1009 111 1001140 GAG668-1012 112 1001017 GAG665-1012 113 1001033 GAG667-1012 114 1001253 GAG667-1009 177 R11560 GAG642-1015 115 VP62 reference (peptide) GAG629-1000 175 VP42 reference (peptide) GAG629-1000 176 VP35 reference (peptide) GAG629-1000 116 1001074 (peptide) GAG667-1000 117 1001082 (peptide) GAG672-1003 118 1001085 (peptide) GAG667-1003 119 1001090 (peptide) GAG666-1004 120 1001148 (peptide) GAG667-997 121 1001171 (peptide) GAG667-991 122 1001184 (peptide) GAG667-1002 123 1001221 (peptide) GAG665-1010 124 1001235 (peptide) GAG666-999 125 1001748 (peptide) GAG666-1005 126 1001764 (peptide) GAG668-1011 127 1001770 (peptide) GAG661-1007 128 1001849 (peptide) GAG666-1012 129 1001788 (peptide) GAG666-1005 130 1001550 (peptide) GAG666-1012 131 1001557 (peptide) GAG669-1011 132 1001559 (peptide) GAG677-1001 133 1001574 (peptide) GAG669-1012 134 1001578 (peptide) GAG667-994 135 1001581 (peptide) GAG666-1005 136 1001583 (peptide) GAG666-1015 137 1001584 (peptide) GAG665-1007 138 1001596 (peptide) GAG670-1015 139 1001601 (peptide) GAG667-995 140 1001602 (peptide) GAG666-1014 141 1001603 (peptide) GAG667-995 142 1001604 (peptide) GAG665-1015 143 1001613 (peptide) GAG666-1015 144 1001616 (peptide) GAG667-1013 145 1001216 (peptide) GAG665-996 146 1001201 (peptide) GAG666-994 147 1001145 (peptide) GAG695-1010 148 1001210 (peptide) GAG679-1012 149 1001037 (peptide) GAG668-1007 150 1001146 (peptide) GAG668-1010 151 1001036 (peptide) GAG666-1009 152 1001140 (peptide) GAG668-1012 153 1001017 (peptide) GAG665-1012 154 1001033 (peptide) GAG667-1012 155 1001253 (peptide) GAG666-999 178 R11560 GAG642-1015 Numbering for all sequences refers to corresponding positions on the reference VP62 sequence (SEQ ID NO: 1). Peptide sequences were determined by in silico translation of the nucleotide sequence isolated from the same subject: nucleotide SEQ ID NOs: 44-49 correspond to peptide SEQ ID NOs: 50-55 respectively; nucleotide SEQ ID NOs: 56-64 correspond to peptide SEQ ID NOs: 65-73, respectively; and nucleotide SEQ ID NOs: 74-114 correspond to peptide SEQ ID NOs: 115-155, respectively.

TABLE-US-00004 TABLE 4 Additional ***XMRV*** Sequences Position of sequence from Source of sequence subject relative to VP62 SEQ ID NO: (subject number) reference sequence 23 VP62 reference GAG 24 11 GAG 25 10 ENV5798-6105 26 VP62 reference 27 17 5724-5940 28 VP62 reference ENV 29 18 ENV5814-5897 30 GAG 31 GAG667-1015 32 4 5798-6168 33 VP62 reference ENV 34 8 ENV7185-7324 35 GAG 36 GAG628-964 37 1 ENV5806-6197 38 WPI-1106 39 1-23 40 WPI1138 41 2-1

TABLE-US-00005 TABLE 5 Variation in ***XMRV*** sequences. Chronic Fatigue Syndrome Cases WPI-1104 Prostate Cancer Cells (36- VP 62 VP 42 VP 35 WPI-1106 WPI-1178C 1152; 5923- nt (number) (4-8174 nt) (1-8186 nt) (1-8186 nt) (36-8144 nt) (36-8144 nt) 8147 nt) 375 A 450 C 790 A 1013 T 1477 G 1565 G 1824 G G 2413 A/G 2416 2559 A 2602 A 2622 G 4159 G 4229 C deletion 4236 G insertion 4883 T 4985 A 5083 T 5087 A 5313 G 5823 C 5830 G 6373 G 6651 A 7064 G 7357 A 7437 G 7451 G G G 7456 G G 7692 T insertion 7782 G insertion G insertion G insertion

[0085] TABLE 5 identifies amino acid positions in the ***XMRV*** MA (gag) protein that are conserved in closely related gammaretroviruses.

TABLE-US-00006 TABLE 5 Amino acid substitutions of ***XMRV*** MA found in other gammaretroviruses. aa change aa identical to substitution Lys (31)-Arg/Gly FeLV, Fr-MLV, KoRV (Arg); none (Gly) Val (36)-Ile FeLV Gly (59)-Ser GaLV, KoRV, Val (60)-Ile AKV-MLV, Ampho-MLV, Cas-BrE, Fr-MLV, Mo-MLV, X-MLV Pro (105)-Leu AKV-MLV, X-MLV Accession numbers: AKV MLV (MLOCG), Amphotropic MLV (AF411814), Cas-BrE (X57540), FeLV (AF052723) Friend MLV (Fr-MLV) (NC 001362), GaLV (NC 001885), KoRV (QT9TTC2), Moloney-MLV (NC 001501), and xenotropic MLV (X-MLV)(EU035300).

[0086] ***XMRV*** Function

[0093] The mature envelope protein (Env) consists of a trimer of SU-TM heterodimers attached by a labile interchain disulfide bond. The activated Env consists of SU monomers and TM trimers. The SU protein is not anchored to the ***XMRV*** viral envelope, but associates with the ***XMRV*** virion surface through its binding to TM. Both SU and TM proteins may be concentrated at the site of budding and incorporated into an ***XMRV*** virion by contacts between the cytoplasmic tail of Env and the N-terminus of Gag. The surface protein (SU) attaches the ***XMRV*** virus to the host cell by binding to its receptor. This interaction activates a thiol in a CXXC motif of the C-terminal domain, where the other Cys residue participates in the formation of the intersubunit disulfide.

[0094] The CXXC motif is highly conserved across a broad range of retroviral envelope proteins, including ***XMRV*** envelope protein. The CXXC motif may participate in the formation of a labile disulfide bond (e.g., with the CX6CC motif present in the transmembrane protein). Isomerization of the intersubunit disulfide bond to an SU intrachain disulfide bond may occur upon receptor recognition in order to allow membrane fusion. The activated thiol can attack the disulfide and cause its isomerization into a disulfide isomer within the motif This can lead to SU displacement and TM refolding, and may activate its fusogenic potential by unmasking its fusion peptide. Fusion can occur at the host cell plasma membrane. The transmembrane protein (TM) can act as a class I viral fusion protein. The TM protein can have at least 3 conformational states: pre-fusion native state, pre-hairpin intermediate state, and post-fusion hairpin state. During ***XMRV*** viral and target cell membrane fusion, the coiled coil regions (heptad repeats) assume a trimer-of-hairpins structure, positioning the fusion peptide in close proximity to the C-terminal region of the ectodomain. The formation of this structure may drive apposition and subsequent fusion of viral and target cell membranes. Membranes fusion leads to delivery of the nucleocapsid into the cytoplasm.

[0095] The CC amino acid sequence comprised by AALKEECCFYADHT (SEQ ID NO: 6), amino acids 420-433 of the ***XMRV*** ENV polypeptide, is thought to interact with host kinases.

[0096] Gag-Pol Polypeptide Activity Assay

[0097] Gag-Pol polypeptide is a transcribed polypeptide corresponding to the Gag-Pol region of the ***XMRV*** genome (see FIG. 1). Gag-Pol polypeptide of VP62 has a UniProt Accession number of AlZ651 (SEQ ID NO: 161) and can be 1733 amino acids in length Amino acid positions discussed below are according to UniProt Accession number of AlZ651; one of ordinary skill can determine corresponding amino acid positions in an ***XMRV*** variant described herein.

[0098] A functional ***XMRV*** Gag-Pol polypeptide, a functional fragment thereof, or a functional component thereof (e.g., matrix protein p15; RNA-binding phosphoprotein p12; capsid protein p30; nucleocapsid protein p10; protease p14; reverse transcriptase/ribonuclease H; integrase p46) can have one or more of the following structural features or functions: a peptidase A2 domain at amino acid position 559-629; a reverse transcriptase domain at amino acid position 739-930; and RNase H domain at amino acid position 1172-1318; an integrase catalytic domain at amino acid position 1442-1600; a CCHC-type domain at amino acid position 500-517; a coiled coil at amino acid position 436-476; a PTAP/PSAP motif at amino acid position 109-112; a LYPX(n)L motif at amino acid position 128-132; a PPXY motif at amino acid position 161-164; a Pro-rich region at amino acid position 71-191; and Pro-rich region at amino acid position 71-168. A functional ***XMRV*** Gag-Pol polypeptide, a functional fragment thereof, or a functional component thereof (e.g., matrix protein p15; RNA-binding phosphoprotein p12; capsid protein p30; nucleocapsid protein p10; protease p14; reverse transcriptase/ribonuclease H; integrase p46) can have one or more of the following structural features or functions: a protease active site at amino acid position 564; a magnesium metal binding catalytic site for reverse transcriptase activity at amino acid positions 807, 881, or 882; a magnesium metal binding site for RNase H activity at amino acid positions 1181, 1219, 1240, or 1310; a magnesium metal binding catalytic site for integrase activity at amino acid

[0104] A functional p14 protease, or a functional fragment or component thereof, can have one or more of the structural features or functions discussed herein. Aspartyl protease (EC=3.4.23.-) can mediate proteolytic cleavages of Gag and Gag-Pol polyproteins during or shortly after the release of the virion from the plasma membrane. Cleavages can take place as an ordered, step-wise cascade to yield mature proteins, a process called maturation. Aspartyl protease can display maximal activity during the budding process just prior to particle release from the cell. The protease is a homodimer, whose active site consists of two apposed aspartic acid residues. A p14 protease can be located at amino acid position 533-657 of the Gag-Pol polypeptide. Such position can be relative where functionality is preserved, depending on the ***XMRV*** variant.

[0105] A functional p80 Reverse transcriptase/ribonuclease H, or a functional fragment or component thereof, can have one or more of the structural features or functions discussed herein. Reverse transcriptase/ribonuclease H (EC=2.7.7.49; EC=2.7.7.7; EC=3.1.26.4) (RT) is a multifunctional enzyme that can convert the viral dimeric ***XMRV*** RNA genome into dsDNA in the cytoplasm, shortly after virus entry into the cell. The reverse transcriptase is a monomer. Reverse transcriptase/ribonuclease H can display a DNA polymerase activity that can copy either DNA or RNA templates, and a ribonuclease H (RNase H) activity that can cleave the RNA strand of RNA-DNA heteroduplexes in a partially processive 3' to 5' endonucleasic mode. Conversion of viral genomic RNA into dsDNA can requires multiple steps, as follows. A tRNA can bind to the primer-binding site (PBS) situated at the 5' end of the viral RNA. RT can use the 3' end of the tRNA primer to perform a short round of RNA-dependent minus-strand DNA synthesis. The reading can proceed through the U5 region and can end after the repeated (R) region which is present at both ends of viral RNA. The portion of the RNA-DNA heteroduplex can be digested by the RNase H, resulting in a ssDNA product attached to the tRNA primer. This ssDNA/tRNA can hybridize with the identical R region situated at the 3' end of viral RNA. This template exchange, known as minus-strand DNA strong stop transfer, can be either intra- or intermolecular. RT can use the 3' end of this newly synthesized short ssDNA to perfom the RNA-dependent minus-strand DNA synthesis of the whole template. RNase H can digest the RNA template except for a polypurine tract (PPT) situated at the 5' end of the ***XMRV*** genome. RNase H can proceed both in a polymerase-dependent (RNA cut into small fragments by the same RT performing DNA synthesis) and a polymerase-independent mode (cleavage of remaining RNA fragments by free RTs). Secondly, RT can perform DNA-directed plus-strand DNA synthesis using the PPT that has not been removed by RNase H as primers. PPT and tRNA primers can then removed by RNase H. The 3' and 5' ssDNA PBS regions can hybridize to form a circular dsDNA intermediate. Strand displacement synthesis by RT to the PBS and PPT ends can produce a blunt ended, linear dsDNA copy of the ***XMRV*** viral genome that includes long terminal repeats (LTRs) at both ends. The reverse transcriptase is an error-prone enzyme that lacks a proof-reading function. High mutations rate can be a direct consequence of this characteristic. RT can also display frequent template switching leading to high recombination rate. Recombination mostly occurs between homologous regions of the two copackaged RNA genomes. If these two RNA molecules derive from different viral strains (e.g., different ***XMRV*** strains), reverse transcription can give rise to highly recombinated proviral DNAs. A p80 Reverse transcriptase/ribonuclease H can be located at amino acid position 658-1328 of the Gag-Pol polypeptide. Such position can be relative where functionality is preserved, depending on the ***XMRV*** variant.

[0106] A functional p46 integrase, or a functional fragment or component thereof, can have one or more of the structural features or functions discussed herein. Integrase can catalyze viral DNA integration into a host chromosome, by performing a series of DNA cutting and joining reactions. Integrase activity can take place after ***XMRV*** virion entry into a cell and reverse transcription of the ***XMRV*** RNA genome in dsDNA. The first step in the integration process can be 3' processing. This step can require a complex comprising the ***XMRV*** viral genome, matrix protein and integrase (i.e., a pre-integration complex (PIC)). The integrase protein can remove 2 nucleotides from each 3' end of the ***XMRV*** viral DNA, leaving

[0117] Function of ***XMRV,*** or a functional fragment or component thereof, can be according to an assay that determines the ability of an ***XMRV*** to infect a cell (e.g., in vitro tissue culture) or a subject (e.g., an animal model for viral infectivity). For example, a functional ***XMRV,*** or a functional fragment or component thereof, can be an ***XMRV*** that can infect a cell in culture according to a modified Derse assay, which measures infectious viral particles (see e.g., KyeongEun , 18th Conference of Retrovirus and Opportunistic Infections, Session 43, Paper #215, Development of a GFP-indicator Cell Line for the Detection of ***XMRV***).

[0118] Reverse Transcriptase Activity

[0119] Function of ***XMRV,*** or a functional fragment or component thereof, can be according to a reverse transcriptase activity assay. For example, reverse transcriptase activity can be detected in a viral suspension prepared from a cell culture exposed to an ***XMRV***. Assaying reverse transcriptase activity can be according to methods know in the art (e.g., Colorimetric Reverse Transcriptase Immunoassay, Roche Applied Science; Chemiluminescence Reverse Transcriptase Assay, Promega).

[0120] Transformation Ability Assay

[0121] Function of ***XMRV,*** or a functional fragment or component thereof, can be according to an assay that determines the ability of ***XMRV*** infection to immortalize or modify a phenotype of primary cell or cell culture. For example, a change in cluster of differentiation (CD) or cell receptors on a cell surface can be monitored or determined so as to characterize transformation ability of an ***XMRV***.

[0122] Cell Death

[0123] Function of ***XMRV,*** or a functional fragment or component thereof, can be according to an assay that determines susceptibility of cells (e.g., cells of a subject, sample, or a cell line) to cell syncytia or cell death. Analysis of the response of cells to exposure or infection to ***XMRV,*** including cell syncytia or cell death, as a means of assessing ***XMRV*** function can be according to electron micrographic analysis. Analysis of cell syncytia can be from direct isolation from a subject, from cultured primary cells, or from co-cultured indicator cells (e.g., LNCaP cells).

[0124] Plaque Assays

[0125] Function of ***XMRV,*** or a functional fragment or component thereof, can be according to an assay that determines plaque assays formed in cell culture (e.g., agar suspended cell culture; adherent cell culture) as a result of ***XMRV*** infection.

[0126] TCID.sub.50

[0127] Function of ***XMRV,*** or a functional fragment or component thereof, can be according to an assay that determines tissue culture infective dose (TCID.sub.50). Tissue culture infective dose is the quantity of cytopathic agent (e.g., ***XMRV*** titer) that will produce cell death in fifty percent of cell cultures inoculated.

[0128] Molecular Engineering

[0129] Design, generation, and testing of the variant nucleotides, and their encoded polypeptides, having the above required percent identities and retaining a required function or activity is within the skill of the art. For example, directed evolution and rapid isolation of mutants can be according to methods described in references including, but not limited to, Link et al. (2007) Nature Reviews 5(9), 680-688; Sanger et al.

ISBN-10: 0954523253).

[0134] Methods of down-regulation or silencing genes are known in the art. For example, expressed protein activity can be down-regulated or eliminated using antisense oligonucleotides, protein aptamers, nucelotide aptamers, and RNA interference (RNAi) (e.g., small interfering RNAs (siRNA), short hairpin RNA (shRNA), and micro RNAs (miRNA) (see e.g., Fanning and Symonds (2006) Handb Exp Pharmacol. 173, 289-303G, describing hammerhead ribozymes and small hairpin RNA; Helene, C., et al. (1992) Ann. N.Y. Acad. Sci. 660, 27-36; Maher (1992) Bioassays 14(12): 807-15, describing targeting deoxyribonucleotide sequences; Lee et al. (2006) Curr Opin Chem Biol. 10, 1-8, describing aptamers; Reynolds et al. (2004) Nature Biotechnology 22(3), 326-330, describing RNAi; Pushparaj and Melendez (2006) Clinical and Experimental Pharmacology and Physiology 33(5-6), 504-510, describing RNAi; Dillon et al. (2005) Annual Review of Physiology 67, 147-173, describing RNAi; Dykxhoorn and Lieberman (2005) Annual Review of Medicine 56, 401-423, describing RNAi). RNAi molecules are commercially available from a variety of sources (e.g., Ambion, Tex.; Sigma Aldrich, Mo.; Invitrogen). Several siRNA molecule design programs using a variety of algorithms are known to the art (see e.g., Cenix algorithm, Ambion; BLOCK-iT.TM. RNAi Designer, Invitrogen; siRNA Whitehead Institute Design Tools, Bioinofrmatics & Research Computing). Traits influential in defining optimal siRNA sequences include G/C content at the termini of the siRNAs, Tm of specific internal domains of the siRNA, siRNA length, position of the target sequence within the CDS (coding region), and nucleotide content of the 3' overhangs.

[0135] Methods of Detecting ***XMRV*** Strains

[0136] One aspect of the present disclosure provides methods of identifying polynucleotides or polypeptides characteristic of an ***XMRV*** strain or group thereof. For example, analysis of nucleotide or amino acid positions/residues that vary between ***XMRV*** strains can allow detection of identification of such strains. As another example, methods described herein can be used to detect and distinguish between various groupings of ***XMRV*** strains, such as P- and X-***XMRV*** isolates. For example, FIG. 4 shows a comparison of the N-terminal regions of the Env protein of ***XMRV*** and SFFV according to the methods described herein. This type of amino acid comparison can be used to assign a sequence from a clinically isolated ***XMRV*** as a particular ***XMRV*** strain, or group thereof, such as P- or X-***XMRV***.

[0137] Methods described herein can provide for identification of nucleotide or amino acid variation in an ***XMRV*** strain. In some cases, variation in ***XMRV*** sequence can be clinically relevant, and lead to variation in ***XMRV*** pathogenicity, immune response, or disease response. Such variation can be in one or more ***XMRV*** polynucleotide sequence, variation in one or more ***XMRV*** polypeptide sequence, or variation in one or more of both ***XMRV*** polynucleotide and ***XMRV*** polypeptide sequences.

[0138] Retrovirus detection methods are generally known in the art and, provided with sequence information herein, can be adapted for detection of ***XMRV*** strains.

[0139] ***XMRV*** can be detected by detecting antibodies to ***XMRV*** in a subject. To detect anti-***XMRV*** antibodies, a cell line expressing SFFV Env proteins can be incubated with plasma of a subject. The cell line can then be subjected to methods of determining whether an antibody from the subject bound to the SFFV Env protein, such as by flow cytometry. Detecting anti-***XMRV*** antibodies can be done by subjecting subject plasma to ELISA and identifying antibodies. Methods for the detection of ***XMRV*** by detecting antibodies are described in PCT/US2010/039208, U.S. patent application Ser. No. 12/818,880 and U.S. patent application Ser. No. 12/818,893, each of which is incorporated herein by reference in its entirety.

[0140] ***XMRV*** can be detected by detecting ***XMRV*** proteins. ***XMRV*** proteins can be detected by running

[0148] Based on disclosure of sequences described herein, one of ordinary skill can design primers specific for an ***XMRV*** strain, or a group thereof, such as X-***XMRV,*** P-***XMRV,*** or X-***XMRV*** and P-***XMRV,*** where, for example, such primers can be used to detect one of X-***XMRV*** or P-***XMRV,*** or distinguish between X-***XMRV*** and P-***XMRV***. Primers can be designed for any region of ***XMRV*** that contains a difference in nucleic acid sequence between two or more ***XMRV*** strains, or groups such as X-***XMRV*** or P-***XMRV***. For example, primers can be designed for one of more of an envelope or gag region of ***XMRV***.

[0149] For example, primer(s) specific for an ***XMRV*** strain, or a group thereof, such as X-***XMRV*** or P-***XMRV,*** can be used, where detection can be based on presence or absence of an amplification product (e.g., presence or absence of a band on gel electrophoresis).

[0150] As another example, primer(s) specific for an ***XMRV*** strain, or a group thereof, such as X-***XMRV*** or P-***XMRV,*** can be used, where detection can be based on an amplification product size (e.g., band size on gel electrophoresis).

[0151] In some embodiments, the primers used to amplify the viral polynucleotides can be primers designed to amplify Env-encoding polynucleotides. Such primers can comprise P5588F (5'-GTGTGGGTACGCCGGCACCAGAC-3', SEQ ID NO:2) and P6304R (5'-TGCATCGACCCCCCGGTGTGGC-3', SEQ ID NO:3). In some embodiments, the polynucleotide amplification can comprise two rounds of PCR, wherein the primers for the second round amplify Env-encoding polynucleotides, and comprise P5641F (5'-CTACACCGTCCTGCTGACAACC-3', SEQ ID NO:4) and P6171R (5'-TGCCTGTCCAGTGGTCTCACATC-3', SEQ ID NO:5).

[0152] Variation between polypeptide sequences can be identified through the use of antibodies that are specific for a particular amino acid motif which is present in a first, but not in a second, polypeptide sequence. Based on disclosure of sequences described herein, one of ordinary skill can generate antibodies useful for detection of ***XMRV*** strains, or a group thereof, such as X-***XMRV*** or P-***XMRV,*** or distinguishing there between. Antibodies can be generated to be specific for any region of ***XMRV*** that contains a difference in amino acid sequence between ***XMRV*** strains, or groups thereof, such as X-***XMRV*** or P-***XMRV***. For example, antibodies can be designed for one of more of an envelope or gag region of ***XMRV, or the XMRV*** virion.

[0153] Capture epitopes can be designed that specifically recognize one of an anti-***XMRV*** strain antibody, or a group thereof, such as an anti-X-***XMRV*** antibody or an anti-P-***XMRV*** antibody, in a subject or a sample from the subject. For example, antibodies in a subject can be detected according to a standard protocol, such as ELISA

[0154] Antibodies specific for an ***XMRV*** strain, or a group thereof, such as X-***XMRV*** or P-***XMRV,*** (see Table 1, e.g., 20 amino acid insert of P-***XMRV***) can be directly detected in a sample (e.g., a sample from a subject), where presence of such antibodies indicates a humoral immune response to the ***XMRV*** strain or group thereof, such as X-***XMRV*** or P-***XMRV***.

[0155] Antibodies can be developed with specific affinity for an ***XMRV*** strain associated proteins, or a proteins associated with group thereof, such as X-***XMRV*** or P-***XMRV***. Such antibodies specific for associated proteins can be used in an antibody-based assay for direct detection of ***XMRV*** virions or proteins in a sample (e.g., a sample from a subject).

[0156] One aspect provides distinguishing an ***XMRV*** strain described herein, for example on the basis of a polynucleotide or polypeptide described herein, from another ***XMRV*** virus, such as VP62 (SEQ ID NO: 1, SEQ ID NO: 162), VP35 (SEQ ID NO: 163), or VP42 (SEQ ID NO: 164). For example, detection of

[0164] As another example, the subject can be an animal, such as a laboratory animal that can serve as a model system for investigating a neuroimmune disease or lymphoma (see e.g., Chen, R. et al., Neurochemical Research 33: 1759-1767, 2008; Kumar, A., et al., Fundam. Clin. Pharmacol. Epub ahead of print, Jan. 10, 2009; Gupta, A., et al., Immunobiology 214: 33-39, 2009; Singh, A., et al., Indian J. Exp. Biol. 40: 1240-1244, 2002; Ford, R. J., et al. Blood 109: 4899-4906, 2007; Smith, M. R., et al., Leukemia 20: 891-893, 2006; Bryant, J., et al., Lab. Invest. 80: 557-573, 2000; M'kacher, R., et al., Cancer Genet Cytogenet. 143: 32-38, 2003).

[0165] A sample can be a blood sample, a serum sample, a plasma sample, a cerebrospinal fluid sample, or a solid tissue sample. For example, the sample can be a blood sample, such as a peripheral blood sample. As another example, a sample can be a solid tissue sample, such as a prostate tissue sample.

[0166] A sample can include cells of a subject. For example, a sample can include cells such as fibroblasts, endothelial cells, peripheral blood mononuclear cells, haematopoietic cells, or a combination thereof

[0167] Correlation of Presence of an ***XMRV*** Strain to Disease

[0168] Provided herein are methods for detecting, diagnosing, monitoring, or managing an ***XMRV***-related disease or condition, for example, a. neuroimmune disease, an ***XMRV***-related lymphoma, or both.

[0169] Detected presence or identification of an ***XMRV*** strain described herein in a subject, or a sample therefrom, can be correlated to a disease or condition associated with ***XMRV***. For example, ***XMRV*** has been found at high prevalence in subjects diagnosed with CFS (Lombardi et al., 2009) and in certain types of prostate cancer. However, the present inventors postulate that ***XMRV*** can be a causal factor in many neurological and neuroimmune diseases, including but not limited to autism and autism spectrum disorders, gulf war syndrome (GWS), Amyotrophic Lateral Sclerosis (ALS), Niemann-Pick Type C Disease, fibromyalgia, autism, chronic Lyme disease, Gulf War Syndrome, and non-epileptic seizures; and that different disease diagnoses or symptoms are caused by various ***XMRV*** strains described herein.

[0170] Examples of an ***XMRV***-related lymphoma include, but are not limited to an ***XMRV***-related Mantle Cell Lymphoma (MCL) and a Chronic Lymphocytic Leukemia lymphoma (CLL). Examples of an ***XMRV***-related neuroimmune disease include, but are not limited to Chronic Fatigue Syndrome (CFS), fibromyalgia, Multiple Sclerosis (MS), Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS), autism spectrum disorder (ASD), and chronic lyme disease. For example, CFS can be treated in a subject by administering a therapeutically effective amount of an anti-retroviral compound. As another example, MS, such as Atypical Multiple Sclerosis, can be treated in a subject by administering a therapeutically effective amount of an anti-retroviral compound or pharmaceutical composition including an anti-retroviral compound

[0171] In some cases, subjects infected with ***XMRV*** exhibit no persistent symptoms; i.e., they are apparently healthy. In other cases, subjects infected with ***XMRV*** are diagnosed with CFS. In other cases, subjects infected with ***XMRV*** are diagnosed with one or more cancer. In other cases, subjects infected with ***XMRV*** exhibit altered immune responses. In some cases, subjects infected with ***XMRV*** exhibit digestive-tract symptoms. Some subjects infected with ***XMRV*** develop multiple clinical symptoms, for example both CFS and cancer.

[0172] Therapeutic Methods

[0173] Also provided is a process of treating infection by an ***XMRV*** strain disclosed herein in a subject.

replication, or to suppress symptoms related to ***XMRV*** infection.

[0179] The amount of a composition described herein that can be combined with a pharmaceutically acceptable carrier to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be appreciated by those skilled in the art that the unit content of agent contained in an individual dose of each dosage form need not in itself constitute a therapeutically effective amount, as the necessary therapeutically effective amount could be reached by administration of a number of individual doses.

[0180] Toxicity and therapeutic efficacy of compositions described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals for determining the LD50 (the dose lethal to 50% of the population) and the ED50, (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index that can be expressed as the ratio LD50/ED50, where large therapeutic indices are preferred.

[0181] The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the composition employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts (see e.g., Koda-Kimble et al. (2004) Applied Therapeutics: The Clinical Use of Drugs, Lippincott Williams & Wilkins, ISBN 0781748453; Winter (2003) Basic Clinical Pharmacokinetics, 4th ed., Lippincott Williams & Wilkins, ISBN 0781741475; Sharqel (2004) Applied Biopharmaceutics & Pharmacokinetics, McGraw-Hill/Appleton & Lange, ISBN 0071375503). For example, it is well within the skill of the art to start doses of the composition at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose may be divided into multiple doses for purposes of administration. Consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by an attending physician within the scope of sound medical judgment.

[0182] Administration of an anti-retroviral agent, or a cocktail of anti-retroviral agents, can occur as a single event or over a time course of treatment. For example, an anti-retroviral agent, or a cocktail of anti-retroviral agents, can be administered daily, weekly, bi-weekly, or monthly. For treatment of acute conditions, the time course of treatment will usually be at least several days. Certain conditions could extend treatment from several days to several weeks. For example, treatment could extend over one week, two weeks, or three weeks. For more chronic conditions, treatment could extend from several weeks to several months or even a year or more.

[0183] Treatment in accord with the methods described herein can be performed prior to, concurrent with, or after conventional treatment modalities for any ***XMRV***-associated disease or condition described herein, such as an ***XMRV***-related neuroimmune disease or an ***XMRV***-related lymphoma.

[0184] An anti-retroviral agent, or a cocktail of anti-retroviral agents, can be administered simultaneously or sequentially with another agent, such as an antibiotic, an antiinflammatory, or another agent. For example, an anti-retroviral agent, or a cocktail of anti-retroviral agents, can be administered simultaneously with another agent, such as an antibiotic or an antiinflammatory. Simultaneous administration can occur through administration of separate compositions, each containing one or more of an anti-retroviral agent, or a cocktail of anti-retroviral agents, an antibiotic, an antiinflammatory, or another agent. Simultaneous administration can occur through administration of one composition

[0192] Also provided are kits. Such kits can include the compositions of the present invention and, in certain embodiments, instructions for use. Such kits can facilitate performance of the methods described herein. When supplied as a kit, the different components of the composition can be packaged in separate containers and admixed immediately before use. Components include, but are not limited to probes, antigens, primers, reaction mixture components, anti-retroviral agents, etc., useful for detecting or identifying an ***XMRV*** strain described herein. Such packaging of the components separately can, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the composition. The pack may, for example, comprise metal or plastic foil such as a blister pack. Such packaging of the components separately can also, in certain instances, permit long-term storage without losing activity of the components.

[0193] Kits may also include reagents in separate containers such as, for example, sterile water or saline to be added to a lyophilized active component packaged separately. For example, sealed glass ampules may contain a lyophilized component and in a separate ampule, sterile water, sterile saline or sterile each of which has been packaged under a neutral non-reacting gas, such as nitrogen. Ampules may consist of any suitable material, such as glass, organic polymers, such as polycarbonate, polystyrene, ceramic, metal or any other material typically employed to hold reagents. Other examples of suitable containers include bottles that may be fabricated from similar substances as ampules, and envelopes that may consist of foil-lined interiors, such as aluminum or an alloy. Other containers include test tubes, vials, flasks, bottles, syringes, and the like. Containers may have a sterile access port, such as a bottle having a stopper that can be pierced by a hypodermic injection needle. Other containers may have two compartments that are separated by a readily removable membrane that upon removal permits the components to mix. Removable membranes may be glass, plastic, rubber, and the like.

[0194] In certain embodiments, kits can be supplied with instructional materials. Instructions may be printed on paper or other substrate, or may be supplied as an electronic-readable medium, such as a floppy disc, mini-CD-ROM, CD-ROM, DVD-ROM, Zip disc, videotape, audio tape, and the like. Detailed instructions may not be physically associated with the kit; instead, a user may be directed to an Internet web site specified by the manufacturer or distributor of the kit.

[0195] Definitions and methods described herein are provided to better define the present invention and to guide those of ordinary skill in the art in the practice of the present invention. Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

[0196] In some embodiments, the numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth, used to describe and claim certain embodiments of the invention are to be understood as being modified in some instances by the term "about." Accordingly, in some embodiments, the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. In some embodiments, the numerical parameters should be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of some embodiments of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as practicable. The numerical values presented in some embodiments of the invention may contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0197] In some embodiments, the terms "a" and "an" and "the" and similar references used in the context of describing a particular embodiment of the invention (especially in the context of certain of the following claims) can be construed to cover both the singular and the plural. The recitation of ranges of

it once in PBS. The PBMCs (approximately 2.times.10.sup.7 cells) can be centrifuged at 500 g for 7 min and either stored as frozen unactivated cells in 90% FBS and 10% DMSO at -80.degree. C. for further culture and analysis or resuspended in TRIzol (Invitrogen) and stored at -80.degree. C. for DNA and RNA extraction and analysis. DNA can be isolated from TRIzol according the to manufacturer's protocol and also can be isolated from frozen PBMC pellets using the QIAamp DNA Mini purification kit (QIAGEN) according to the manufacturer's protocol and the final DNA can be resuspended in RNase/DNase free water and quantified using the Quant-iT.TM. Pico Green dsDNA Kit (Invitrogen). RNA can be isolated from TRIzol according to the manufacturer's protocol and quantified using the Quant-iT Ribo Green RNA kit (Invitrogen). cDNA can be made from RNA using the iScript Select cDNA synthesis kit (Bio-Rad) according to the manufacturer's protocol.

Example 2

[0205] This example describes methods of amplifying, and determining the nucleic acid sequence of, ***XMRV*** polynucleotides.

[0206] PCR. Nested PCR can be performed with separate reagents in a separate laboratory room designated to be free of high copy amplicon or plasmid DNA. Negative controls in the absence of added DNA can be included in every experiment. Identification of ***XMRV*** gag and env genes can be performed by PCR in separate reactions. Reactions can be performed as follows: 100 to 250 ng DNA, 2 .mu.L of 25 mM MgCl2, 25 .mu.L of HotStart-IT FideliTaq Master Mix (USB Corporation), 0.75 .mu.L of each of 20 .mu.M forward and reverse oligonucleotide primers in reaction volumes of 50 .mu.L. For identification of gag, 419F (5'-ATCAGTTAACCTACCCGAGTCGGAC-3') (SEQ ID NO: 7) and 1154R (5'-GCCGCCTCTTCTTCATTGTTCTC-3') (SEQ ID NO: 8) can be used as forward and reverse primers. For env, 5922F (5'-GCTAATGCTACCTCCCTCCTGG-3') (SEQ ID NO: 9) and 6273R (5'-GGAGCCCACTGAGGAATCAAAACAGG-3') (SEQ ID NO: 10) can be used. For both gag and env PCR, 94.degree. C. for 4 min initial denaturation can be performed for every reaction followed by 94.degree. C. for 30 seconds, 57.degree. C. for 30 seconds and 72.degree. C. for 1 minute The cycle can be repeated 45 times followed by final extension at 72.degree. C. for 2 minutes. Six microliters of each reaction product can be loaded onto 2% agarose gels in TBE buffer with 1 kb+ DNA ladder (Invitrogen) as markers. PCR products can be purified using Wizard SV Gel and PCR Clean-Up kit (Promega) and sequenced. PCR amplification for sequencing full-length ***XMRV*** genomes can be performed on DNA amplified by nested or semi-nested PCR from overlapping regions from PBMC DNA. For 5' end amplification of R-U5 region, 4F (5'-CCAGTCATCCGATAGACTGAGTCGC-3') (SEQ ID NO: 11) and 1154R can be used for first round and 4F and 770R (5'-TACCATCCTGAGGCCATCCTACATTG-3') (SEQ ID NO: 12) can be used for second round. For regions including gag-pro and partial pol, 350F(5'-GAGTTCGTATTCCCGGCCGCAGC-3') (SEQ ID NO: 13) and 5135R (5'-CCTGCGGCATTCCAAATCTCG-3') (SEQ ID NO: 14) can be used for first round followed by second round with 419F and 4789R (5'-GGGTGAGTCTGTGTAGGGAGTCTAA-3') (SEQ ID NO: 15). For regions including partial pol and env region, 4166F (5'- CAAGAAGGACAACGGAGAGCTGGAG-3') (SEQ ID NO: 16) and 7622R (5'- GGCCTGCACTACCGAAAT TCTGTC-3') (SEQ ID NO: 17) can be used for first round followed by 4672F (5'-GAGCCACCTACAATCAGACAAAAGGAT-3') (SEQ ID NO: 18) and 7590R (5'-CTGGACCAAGCGGTTGAGAATACAG-3') (SEQ ID NO: 19) for second round. For the 3' end including the U3-R region, 7472F (5'-TCAGGACAAGGGTGGTTTGAG-3') (SEQ ID NO: 20) and 8182R (5'-CAAACAGCAAAAGGCTTTATTGG-3') (SEQ ID NO: 21) can be used for first round followed by 7472F and 8147R (5'-CCGGGCGACTCAGTCTATC-3') (SEQ ID NO: 22) for second round. The reaction mixtures and conditions can be as described above except for the following: For larger fragments, extension can be done at 68.degree. C. for 10 min instead of 72.degree. C. All second round PCR products can be column purified as mentioned above and overlapping sequences can be determined with internal primers. Nested RT-PCR for gag sequences can be done as described with modifications. GAG-O-R primer can be used for 1st strand synthesis; cycle conditions can be 52.degree.

[0214] Analysis of the MA sequences revealed the variants could be classified into three subgroups (see e.g., FIG. 5C). These subgroup delineations are supported by unrooted neighbor-joining analysis of the MA nucleotide sequence fragment. Seven of the sequences, which fell into subgroup A, are closely related to the previously published sequences of ***XMRV*** in this region (see e.g., FIG. 5C, lines 2-8, compare with line 1). At most, this group differed by 3 nucleotides from the reference strain VP62; one resulted in a synonymous change (i.e., the same residue was encoded). and two were non-synonymous (see e.g., TABLE 1). The non-synonymous substitution, nt 178: G.fwdarw.A, is present in all of the sequences in subgroup A (G178A), and has also been previously reported to be present in other ***XMRV*** sequences (see e.g., TABLE 1).

[0215] Eight of the seventeen (8/17) sequences analyzed fell into a second group (subgroup B), all of which had a 21 by deletion, resulting in an in-frame deletion of seven amino acid residues. All sequences in subgroup B also had seven specific nucleotide substitutions relative to the sequence of the ***XMRV*** reference strain (nt 75: C.fwdarw.T, nt 85: G.fwdarw.A, nt 91: A.fwdarw.G, nt 92: A.fwdarw.G, nt 304: C.fwdarw.G, nt 315: C.fwdarw.T, and nt 316: C.fwdarw.T) (see e.g., FIG. 1B lines 9-17), of which were four were synonymous and three were non-synonymous changes (see e.g., TABLE 1).

[0216] Subgroup C contained two sequences and was characterized by three unique nucleotide substitutions (nt 106: G.fwdarw.A, nt 175: G.fwdarw.A, and nt 192: C.fwdarw.T) (see e.g., FIG. 4, lines 17 and 18; and TABLE 1), of which two were synonymous and one was a non-synonymous change. This group also had three nucleotide substitutions relative to VP62 that were in common with members of groups A and B (nt 92: A.fwdarw.G, nt 178: G.fwdarw.A, nt 325: A.fwdarw.G).

[0217] To gain insight into whether the variation observed in the ***XMRV*** sequences could be tolerated by the MA protein and persist in nature, MA protein sequences of gammaretroviruses from other mus muculus and other species examined Alignment of MA proteins of other members gammaretrovirus genus revealed that 5 of the 6 amino acid changes in the ***XMRV*** variants are present in other infectious gammaretroviruses (see e.g., TABLE 4 and FIG. 2).

Example 5

[0218] This example describes analysis of ***XMRV*** MA sequences in lymphocytes following ex vivo ***XMRV*** culture. Unless otherwise described, methods are as in Examples, 1-4.

[0219] ***XMRV*** RNA could not always be detected in the PBMCs of subjects from which infectious virus had been isolated from plasma. This suggests that the virus is expressed at very low frequency in PBMCs isolated directly from infected individuals. We have observed that culturing these PBMCs under conditions that induce activation of T cells increases the frequency of ***XMRV*** detected by RT-PCR in the cells maintained in culture. This increase appears to be dependent on the spread of the virus, since the addition of a reverse transcriptase inhibitor to the cultures prior to activation prevents the increase ***XMRV*** expression, as measured by cell surface expression of Env (see e.g., FIG. 3). To biologically increase the level of ***XMRV*** and increase the probability that ***XMRV*** sequences could be detected by PCR, PBMCs were cultured under conditions that activated T cells for 7-10 days, the RNA isolated, and nested RT-PCR analysis performed as described above.

[0220] All MA sequences amplified following ex vivo culture could be classified into two out of the three subgroups observed in the analysis of RNA from unactivated PBMCs. Sequences for 4/11 individuals were similar to the previously published sequences (subgroup A) (see e.g., FIG. 6A, lines 2-5). Sequences amplified from another 6 individuals fell into subgroup C(see e.g., FIG. 6A, lines 6-12). Unrooted neighbor-joining analysis of nucleotide sequences direct from subject PBMCs and after ex vivo culture reflected the variability noted in the sequence analysis and confirmed that post-culture, only variants A

gag and pol (Rmcf provirus) (see Jorgensen et al. 1992 J Virol 66(7) 4479-4487). Others in this group differed in nucleotide sequence from sequenced variants. But these substitutions were generally synonymous ands resulted in conservation of the MA sequences at the amino acid level. Thus, in this study, MA sequences of ***XMRV*** subgroup B and C are more homologous to known endogenous sequences that the ***XMRV*** subgroup A viruses.

[0230] ***XMRV*** sequences were also analyzed to determine their relatedness to MLVs generally. The consensus sequence for the N-terminus of the Env protein of ***XMRV*** is similar to the Env protein of Spleen Focus Forming Virus (SFFV; see e.g., FIG. 4), consistent with the inventors' previous use of antibodies originally raised against SFFV to recognize ***XMRV***. FIG. 8 shows the nucleotide variation between sequences encoding MA protein in several ***XMRV*** isolates, and in two other MLVs. FIGS. 9 is a phylogenetic tree showing the relatedness of a number of separate ***XMRV*** isolates to each other and to other gammaretroviruses. FIGS. 11A-B show the sequence variation in clinical isolates of ***XMRV, the XMRV*** reference strain VP62, and other MLVs.

Example 8

[0231] This example shows that APOBEC may be responsible for variation in clinically isolated ***XMRV*** sequences.

[0232] APOBEC3 restriction factors are cellular proteins capable of blocking replication of many retroviruses. Others (Groom et al., PNAS 2010, 107(11): 5166-5171; Stieler and Fischer, PLoS One 2010, el1738; Paprotka et al., J Virology 2010, 84(11):5719-5729) have shown that expression of human APOBEC3G ("hA3G") in cells infected with ***XMRV*** dramatically reduced viral titer and caused G-to-A hypermutation of the viral DNA. However, it is not clear that APOBEC restriction factors would regulate ***XMRV*** infection: APOBECs are generally expressed at only low levels even in those cells which do express them; ***XMRV*** normally infects a subset of lymphocytes that are known not to express APOBEC proteins; and ***XMRV*** has specific countermeasures to evade hA3G. To determine if hA3G is a natural regulator of ***XMRV*** infection, then, the present inventors looked for hallmarks of APOBEC activity on ***XMRV*** sequences isolated from peripheral blood mononuclear cells ("PBMCs") from ***XMRV***-infected individuals.

[0233] Experiments examined the ***XMRV*** derived from PBMCs from infected individuals for evidence of APOBEC-associated hypermutation using methods as described in Examples 1-8, unless otherwise specified. PBMCs were isolated from ***XMRV***-infected individuals, and B "cell lines" were generated from the PBMCs. ***XMRV*** was then isolated from the cell lines and the DNA was cloned and sequenced.

[0234] Data not shown and FIGS. 12-13 show that the ***XMRV*** sequences from infected individuals have G-to-A changes consistent with hA3G activity in both Gag and Env coding regions. The data shows a clear preference for substitutions at GG dinucleotides, consistent with the A3G form of APOBEC, as opposed to the A3F form, which targets GA dinucleotides. These highly mutated ***XMRV*** isolates were nevertheless able to infect LNCaP cells at similar rates as wild-type ***XMRV*** (data not shown), and were able to produce translatable ***XMRV*** proteins (eg, FIG. 13). The data suggest, therefore, that APOBEC may be responsible for the high amount of sequence diversity between clinically isolated ***XMRV*** sequences.

Example 9

[0235] This example shows the variation in clinically isolated ***XMRV*** sequences. Methods are as in Examples 1-8 unless otherwise specified.

propagated in mice after castration-induced regression and relapse of the parental, androgen-dependent CWR22 xenograft. Recently, it has been shown that 22Rv1 prostate carcinoma cells produce high-titer of ***XMRV***.

[0247] In this blinded study, ***XMRV*** was detected by: PCR was performed directly on patient plasma; serological assay; and isolation of virus. TABLE 6 shows the results from different types of assays for the presence of ***XMRV,*** and the results of experiments to determine the sequences of the isolated viruses.

TABLE-US-00007 TABLE 6 Results of assays for ***XMRV*** in the study of German CFS patients. Sample Antibody Plasma PCR 100% Sequence Homology 3101 HD6E - + 22Rv1 3102 HD7E - + 22Rv1 3103 HD8E - + 22Rv1 1748 HD9E - + VP62 1716 HD18E - + VP62 1723 HD19E + + VP62

Example 14

[0248] This example shows that clones of Env sequences amplified from PBMCs from subject WPI-1104 are similar to sequences from polytropic MLVs. Methods are as in Examples 1-14 unless otherwise specified.

[0249] In this example, virus was cultured from PBMCs from subject WPI-1104. The cultured viruses were then used to infect LNCaP cells, and virus was reisolated from those cells and the polynucleic acids were sequenced. Greater than 50 cultures of LNCaP cells have been infected using WPI-1104-derived virus. A representative selection of resulting sequence data is shown in an alignment in FIG. 22. The sequences isolated from this subject are more closely related to polytropic MLVs than to VP62.

[0250] This finding suggests that some ***XMRV***-type viruses may replicate more efficiently in LNCaP cells.

Sequence CWU 1

18018185DNAXenotropic murine leukemia virus 1gcgccagtca tccgatagac tgagtcgccc gggtacccgt gttcccaata aagccttttg 60ctgtttgcat ccgaagcgtg gcctcgctgt tccttgggag ggtctcctca gagtgattga 120ctaccccagct cgggggtctt tcatttgggg gctcgtccgg gatttcggaga ccccccgccca 180gggaccaccg accccaccgtc gggaggtaag ccggccggcg atcgttttgt ctttgtctct 240gtctttgtgc gtgtgtgtgt gtgccggcat ctaatcctcg cgcctgcgtc tgaatctgta 300ctagttagct aactagatct gtatctggcg gttccgcgga agaactgacg agttcgtatt 360ccccgggccgca gcccctgggag acgtcccagc ggcctcgggg gcccgttttg tggcccattc 420tgtatcagtt aacctacccg agtcggactt tttggagtgg ctttgttggg ggacgagaga 480cagagacact tcccgccccc gtctgaattt ttgctttcgg ttttacgccg aaaccgcgcc 540gcgcgtctga tttgttttgt tgttcttctg ttcttcgtta gttttcttct gtctttaagt 600gttctcgaga tcatgggaca gaccgtaact acccctctga gtctaacctt gcagcactgg 660ggagatgtcc agcgcattgc atccaaccag tctgtggatg tcaagaagag gcgctgggtt 720accttctgtt ccgccgaatg gccaactttc aatgtaggat ggcctcagga tggtactttt 780aatttaggtg ttatctctca ggtcaagtct agagtgtttt gtcctggtcc ccacggacac 840ccggatcagg tcccatatat cgtcacctgg gaggcacttg cctatgaccc cgctccgtgg 900gtcaaaccgt ttgtctctcc taaacccccc cctttaccga cagctcccgt cctcccgccc 960ggtccttctg cgcaacctcc gtcccgatct gccctttacc ctgcccttac ccctctata 1020aagtccaaac ctcctaagcc ccaggttctc cctgatagcg gcggacctct cattgacctt 1080ctcacagagg atcccccgcc gtacggagca caaccttcct cctctgccag ggagaacaat 1140gaagaagagg cggccaccac ctccgaggtt tccccccctt ctcccatggt gtctcgactg 1200cggggaagga gagaccctcc cgcagcggac tccaccacct cccaggcatt cccactccgc 1260atgggggggag atggccagct tcagtactgg ccgttttcct cctctgattt atataattgg 1320aaaaataata acccttcctt ttctgaagat ccaggtaaat tgacggcctt gattgagtcc 1380gtcctcatca cccaccagcc cacctgggac gactgtcagc agttgttggg gacccctgctg 1440accggagaag aaaagcagcg ggtgctccta gaggctagaa aggcagtccg gggcaatgat 1500ggacgccccca ctcagttgcc taatgaagtc aatgctgctt ttcccccttga gcgccccgat 1560tgggattaca ccactacaga aggtaggaac cacctagtcc tctaccgcca gttgctctta 1620gcgggtctcc aaaacgcggg caggagcccc accaatttgg ccaaggtaaa agggataacc 1680cagggaccta atgagtctcc ctcagccttt ttagagagac tcaaggaggc ctatcgcagg 1740tacactcctt atgaccctga ggacccaggg caagaaacca atgtgtccat gtcattcatc 1800tggcagtctg ccccggatat

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Ala Leu1 5 10 15Glu Lys Ser Val Ser Ala Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu 20 25 30Val Val Leu Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe Leu Lys Glu 35 40 45Gly Gly Leu Cys Ala Ala Leu Lys Glu Glu Cys Cys Phe Tyr Ala Asp 50 55 60His Thr Gly Val Val Arg Asp Ser Met Ala Lys Leu Arg Glu Arg Leu65 70 75 80Asn Gln Arg Gln Lys Leu Phe Glu Ser Arg Gln Gly Trp Phe Glu Gly 85 90 95Leu Phe Asn Arg Ser Pro Trp Phe Thr Thr Leu 100 1056647PRTXenotropic murine leukemia virus 66Phe Glu Gln Leu Gln Ala Ala Ile His Thr Asp Leu Gly Ala Leu Glu1 5 10 15Lys Ser Val Ser Ala Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu Val 20 25 30Val Leu Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe Leu Lys Glu 35 40 4567104PRTXenotropic murine leukemia virus 67Phe Glu Gln Leu Gln Ala Ala Ile His Thr Asp Leu Gly Ala Leu Glu1 5 10 15Lys Ser Val Ser Ala Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu Val 20 25 30Val Leu Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe Leu Lys Glu Gly 35 40 45Gly Leu Cys Ala Ala Leu Lys Glu Glu Cys Cys Phe Tyr Ala Asp His 50 55 60Thr Gly Val Val Arg Ala Ser Met Ala Lys Leu Arg Glu Arg Leu Asn65 70 75 80Gln Arg Gln Lys Leu Phe Glu Ser Gly Gln Gly Trp Phe Glu Gly Leu 85 90 95Phe Asn Arg Ser Pro Trp Phe Thr 10068102PRTXenotropic murine leukemia virus 68Gln Leu Gln Ala Ala Ile His Thr Asp Leu Gly Ala Leu Glu Lys Ser1 5 10 15Val Ser Ala Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu Val Val Leu 20 25 30Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe Leu Lys Glu Gly Gly Leu 35 40 45Cys Ala Ala Leu Lys Glu Glu Cys Cys Phe Tyr Ala Asp His Thr Gly 50 55 60Val Val Arg Asp Ser Met Ala Lys Leu Arg Glu Arg Leu Asn Gln Arg65 70 75 80Gln Lys Leu Phe Glu Ser Gly Gln Gly Trp Phe Glu Gly Leu Phe Asn 85 90 95Arg Ser Pro Trp Phe Thr 10069122PRTXenotropic murine leukemia virus 69Gln Leu Gln Ala Ala Ile His Thr Asp Leu Gly Ala Leu Glu Lys Ser1 5 10 15Val Ser Ala Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu Val Val Leu 20 25

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tt 332105329DNAXenotropic murine leukemia virus 105tgtccagcgc attgcatcca accagtctgt ggatgtcaag aagaggcgct gggttacctt 60ctgttccgcc gaatggccaa ctttcaatgt aggatggcct caggatggta cttttaattt 120aggtgttatc tctcaggtca atctagagtg ttttgtcctg gtccccacgg acacccggat 180caggtcccat atatcgtcac ctgggaggca cttgcctatg acccccctcc gtgggtcaaa 240ccgtttgtct ctcctaaacc ccctccttta ccgacagctc ccgtcctccc gccccggtcct 300tctgcgcaac ctccgtcccg atctgccca 329106316DNAXenotropic murine leukemia virus 106tggatgtcaa gaagaggcgc tgggttacct tctgttccgc cgaatggcca actttcaatg 60taggatggcc tcaggatggt acttttaatt taggtgttat ctctcaggtc aagtctagag 120tgttttgtcc tggtccccac ggacacccgg atcaggtccc atatatcgtc acctgggagg 180cacttgccta tgaccccccct ccgtgggtca aaccgtttgt ctctcctaaa ccccctcctt 240taccgacagc tcccgtcctc ccgccccggtc cttctgcgca acctccgtcc cgatctgccc 300tttaccctgc ccttac 316107334DNAXenotropic murine leukemia virus 107gcatccaacc agtctgtgga tgtcaagaag aggcgctggg ttaccttctg ttccgccgaa 60tggccaactt tcaatgtagg atggcctcag gatggtactt ttaatttagg tgttatctct 120caggtcaagt ctagagtgtt ttgtcctggt ccccacggac acccggatca ggtcccatat 180atcgtcacct gggaggcact tgcctatgac ccccctccgt gggtcaaacc gtttgtctct 240cctaaacccc ctcctttacc gacagctccc gtcctcccgc cccggtccttc tgcgcaacct 300ccgtcccgat ctgcccttta ccctgccctt accc 334108340DNAXenotropic murine leukemia virus 108tccagcgcat tgcatccaac cagtctgtgg atgtcaagaa gaggcgctgg gttaccttct 60gttccgccga atggccaact ttcaatgtag gatggcctca ggatggtact tttaatttag 120gtgttatctc tcaggtcaag tctagagtgt tttgtcctgg tccccacgga cacccggatc 180aggtcccata tatcgtcacc tgggaggcac ttgcctatga ccccccctccg tgggtcaaac 240cgtttgtctc tcctaaaccc cctcctttac cgacagctcc cgtcctcccg ccccggtcctt 300ctgcgcaacc tccgtcccga tctgcccttt accctgccct 340109343DNAXenotropic murine leukemia virus 109tccagcgcat tgcatccaac cagtctgtgg atgtcaagaa gaggcgctgg gttaccttct 60gttccgccga atggccaact ttcaatgtag gatggcctca ggatggtact tttaatttag 120gtgttatctc tcaggtcaag tctagagtgt tttgtcctgg tccccacgga cacccggatc 180aggtcccata tatcgtcacc tgggaggcac 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114gtccagcgca ttgcatccaa ccagtctgtg gatgtcaaga agaggcgctg ggttaccttc 60tgttccgccg aatggccaac tttcaatgta ggatggcctc aggatggtac ttttaattta

Pro His Gly His Pro Asp Gln Val Pro Tyr 50 55 60Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys65 70 75 80Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu 85 90 95Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro 100 105 110Ala Leu124111PRTXenotropic murine leukemia virus 124Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg1 5 10 15Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp 20 25 30Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser 35 40 45Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr 50 55 60Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys65 70 75 80Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu 85 90 95Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr 100 105 110125113PRTXenotropic murine leukemia virus 125Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg1 5 10 15Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp 20 25 30Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser 35 40 45Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr 50 55 60Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys65 70 75 80Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu 85 90 95Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro 100 105 110Ala126114PRTXenotropic murine leukemia virus 126Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg Trp1 5 10 15Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe

Asn Val Gly Trp Pro 20 25 30Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser Arg 35 40 45Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr Ile 50 55 60Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys Pro65 70 75 80Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu Pro 85 90 95Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro Ala 100 105 110Leu Thr127116PRTXenotropic murine leukemia virus 127Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg1 5 10 15Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp 20 25 30Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser 35 40 45Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr 50 55 60Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys65 70 75 80Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu 85 90 95Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro 100 105 110Ala Phe Thr Leu 115128115PRTXenotropic murine leukemia virus 128Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg1 5 10 15Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp 20 25 30Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser 35 40 45Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr 50 55 60Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys65 70 75 80Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu 85 90 95Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro 100 105 110Ala Leu Thr 115129114PRTXenotropic murine leukemia virus 129Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg1 5 10 15Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp 20 25 30Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser 35 40 45Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr 50 55 60Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys65 70 75 80Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu 85 90 95Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro 100 105 110Ala Tyr130116PRTXenotropic murine leukemia virus 130Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg1 5 10 15Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp 20 25 30Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser 35 40 45Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr 50 55 60Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys65 70 75 80Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu 85 90 95Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro 100 105 110Ala Leu Thr Leu 115131114PRTXenotropic murine leukemia virus 131Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg Trp1 5 10 15Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp Pro 20 25 30Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser Arg 35 40 45Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr Ile 50 55 60Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys Pro65 70 75 80Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu Pro 85 90 95Pro

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Trp Pro1 5 10 15Thr Phe Asn Val Gly Trp Pro Gln Asp Gly Thr Phe Asn Leu Gly Val 20 25 30Ile Ser Gln Val Lys Ser Arg Val Phe Cys Pro Gly Pro His Gly His 35 40 45Pro Asp Gln Val Pro Tyr Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp 50 55 60Pro Pro Pro Trp Val Lys Pro Phe Val Ser Pro Lys Pro Pro Pro Leu65 70 75 80Pro Thr Ala Pro Val Leu Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser 85 90 95Arg Ser Ala Leu Tyr Pro Ala Leu 100148111PRTXenotropic murine leukemia virus 148Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg Trp Val Thr Phe1 5 10 15Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp Pro Gln Asp Gly 20 25 30Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser Arg Val Phe Cys 35 40 45Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr Ile Val Thr Trp 50 55 60Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys Pro Phe Val Ser65 70 75 80Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu Pro Pro Gly Pro 85 90 95Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro Ala Leu Thr 100 105 110149112PRTXenotropic murine leukemia virus 149Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg Trp1 5 10 15Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp Pro 20 25

Arg Cys Asn Pro Leu Val Leu Glu Phe 180 185 190Thr Asp Ala Gly Lys Arg Ala Ser Trp Asp Ala Pro Lys Thr Trp Gly 195 200 205Leu Arg Leu Tyr Arg Ser Thr Gly Ala Asp Pro Val Thr Leu Phe Ser 210 215 220Leu Thr Arg Gln Val Leu Asn Val Gly Pro Arg Val Pro Ile Gly Pro225 230 235 240Asn Pro Val Ile Thr Glu Gln Leu Pro Pro Ser Gln Pro Val Gln Ile 245 250 255Met Leu Pro Arg Thr Pro Arg Pro Pro Pro Ser Gly Ala Ala Ser Met 260 265 270Val Pro Gly Ala Pro Pro Pro Ser Gln Gln Pro Gly Thr Gly Asp Arg 275 280 285Leu Leu Asn Leu Val Glu Gly Ala Tyr Leu Ala Leu Asn Leu Thr Ser 290 295 300Pro Asp Lys Thr Gln Glu Cys Trp Leu Cys Leu Val Ser Gly Pro Pro305 310 315 320Tyr Tyr Glu Gly Val Ala Val Leu Gly Thr Tyr Ser Asn His Thr Ser 325 330 335Ala Pro Ala Asn Cys Ser Val Thr Ser Gln His Lys Leu Thr Leu Ser 340 345 350Glu Val Thr Gly Gln Gly Leu Cys Ile Gly Ala Val Pro Lys Thr His 355 360 365Gln Ala Leu Cys Asn Thr Thr Gln Lys Thr Ser Asp Gly Ser Tyr Tyr 370 375 380Leu Ala Ser Pro Ala Gly Thr Ile Trp Ala Cys Ser Thr Gly Leu Thr385 390 395 400Pro Cys Leu Ser Thr Thr Val Leu Asn Leu Thr Thr Asp Tyr Cys Val 405 410 415Leu Val Glu Leu Trp Pro Lys Val Thr Tyr His Ser Pro Asn Tyr Val 420 425 430Tyr Gly Gln Phe Glu Lys Lys Thr Lys Tyr Lys Arg Glu Pro Val Ser 435 440 445Leu Thr Leu Ala Leu Leu Leu Gly Gly Leu Thr Met Gly Gly Ile Ala 450 455 460Ala Gly Val Gly Thr Gly Thr Thr Ala Leu Val Ala Thr Lys Gln Phe465 470 475 480Glu Gln Leu Gln Ala Ala Ile His Thr Asp Leu Gly Ala Leu Glu Lys 485 490 495Ser Val Ser Ala Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu Val Val 500 505 510Leu Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe Leu Lys Glu Gly Gly 515 520 525Leu Cys Ala Ala Leu Lys Glu Glu Cys Cys Phe Tyr Ala Asp His Thr 530 535 540Gly Val Val Arg Asp Ser Met Ala Lys Leu Arg Glu Arg Leu Asn Gln545 550 555 560Arg Gln Lys Leu Phe Glu Ser Gly Gln Gly Trp Phe Glu Gly Leu Phe 565 570 575Asn Arg Ser Pro Trp Phe Thr Thr Leu Ile Ser Thr Ile Met Gly Pro 580 585 590Leu Ile Val Leu Leu Leu Leu Ile Leu Leu Phe Gly Pro Cys Ile Leu Asn 595 600 605Arg Leu Val Gln Phe Val Lys Asp Arg Ile Ser Val Val Gln Ala Leu 610 615 620Val Leu Thr Gln Gln Tyr His Gln Leu Lys Ser Ile Asp Pro Glu Glu625 630 635 640Val Glu Ser Arg Glu 6451611733PRTXenotropic murine leukemia virusmisc_feature(537)..(537)Xaa can be any naturally occurring amino acid 161Met Gly Gln Thr Val Thr Thr Pro Leu Ser Leu Thr Leu Gln His Trp1 5 10 15Gly Asp Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys 20 25 30Arg Arg Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val 35 40 45Gly Trp Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val 50 55 60Lys Ser Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val65 70 75 80Pro Tyr Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp 85 90 95Val Lys Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro 100 105 110Val Leu Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu 115 120 125Tyr Pro Ala Leu Thr Pro Ser Ile Lys Ser Lys Pro Pro Lys Pro Gln 130 135 140Val Leu Pro Asp Ser Gly Gly Pro Leu Ile Asp Leu Leu Thr Glu Asp145 150 155 160Pro Pro Pro Tyr Gly Ala Gln Pro Ser Ser Ser Ala Arg Glu Asn Asn 165 170 175Glu Glu Glu Ala Ala Thr Thr Ser Glu Val Ser Pro Pro Ser Pro Met 180 185 190Val Ser Arg Leu Arg Gly Arg Arg Asp Pro Pro Ala Ala Asp Ser Thr 195 200 205Thr Ser Gln Ala Phe Pro Leu Arg Met Gly Gly Asp Gly Gln Leu Gln 210 215 220Tyr Trp Pro Phe Ser Ser Ser Asp Leu Tyr Asn Trp Lys Asn Asn Asn225 230 235 240Pro Ser Phe Ser Glu Asp Pro Gly Lys Leu Thr Ala Leu Ile Glu Ser 245 250 255Val Leu Ile Thr His Gln Pro Thr Trp Asp Asp Cys Gln Gln Leu Leu 260 265 270Gly Thr Leu Leu Thr Gly Glu Glu Lys Gln Arg Val Leu Leu Glu Ala 275 280 285Arg Lys Ala Val Arg Gly Asn Asp Gly Arg Pro Thr Gln Leu Pro Asn 290 295 300Glu Val Asn Ala Ala Phe Pro Leu Glu Arg Pro Asp Trp Asp Tyr Thr305 310 315 320Thr Thr Glu Gly Arg Asn His Leu Val Leu Tyr Arg Gln Leu Leu Leu 325 330 335Ala Gly Leu Gln Asn Ala Gly Arg Ser Pro Thr Asn Leu Ala Lys Val 340 345 350Lys Gly Ile Thr Gln Gly Pro Asn Glu Ser Pro Ser Ala Phe Leu Glu 355 360 365Arg Leu Lys Glu Ala Tyr Arg Arg Tyr Thr Pro Tyr Asp Pro Glu Asp 370 375 380Pro Gly Gln Glu Thr Asn Val Ser Met Ser Phe Ile Trp Gln Ser Ala385 390 395 400Pro Asp Ile Gly Arg Lys Leu Glu Arg Leu Glu Asp Leu Lys Ser Lys 405 410 415Thr Leu Gly Asp Leu Val Arg Glu Ala Glu Lys Ile Phe Asn Lys Arg 420 425 430Glu Thr Pro Glu Glu Arg Glu Glu Arg Ile Arg Arg Glu Ile Glu Glu 435 440 445Lys Glu Glu Arg Arg Arg Ala Glu Asp Glu Gln Arg Glu Arg Glu Arg 450 455 460Asp Arg Arg Arg His Arg Glu Met Ser Lys Leu Leu Ala Thr Val Val465 470 475 480Ile Gly Gln Arg Gln Asp Arg Gln Gly Gly Glu Arg Arg Arg Pro Gln 485 490 495Leu Asp Lys Asp Gln Cys Ala Tyr Cys Lys Glu Lys Gly His Trp Ala 500 505 510Lys Asp Cys Pro Lys Lys Pro Arg Gly Pro Arg Gly Pro Arg Pro Gln 515 520 525Thr Ser Leu Leu Thr Leu Gly Asp Xaa Gly Gly Gln Gly Gln Glu Pro 530 535 540Pro Pro Glu Pro Arg Ile Thr Leu Lys Val Gly

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