VP1 DNA sequences of JC and BK viruses detected in urine of systemic lupus erythematosus patients reveal no differences from strains expressed in normal individuals

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The ubiquitous human polyomaviruses BK (BKV) and JC (JCV) persist with no adverse effects in immunocompetent individuals. Virus-induced pathogenesis has been linked to virus reactivation during impaired immune conditions. Previous studies have shown a significant difference between the VP1 DNA sequences of JCV obtained from control urine samples and those in progressive multifocal leukoencephalopathy brain samples. This difference could not be detected when comparing normal control urinary JCV DNA with DNA sequences from chronic progressive multiple sclerosis patients. Since BKV and JCV are readily activated in systemic lupus erythematosus (SLE) patients, the presence of specific strains, related to VP1 DNA sequences, was investigated in these patients. VP1 DNA sequences in 100 urine samples from 21 SLE patients and 75 urine samples from 75 healthy pregnant women were analysed and compared to previously reported sequences. The results show that the VP1 sequence profiles of JCV and BKV excreted by SLE patients do not differ significantly from those excreted by immunocompetent individuals. The European JCV subtypes 1A or 1B were represented among all JCV-positive urine specimens, while BKV VP1 sequences showed complete, or almost complete, identity with the MM or JL strains. Different urine samples from the same patient collected over a 1 year period were predominantly stable. BKV VP1 DNA in urine specimens from healthy pregnant women was only detected during the third trimester of their pregnancy. These results argue against SLE-specific JCV and BKV strains and suggest reactivation of the viruses rather than recurrent re-infections of patients with SLE.

Introduction
Serological studies have shown that the human polyomaviruses BK (BKV) and JC (JCV) are residing in almost the entire population. Primary infection occurs predominantly during childhood and appears, with a few exceptions, to be subclinical. Few cases of BKV-induced mild respiratory or urinary tract diseases, pyrexia, fatal disseminated infection and haemorrhagic cystitis have been reported in immunosuppressed patients (Mäntyrävi et al., 1973; Goudsmit et al., 1982; Valbracht et al., 1993; reviewed by Dörries, 1997; Imperiale, 2000). Primary infection is, however, normally followed by a lifelong, asymptomatic persistence in immunocompetent individuals (reviewed by Shah, 1996). The route of infection and the targets for persistence remain largely unknown, but the brain, kidneys and peripheral blood cells have been shown to harbour these viruses (reviewed by Dörries, 1997). BKV DNA has also been found in tonsils (Goudsmit et al., 1982), while JCV DNA was detected in spleen, liver, lymph nodes and lung cells (Chester et al., 1983; Greenlee, 1983; Newman & Frisque, 1999). Under conditions of immune suppression, JCV can cause progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease (Pajunen et al., 1971).

Monitoring the presence of viruria in a patient provides a good indication of the activation state of BK and JC viruses. In healthy Asian individuals JCV viruria occurs in about 6% of youngsters, but increases to 30–50% after the age of 20 and then gradually rises to over 60% in the older population, as assayed by PCR (Kitamura et al., 1990; Agostini et al., 1996). However, it seems that JCV viruria has a higher prevalence in...
Asian countries compared to Western countries (Kitamura et al., 1990; Markowitz et al., 1993; Sundsfjord et al., 1994; Agostini et al., 1996; Tsai et al., 1997). BKV viruria is rare (<1%) in healthy individuals (Rekvig et al., 1997; Itoh et al., 1998). During pregnancy an increasing number of women excreted human polyomavirus as a result of reactivation rather than primary infection. The onset of viruria was late in the second trimester and during the third trimester (Arthur & Shah, 1989). In a later study, up to 15% and 7% of urine samples contained BKV or JCV, respectively (Markowitz et al., 1997; Guo et al., 1998). The BKV and JCV DNA in the urine of these patients revealed predominantly stable archetypal regulatory regions for up to 3 years of observation, indicating the presence of naturally occurring archetypal strains (Sundsfjord et al., 1999). Sequence analysis of VP1 DNA obtained by PCR from cerebrospinal fluid samples of two human immunodeficiency virus type 1-positive patients with PML revealed a deletion of eight or nine amino acid residues, respectively. Although not examined by the authors, Melucci-Vigo et al. (1994) postulated that these strains could have a selective growth advantage compared to wild-type JCV strains and perhaps even be more virulent. Their hypothesis was based on a recent study with mouse polyomavirus, which showed that a mutation in capsid protein VP2 enhanced virus replication. Accordingly, we reasoned that variations in the VP1 region of BKV or JCV strains present in SLE patients may explain enhanced virus replication and hence greater prevalence of BKV/JCV viruria in these patients compared to healthy individuals. This prompted us to perform VP1 genotyping of JCV and BKV DNA amplified from urine samples of these SLE patients. We expanded our SLE patient group with 73 urine samples from pregnant women as a control. The selection of pregnant women as a normal control group is justified by the sex distribution of SLE; only 5% of SLE patients are male. Moreover, pregnancy is one of the very rare situations in which polyomavirus reactivation can occur in normal individuals. Our results revealed that, based on VP1 genotyping, urinary BKV and JCV DNA displayed no unique subtypes and all amino acid substitutions in the VP1 coding region have been reported by others. One SLE patient from Stavanger had a novel amino acid substitution. Moreover, the VP1 sequences remained stable over time for most of the patients. Therefore, the genotype profiles of JCV and BKV excreted by SLE patients do not seem to differ significantly from those characterized in immunocompetent individuals.

Methods

Study population. The SLE patient group from Tromsø has been described in detail elsewhere (Rekvig et al., 1997; Sundsfjord et al., 1999; Bendiksen et al., 2000). This study includes 73 new urine samples collected over 1 year from five SLE patients living in the south of Norway (Stavanger, about 1500 km south of Tromsø). These patients, one male and four females, fulfilled the criteria for SLE and are referred to as patients Stav1 to Stav5. The urine specimens from the Stavanger SLE patients were kindly provided by Roald Omdal (Central Hospital of Rogaland). Twenty-five single urine samples were collected from healthy women who were 3–14 weeks pregnant and 50 single urine specimens were obtained from healthy women who were 18–39 weeks pregnant. The urine samples were kindly collected by Bjørn Backe (University Hospital of Trondheim) and Margareta Verelst (University Hospital of Tromsø).

PCR amplification of viral VP1 DNA sequences. Preparation of the urine samples and PCR precautions were as previously described (Bendiksen et al., 2000). The primers BKV-P1 (5′ GAAAATCTACTGATTGGGAGGCTG 3′), BKV-P5 (5′ ATGATTACCACTTGGGACCTGGGC 3′), BKV-P2 (5′ GTACATCTGGGTACCTGGTCTG 3′) and JCV-P6 (5′ CTATCTAGGTACGCTTGGCTGCTC 3′) used in this study were purchased from Eurogentech. The location of the primers in the BKV and JCV genomes is shown in Fig. 1. To amplify BKV VP1 sequences, PCR was run with BKV-P1 and BKV-P5 primers. This generates a 259 bp fragment. Subsequently, a nested PCR was performed with BKV-P1 and BKV-P2 primers, yielding a 214 bp DNA fragment. JCV VP1 DNA was amplified with BKV-P1 and JCV-P6 primers, generating a 321 bp fragment. Subsequently, a nested PCR was performed with BKV-P1 and BKV-P2 primers, yielding a 214 bp PCR product. The PCR initiation step was for 6 min at 96 °C followed by 40 cycles of 96 °C for 30 s and 64 °C for 1 min. After a final 7 min extension at 72 °C, reactions were stopped at 4 °C. PCR was performed with a Cetus thermal cycler (Perkin Elmer). Positive and negative controls were included in each experiment. To ascertain that the negative PCR results were not due to the presence of inhibitors, a selection of these samples were spiked with BKV DNA. Amplified bands of the correct size were obtained in all these modified samples (Rekvig et al., 1997; Bendiksen et al., 2000).

Cloning and sequencing of amplified DNA. PCR products from the nested PCR were purified from agarose gels by the Concert rapid gel extraction system (Life Technologies) according to the recommendations of the manufacturer and cloned in the pGEM-T easy vector (Promega). Cycle sequencing was performed with the Big Dye cycle sequencing kit (Perkin Elmer) with primers BKV-P1 and BKV-P2, thus allowing both

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Fig. 1. Comparison of the nucleotide sequences (a) and amino acid sequences (b) of BKV (Dun) and JCV (Mad1) spanning the part of the VP1 gene that was analysed in this study. A dot represents an identical nucleotide or amino acid residue. The numbering is according to the published sequences in GenBank (accession no. J02038 for BKV and J02226 for JCV). The positions of primers BKV-P1, BKV-P2, BKV-P5 and JCV-6 are underlined. The one-letter code for amino acids is used.

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**Results**

Detection of BKV and JCV VP1 DNA sequences in the urine of SLE patients and healthy pregnant women

Nested PCR with BKV- or JCV-specific primers was performed on 27 BKV- or JCV-positive urine samples collected in 1993 from the Tromsø SLE patients that have been previously described (Rekvig et al., 1997; Sundsfjord et al., 1999; Bendiksen et al., 2000). In addition, human polyomavirus VP1 DNA sequences were amplified in 33 out of 73 urine samples collected from SLE patients Stav1 to Stav5 and 75 urine specimens from healthy pregnant women. Previously, we have shown that Tromsø SLE patients nos 12, 14 and 23 contained NCCR DNA of JCV, while urine samples from patients nos 2, 4, 5, 8, 9, 10, 13, 16, 17, 18, 20, 24 and 25 were positive for BKV NCCR DNA. All JCV NCCR DNA-positive urine samples also contained JCV VP1 DNA sequences. All BKV NCCR DNA-positive urine samples (except for patients nos 13 and 16 where we were not able to generate VP1 sequences, although NCCR sequences have been previously established) were positive for BKV VP1 DNA (Table 1).

Moreover, we found that two urine samples that previously were positive for JCV, but not for BKV NCCR DNA (Tromsø SLE patients nos 12 and 14), were positive for BKV and JCV VP1 DNA (see Discussion). Four of the five Stavanger patients (Stav1, 2, 4 and 5) had BKV VP1 DNA in their urine, while JCV VP1 DNA sequences were present in the urine samples from two patients (Stav2 and Stav3). Patient Stav4 had both JCV and BKV viruria (Table 2). Of the 25 urine samples collected during weeks 3–14 of pregnancy, none contained BKV or JCV VP1 DNA, while in the samples collected between weeks 18 and 39, BKV VP1 DNA was detected in 12 out of 50 (Table 1).

**JCV genotyping in SLE patients**

The alignment of the JCV VP1 sequences found in the urine samples of SLE patients and a comparison with previously published sequences are shown in Fig. 2(a). Most mutations have been previously described in other JCV strains. Urine sample Stav2.72 had a unique mutation at position 1902, replacing T with C. Urine sample 12.548 of Tromsø SLE patient no. 12 exhibited a T → G transversion at position 1936, while sample 23.208 (Tromsø SLE patient no. 23) possessed a G → C transversion at position 1939. Urine sample Stav3.2 had both mutations at positions 1936 and 1939. According to the VP1-based subtype classification devised by Agostini et al. (1998 b), JCV excreted in the urine of Tromsø SLE patient no. 12 belongs to subclass 1B, while all other SLE patients examined here contained subtype 1A strains in their urine. Two urine samples from patient Stav2 (Stav2.44 and Stav2.52) collected at different times had stable JCV VP1 sequences, while two other samples from this patient (Stav2.69 and Stav2.72) possessed single nucleotide substitutions. Different point mutations were observed in VP1 DNA in three separate urine samples from Tromsø SLE patient no. 12 (12.122, 12.380 and 12.548).

Analysing the amino acid sequence of the VP1 fragment indicated that most mutations were silent (Fig. 2 b). However, urine sample Stav2.72 contained an amino acid substitution (F145 → S) that has not previously been described. A unique missense mutation was also found for both Tromsø SLE patient...
Table 1. Prevalence of JCV or BKV VP1 DNA in urine of SLE patients and healthy pregnant women

BKV- and JCV-positive urine samples were assessed for VP1 DNA by PCR analysis. The number of samples tested for each group of patients or number of samples tested per patient is shown (n). For SLE patients from Tromsø, only a selection of urine samples positive for NCCR were tested.

<table>
<thead>
<tr>
<th>Group</th>
<th>BKV-positive</th>
<th>JCV-positive</th>
<th>BKV- and JCV-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE Tromsø patients (n = 27)</td>
<td>22</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>No. 2 (n = 1)</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>No. 4 (n = 2)</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. 9 (n = 1)</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. 10 (n = 3)</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. 12 (n = 4)</td>
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<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No. 14 (n = 1)</td>
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<td>1</td>
<td>1</td>
</tr>
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<td>No. 24 (n = 2)</td>
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<td>No. 25 (n = 2)</td>
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<tr>
<td>SLE Stavanger patients (n = 73)</td>
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<td>3</td>
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<tr>
<td>Stav1 (n = 6)</td>
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<td>0</td>
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<tr>
<td>Stav2 (n = 18)</td>
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<tr>
<td>Stav3 (n = 5)</td>
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<td>Stav4 (n = 32)</td>
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<tr>
<td>Stav5 (n = 12)</td>
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<tr>
<td>Pregnant women (n = 75)</td>
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<tr>
<td>Weeks 3–14 (n = 25)</td>
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<td>0</td>
</tr>
<tr>
<td>Weeks 18–39 (n = 50)</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of JCV and BKV VP1 DNA sequences in consecutive urine samples collected over 1 year from Stavanger SLE patient Stav4

The presence (+) or absence (−) of DNA is indicated.

<table>
<thead>
<tr>
<th>Urine samples</th>
<th>DNA</th>
<th>42 54 56 57 59 60 61 62 64 65 66 67 68 70 71 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCV</td>
<td>+</td>
<td>+ + + + + + + + + + + + + + + + + + + + + + +</td>
</tr>
<tr>
<td>BKV</td>
<td>−</td>
<td>− − − − − − − + + + + + + + + + + + + + + −</td>
</tr>
</tbody>
</table>

no. 12 (urine specimen 12.584) and Stav3 (urine sample Stav3.2), where V157 was replaced by G.

BKV genotyping in SLE patients and healthy pregnant women

Nucleotide sequence comparisons between previously described BKV VP1 sequences and sequences obtained in this study are summarized in Fig. 3(a). Sequence analysis revealed that the VP1 sequences detected in the urine samples could be classified into four genotypes. The 19 urine samples collected from Tromsø SLE patients nos 4, 12, 14 and 24, patients Stav2, 4 and 5, and 12 pregnant women all had the BKV strain MM VP1 genotype. This sequence is referred to as VP1 (MM) in Fig. 3(a). The 16 urine samples from Tromsø SLE patients nos 2, 4, 5, 9, 10, 17, 18, 20 and 25 and one specimen of Stav4 (urine sample Stav4.62) contained VP1 DNA that was 100% identical to that of BKV strain JL. This sequence is referred to as VP1 (JL) in Fig. 3(a). The urine sample from Tromsø SLE patient no. 8 had a VP1 sequence that was 96–7% identical in a 214 bp overlap with the VP1 sequence of BKV strain MM. This sequence is labelled as VP1 (MM8) in Fig. 3(a). Finally, the VP1 DNA sequence in a single urine sample of Tromsø SLE patient no. 24 was 94–0% identical to BKV strain MM in a 214 bp overlap. This sequence is referred to as VP1 (MM24) in Fig. 3(a). Mutations at positions 1938 (C → T), 1965 (A → G), 1977 (G → A), 2007 (T → C), 2013 (C → T), 2034 (A → G), 2058 (G → A), 2061 (A → T) and 2067 (T → C) in urine samples of VP1 (MM8) and VP1 (MM24) are novel. A mutation at position 1965 has been previously described (GenBank accession no. Z19535), but here a T replaces an A.
Different urine samples obtained from the same patients contained identical VP1 DNA sequences, except for patient Stav4 and Tromsø SLE patient no. 4. Patient Stav4 had two urine samples containing VP1 sequences identical to BKV strain MM and one sample with VP1 DNA identical to BKV strain JL. Urinary VP1 sequences from Tromsø SLE patient no. 4 were either BKV strain MM (one urine sample) or BKV strain JL (one urine sample).

Most mutations were silent, with only a few missense mutations (Fig. 3b). Sequences referred to as VP1 (MM) and VP1 (MM8) had two previously described amino acid mutations (E158→D and S171→T), while sequence VP1 (JL) had three previously reported amino acid substitutions (E158→D, S172→T and D175→E). The sequence referred to as VP1 (MM24) had four amino acid substitutions (Q117→K, H139→N, E158→D and S171→T), all of which have been described before.

Discussion

Previously, we have determined that SLE is a condition that, besides the ACR criteria (Arnett et al., 1988), is
Fig. 3. (a) Nucleotide mutations encountered in the VP1 gene of different BKV strains that have been previously described or characterized in this study. The number in parentheses refers to the GenBank accession number. (b) Amino acid comparison of VP1 (residues 107–176) of the different BKV strains. A dot indicates an identical nucleotide.

characterized by frequent human polyomavirus reactivation (Rekvig et al., 1997; Bredholt et al., 1999). SLE may therefore represent a condition where the immune system of patients can no longer control polyomavirus infection, a phenomenon with potential impact on secondary autoimmune pathophysiology characterizing this syndrome. It is now firmly established that polyomaviruses have the potential to induce both B cell and T cell autoimmunity to nucleosomes, and even pathogenic (nephritogenic) anti-DNA antibodies (Flægstad et al., 1988; Fredriksen et al., 1994; Andreassen et al., 1999a, b). Therefore, it is important to explain why polyomavirus reactivation is so intense in this disease. The main purpose of this study was to determine whether SLE patients, as compared to normal individuals, harboured specific strains of polyomaviruses that could explain their frequent reactivation. Previously, we have determined the structure of the NCCR, which did not differ from the structure defined in healthy individuals (Sundsfjord et al., 1999). Here, VP1 genotyping was performed on BKV and JCV DNA excreted in the urine of SLE patients and healthy pregnant women. Our study revealed that urine samples from SLE patients did not possess JCV strains with a unique VP1 genotype. BKV VP1 sequences were mainly of the BKV strain MM genotype in both SLE patients and pregnant women. However, 9 of the 11 Tromsø SLE patients who contained BKV VP1 DNA in their urine excreted BKV strain JL. One Stavanger patient also possessed urinary BKV strain JL DNA in one of the urine samples. This patient had, however, two urine samples containing BKV strain MM DNA. All the pregnant women (from two different geographical locations) had BKV strain MM in their urine specimens.

We found three individuals who excreted both BKV and JCV sequences. Two were Tromsø SLE patients (nos 12 and 14), while one (Stav4) was from Stavanger. Previous PCR amplifications with primers spanning the NCCR had identified the Tromsø SLE patients as excreting JCV (Rekvig et al., 1997; Sundsfjord et al., 1999). One explanation for this discrepancy could be the specificity of the PCR primers. In the previous studies we ran a first-round nested PCR with degenerate primers, followed by a second round with specific primers. In this study, urine samples were first selectively amplified with both BKV- and JCV-specific primers and subsequently nested PCR was performed with a degenerate primer set. It is possible that the degenerate primers for the NCCR had a higher specificity for BKV DNA, therefore explaining why this DNA was preferentially amplified.

PCR amplification and sequencing may introduce mu-
tations. We do, however, believe that the mutations are genuine, as most of them have been previously described and because both the strands were sequenced. Moreover, consecutive samples contained predominantly the same mutations. The stability of the sequences during persistent viruria suggests reactivation rather than re-infection. What is the biological significance of the mutations described in the VP1 region of polyomaviruses excreted by SLE patients? The VP1 region that was sequenced represents the DE loop, a region proposed to contain epitopic loops and to be involved in cellular receptor binding (Liddington et al., 1991). No amino acid substitutions in the VP1 region of JCV result in a change of charge, while in SLE patients with urinary BKV type VP1 (MM24), the positively charged H139 was replaced by an uncharged A, and the uncharged Q117 was substituted by a positively charged K. The net charge, however, remained unaltered. Mutation in the VP2 gene of mouse polyomavirus has been shown to enhance virus replication (Melucci-Vigo et al., 1994), but it remains to be established whether the JCV/BKV variants found in SLE patients replicate better in vivo compared to other strains.

In a previous study with pregnant women, 18 out of 129 (14%) urine samples were BKV DNA-positive, while 5 out of 76 (6.6%) were JCV DNA-positive. Only one sample was positive for both viruses (Markowitz et al., 1991). Studies by Coleman et al. (1980) reported that only 40 women out of 1235 (3.2%) had excreted polyomavirus during pregnancy. The low prevalence of urinary polyomavirus that was monitored in the latter study may be due to the detection method. This study and Markowitz et al. (1991) used PCR, while Coleman et al. (1980) performed cytological examinations of urine. The onset of virus excretion seemed to occur late in the second trimester and during the third trimester of pregnancy (reviewed by Arthur & Shah, 1989). Our study is in agreement with these previous observations. We found among our pregnant individuals that 12 of the 75 urine samples (16%) examined contained BKV VP1 DNA, while none contained secreted JCV VP1 DNA. However, none of the urine samples collected during the first 14 weeks of pregnancy possessed BKV, while 12 out of 50 samples (24%) obtained during weeks 18–39 were positive for BKV DNA. Urinary oestradiol and progesterone levels increase during pregnancy, especially after week 20 (reviewed by Berne & Levy, 1993). We have previously shown that the BKV genome contains a functional hormone response unit composed of an oestrogen response element and a progesterone/glucocorticoid response element. In vivo virus replication was enhanced by oestrogens or progesterone (Moens et al., 1994). These observations may explain the onset of BKV reactivation during late pregnancy, and also why polyomavirus-induced anti-DNA and anti-nucleosome antibody production occurs in SLE, a syndrome mainly affecting women.

SLE BKV/JCV VP1 subtypes are also present in urine samples from healthy controls, and urinary BKV and JCV in SLE patients have archetypal NCCR sequences found in healthy individuals (Sundsfjord et al., 1999). These observations suggest that these strains are co-habitants of the normal population and are not unique to SLE patients. However, our group has previously shown a strong statistically significant correlation between expression of large T-antigen and antibodies to DNA, a hallmark of SLE, in the Tromsø SLE patients included in this study. Furthermore, in some patients the onset of T-antigen antibodies coincided with anti-DNA antibodies (Rekvig et al., 1997). These findings may suggest a causal role for BKV in SLE. Therefore, the explanation for the high prevalence of these human polyomaviruses in urine of SLE patients forms a challenge for future research. However, our results indicate that the sequence of the NCCR and VP1 do not seem to play a fundamental role in processes that lead to frequent reactivation of these viruses in SLE patients.

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References


papovavirus BK and JC in the urine.


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