Virology 380 (2008) 118–123

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Transcriptional control region rearrangements associated with the evolution of JC polyomavirus

Yoshiaki Yogo [a,*], Shan Zhong [a], Ayako Shibuya [a], Tadaichi Kitamura [b], Yukio Homma [a]

[a] Department of Urology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[b] Social Welfare Corporation Asoka Hospital, Tokyo 135-0002, Japan

ARTICLE INFO

Article history:
Received 16 May 2008
Returned to author for revision 25 June 2008
Accepted 21 July 2008
Available online 21 August 2008

Keywords:
Transcriptional control region
Rearrangement
Evolution
JC polyomavirus

ABSTRACT

JC polyomavirus (JCV) isolates worldwide are classified into three super-lineages (A, B and C), with A and B further split into several lineages and sub-lineages. The transcriptional control region (TCR) of the JCV genome generally has the archetypal configuration, but rearranged TCRs have occasionally been detected in isolates from immunocompetent individuals. To investigate the phylogenetic significance of these rearrangements, we analyzed 298 TCR sequences all derived from complete JCV genomes directly cloned from the urine of non-immunocompromised individuals. While sporadic rearrangements were found in many lineages and sub-lineages, common rearrangements were identified in all, or essentially all, isolates belonging to particular lineages or sub-lineages. Interestingly, several common rearrangements were also detected as sporadic rearrangements in other lineages or sub-lineages. This observation suggests that during the course of JCV evolution, JCV strains with sporadic rearrangements became predominant over archetypal TCRs in some JCV lineages or sub-lineages.

Introduction

JC polyomavirus (JCV) was first identified as the causative agent of a fatal demyelinating disease in the central nervous system, known as progressive multifocal leukoencephalopathy (PML) (Padgett et al., 1971). This virus, however, is ubiquitous in humans, infecting children asymptomatically then persisting in renal tissues (Chesters et al., 1983; Padgett and Walker 1973; Tominaga et al., 1992). In most adults, renal JCV is not latent but replicates to generate progeny in the urine (Kitamura et al., 1990, 1994). JCV is usually transmitted from parents to offspring during long-term cohabitation (Kunitake et al., 1995; Kato et al., 1997; Suzuki et al., 2002; Zheng et al., 2004).

All JCV strains are members of a single serotype (Major, 2001). Nevertheless, based on genetic variations in the genome, JCV strains worldwide are classified into three super-lineages (A, B and C) (Sugimoto et al., 2002a). Super-lineages A and B are subdivided into several lineages, many of which are further split into multiple sub-lineages (Supplementary Fig. 1). Each lineage and sub-lineage occupy a unique geographical domain (Yogo et al., 2004) (Table 1), suggesting that the evolution of JCV occurred in association with human populations.

The genome of JCV is a single molecule of double-stranded, covalently circular DNA about 5100 bp in length, and consists of early, late, and regulatory regions (Frisque et al., 1984). The regulatory region contains the origin of replication and the transcriptional control region (TCR). Before 1990, JCV strains were isolated mainly from the brains of PML patients, and TCRs (designated PML-type) of these strains had been shown to be hypervariable, with deletions and amplifications of various segments (Martin et al., 1985; Matsuda et al., 1987; Loeber and Dörries 1988). However, Yogo et al. (1990) found that the TCRs of JCV genomes molecularly cloned directly from the urine of healthy volunteers and non-immunosuppressed patients had the same basic structure (designated as the archetype), having only a few nucleotide mismatches. Based on a comparison between archetype and PML-type TCRs, it was hypothesized that various TCRs from the brains of PML patients were produced from the archetype by deletion and amplification, or deletion alone (Yogo et al., 1990; Iida et al., 1993; Ault and Stoner 1993). JCV strains with archetype TCRs have been detected not only in the urine of non-immunosuppressed patients worldwide (Yogo et al., 1991; Guo et al., 1996; Agostini et al., 1996, 2001; Jeong et al., 2004) but also in renal and tonsillar tissues of non-PML patients (Tominaga et al., 1992; Kato et al., 2004), and hence it appears that JCV strains with archetype TCRs circulate in various human populations (Yogo et al., 2004).

Since the first isolation of JCV strains with archetype TCRs from urine (Yogo et al., 1990), JCV strains with rearranged TCRs have sometime been detected in the urine of non-immunocompromised individuals, albeit with low frequencies (Yogo et al., 1990, 1991; Guo et al., 1996; Agostini et al., 1996, 2001; Jeong et al., 2004). Compared to the complicated rearrangements in PML-type TCRs, these TCRs showed simple rearrangements (deletions or duplications of short segments). To investigate the phylogenetic significance of these rearrangements, we analyzed 298 TCR sequences of JCV all derived from complete viral genomes directly cloned from the urine of non-

* Corresponding author. Fax: +81 3 5800 8917.
E-mail address: yogo-tky@umin.ac.jp (Y. Yogo).

0042-6822/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.virol.2008.07.016

Table 1
Summary of the results of the present analysis

Super-lineage	Lineage[a]	Sub-lineage[a]	Geographic distribution (ethnic origin)	No. of isolates analyzed	Presence (+) or absence (−) of common rearrangement	No. (%) of isolates with sporadic rearrangement
A	EU-a	EU-a1 (Type 1A)	Europe, Mediterranean areas, Japan, Korea, N.E. Siberia (Chukuchi), Arctic areas (Inuit), USA	25	−	3 (12)
		EU-a2 (Type 1B)	Europe, USA	13	−	2 (15)
A	EU-b (Type 4)		Europe, Mediterranean areas, USA	6	−	0 (0)
A	EU-c[b]		N.E. Siberia (Nanai), N. Japan (Ainu)	8	−	3 (38)[c]
C	Af1 (Type 6)		W. and Central Africa, USA	4	−	2 (50)[d]
B	Af2	Af2-a (Type 3B)	S. Africa, USA	6	−	0 (0)
		Af2-b (Type 3A)	Africa, W. Asia, India	42	−	3 (7)
B	B1-a (Type 7C1)		China, Philippines	14	−	2 (14)
B	B1-b	B1-b1 (Type 7D1)	Mongolia, W. China, S.W. and Central Asia, Myanmar	16	+ (2-bp del)	0 (0)
		B1-b2 (Type 7D2)	S. Asia	5	+ (2-bp del)	1 (20)
B	B1-c (Type 2B)		Europe, Mediterranean areas, USA	3	−	0 (0)
B	B1-d (Type 2D3)		Saudi Arabia	4	+ (2-bp del)	0 (0)
B	B2 (Type 7C2)		India, Nepal, Mauritius	3	−	0 (0)
B	B3-a (Type 7B2)		China, Philippines, Indonesia	5	−	0 (0)
B	CY (Type 7B1)	CY-a	Japan, Korea, N. China, USA	15	−	2 (13)
B		CY-b	Japan, Korea, N. China, USA	7	−	1 (14)
B	MX[b]		N. Japan (Ainu)	3	−	0 (0)
B	MY (Type 2A)	MY-a	Japan	3	−	0 (0)
		MY-b	Japan, Korea, USA	10	−	0 (0)
		MY-c	Mexico, Guatemala, USA (Tarahumalan)	6	+ (1-bp del)	0 (0)
		MY-e	Guatemala, Mexico, USA (Mayan)	6	+ (10-bp del)	0 (0)
		MY-f	Peru (Aymara/Quechua)	5	+ (10-bp del)	0 (0)
		MY-g	Canada (Beaver/Dene Tha')	5	−	3 (60)[e]
		MY-x	Japan (Ainu)	1	−	0 (0)
		Others	Mexico	2	−	0 (0)
B	SC (Type 7A)	SC-a	Thailand	2	−	0 (0)
		SC-b	Myanmar, Mongolia	2	−	1 (50)[f]
		SC-c	Thailand	4	−	1 (25)[g]
		SC-d	Myanmar	6	−	0 (0)
		SC-e	Myanmar	4	−	2 (50)[h]
		SC-f	S. China, S.E. Asia, Near Oceania, USA	33	+ (5-bp del)	1 (3)
		SC-g	Kiribati	5	−	0 (0)
		SC-x	Philippines	6	−	0 (0)
		Others	Myanmar	1	−	0 (0)
B	2E (Type 2E)	2E/KB	Kiribati	10	+ (9-bp dup)	0 (0)
		Others	Island S.E. Asia, Oceania	8	−	1 (13)
Total				298		28 (9)

[a] Nomenclature by Stoner's group (Cui et al., 2004) is shown within parentheses.
[b] Corresponding JCV lineages have not been reported by Stoner's group.
[c] $P<0.01$ vs. B1-b1 and SC-f; $P<0.05$ vs. Af2-b, MY-b and 2E/KB.
[d] $P<0.01$ vs. Af2-b, B1-b1 and SC-f; $P<0.05$ vs. MY-b and 2E/KB.
[e] $P<0.01$ vs. Af2-b, B1-b1, MY-b, SC-f and 2E/KB; $P<0.05$ vs. EU-a1,-b, Af2-a, B1-a, B3-a, CY-a, MY-c, -e, -f, SC-d, -g and -x.
[f] $P<0.01$ vs. B1-b1, SC-f; $P<0.05$ vs. Af2-b, MY-b, 2E/KB.
[g] $P<0.05$ vs. B1-b1.
[h] $P<0.01$ vs. Af2-b, B1-b1, SC-f; $P<0.05$ vs. MY-b and 2E/KB.

immunocompromised individuals. This approach allowed us not only to detect TCR rearrangements but also to unambiguously classify the JCV strains into lineages and sub-lineages. We discuss the implications of the obtained results based on a close relationship between JCV lineages (or sub-lineages) and human populations.

Results

Consensus TCR sequences for respective lineages and sub-lineages

We aligned the TCR sequences belonging to the same lineages or sub-lineages together with the representative archetypal TCR [i.e., the TCR of isolate CY (Yogo et al., 1990)]. This alignment identified not only consensus TCR sequences among isolates belonging to respective lineages or sub-lineages but also TCRs having sporadic rearrangements found only in one of a few isolates of the lineages or sub-lineages (the features of the sporadic rearrangements will be described in the next section).

The consensus TCRs of most JCV lineages and sub-lineages were archetypal, that is, identical, or almost identical, with the CY TCR, with a few nucleotide mismatches but without any rearrangements (deletions or duplications) (Fig. 1). These lineages and sub-lineages included all lineages (EU-a, -b and -c) belonging to the super-lineage A, five lineages (Af2, B1-a, -c, B2, B3-a and CY) belonging to super-lineage B, the single lineage (Af1) belonging to super-lineage C, and most sub-lineages of lineages MY, SC and 2E.

However, two lineages (B1-b and -d), three MY sub-lineages (MY-c, -e and -f), one SC sub-lineage (SC-f), and one 2E sub-lineage (2E/KB) had TCRs that deviated from the archetypal TCR by deletion or duplication (these rearrangements were designated as common TCR rearrangements) (Fig. 1 and Table 1). In B1-b1, -b2 and -d, a 2-bp segment spanning nucleotides (nt) 217 to 218 (nucleotide positions will be expressed as those of isolate CY; GenBank/EMBL/DDBJ accession number, AB038249) was deleted; in MY-c, a single nucleotide (nt 223) was deleted; in SC-f, a 5-bp segment (nt 218–222) was deleted; and in 2E/KB, a 9-bp segment (nt 91–99) was duplicated.

Sporadic TCR rearrangements

Although sporadic TCR rearrangements were not detected in lineages, except for Af1, for which only a small number of isolates were examined, they occurred in ten lineages belonging to the three super-

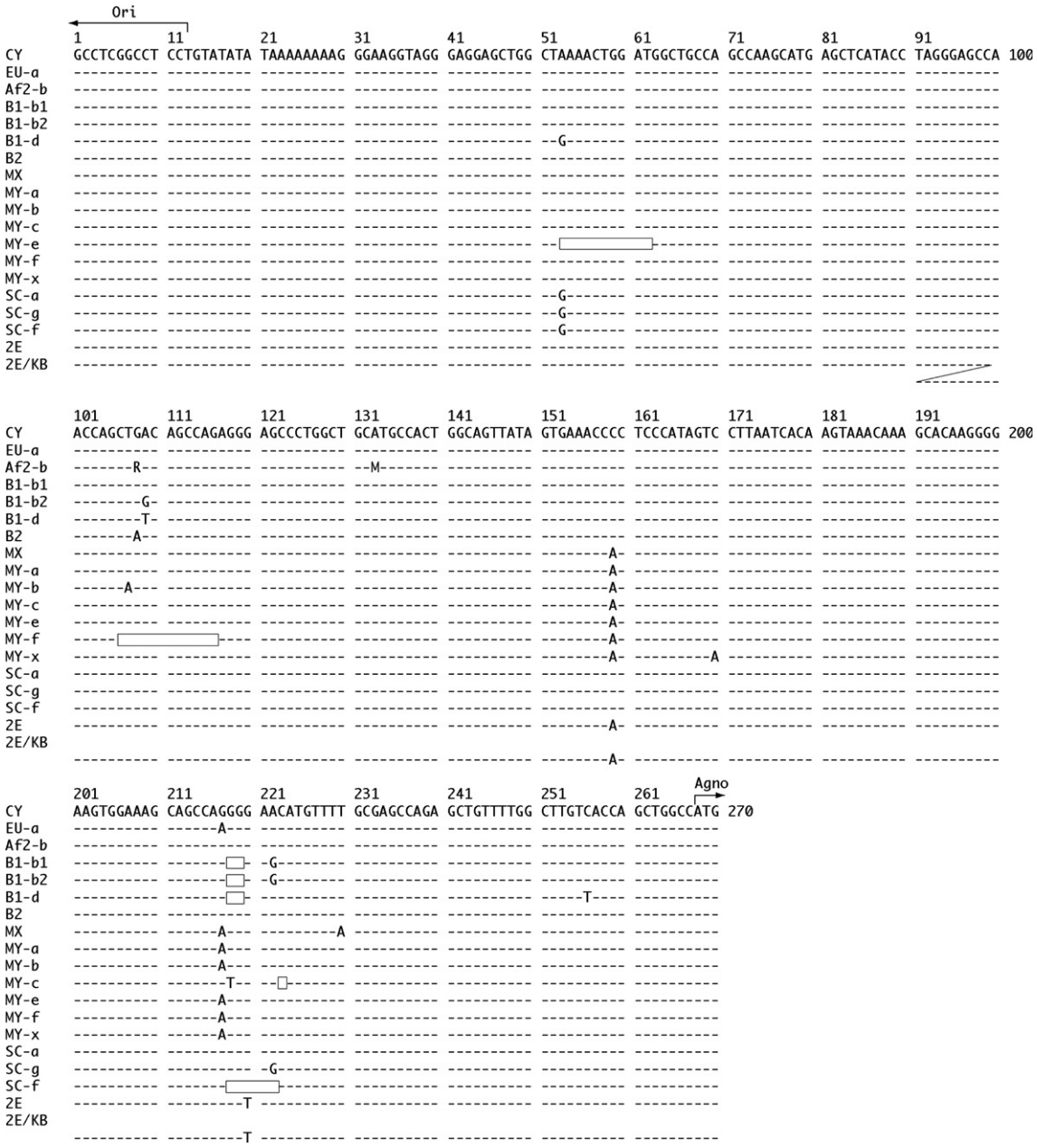
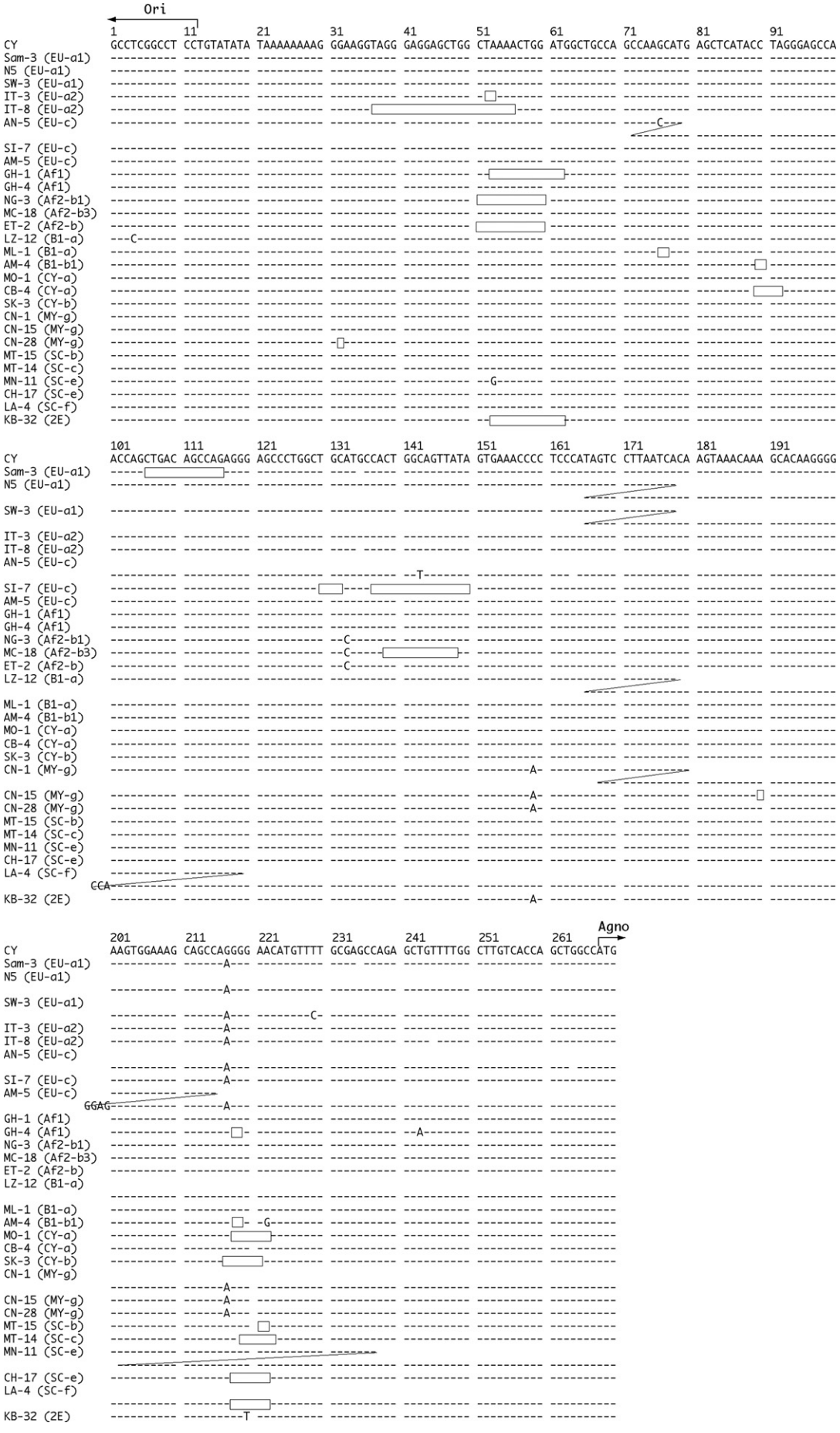


Fig. 1. TCR sequences detected in various JCV lineages and sub-lineages. Sequences between the midpoint of the origin of replication and the start site of the agnogene are shown (the nucleotide numbering starts at the midpoint of the origin of replication). The CY TCR (Yogo et al., 1990) is shown at the top of the figure and the consensus sequences identified for various JCV lineages or sub-lineages are shown below in relation to the CY TCR, with similar nucleotides indicated by dashes and deletions identified by rectangles. Parallel sequences connected with an oblique line in 2E/KB indicate a duplication. M and R in the Af2-b sequence indicate A or C and A or G, respectively. The sequences of lineages CY, Af1, Af2-a, B1-a and B3-a and those of sub-lineages SC-b, -c, -d and -x were identical and represented here by CY. The sequences of lineages EU-a, -b and -c and B1-c were identical and represented here by EU-a. The sequences of sub-lineages MY-a and -b were identical and represented here by MY-a. The sequences of sub-lineages SC-a and -e were identical and represented here by SC-a.

lineages (Fig. 2 and Table 1). (In lineage Af1, two of the four isolates examined had rearrangements, both of which were classified as sporadic; this classification was tentative because the rearrangements may turn out to be common, if a larger number of isolates are examined.) The features of the sporadic TCR rearrangements (Fig. 2 and Table 1) are summarized as follows.

1. Compared to the complicated rearrangements in PML-type TCRs (Yogo and Sugimoto, 2001), all sporadic rearrangements showed simple rearrangements (deletions or duplications of usually short segments).
2. Deletions (n=21) occurred more frequently than duplications (n=7).
3. The incidence of sporadic rearrangements was significantly higher in some lineages or sub-lineages (EU-c, Af1, MY-g, SC-b and -e) than in others (Af2-b, B1-b1, MY-b, SC-f and 2E/KB) (P<0.01 or P<0.05) (Table 1). However, for the small sample sizes (two to eight) in the lineages or sub-lineages in which the incidence of sporadic

Fig. 2. TCR sequences carrying sporadic rearrangements. Sequences between the midpoint of the origin of replication and the start site of the agnogene are shown (the nucleotide numbering starts at the midpoint of the origin of replication). The CY TCR (Yogo et al., 1990) is shown at the top of the figure and the TCR sequences of isolates with sporadic rearrangements are shown below in relation to the CY TCR, with similar nucleotides indicated by dashes and deletions identified by rectangles. Parallel sequences connected with oblique lines indicate duplications. Lineages and sub-lineages are shown within parentheses.


Ori
Agno
CY
Sam-3 (EU-a1)
N5 (EU-a1)
SW-3 (EU-a1)
IT-3 (EU-a2)
IT-8 (EU-a2)
AN-5 (EU-c)
SI-7 (EU-c)
AM-5 (EU-c)
GH-1 (Af1)
GH-4 (Af1)
NG-3 (Af2-b1)
MC-18 (Af2-b3)
ET-2 (Af2-b)
LZ-12 (B1-a)
ML-1 (B1-a)
AM-4 (B1-b1)
MO-1 (CY-a)
CB-4 (CY-a)
SK-3 (CY-b)
CN-1 (MY-g)
CN-15 (MY-g)
CN-28 (MY-g)
MT-15 (SC-b)
MT-14 (SC-c)
MN-11 (SC-e)
CH-17 (SC-e)
LA-4 (SC-f)
KB-32 (2E)

rearrangements was high (Table 1), further analysis with larger numbers of isolates is needed.

4. The same deletions or duplications sometimes occur in different strains. Thus, a 13-bp duplication (location, nt 166–178) occurred in strains N5 (lineage EU-a), SW-3 (EU-a) and strain LZ-12 (B1-a); a 10-bp deletion (nt 51–60) occurred in strains NG-3 (Af2-b) and ET-2 (Af2-b); and a 10-bp deletion (nt 53–62) occurred in strains GH-1 (Af1) and KB-32 (2E).
5. TCR changes identical to four of the six common rearrangements were detected as sporadic rearrangements. Thus, the sporadic TCR rearrangements (10-bp deletion spanning nt 53 to 62) found in isolates GH-1 (lineage Af1) and KB-32 (2E) were identical with the common TCR rearrangement of sub-lineage MY-f; the sporadic rearrangement (11-bp deletion spanning nt 106 to 116) found in isolate Sam-3 (EU-a) was identical with the common TCR rearrangement of sub-lineage MY-f; the sporadic rearrangements (2-bp deletions from nt 218 to 219) in GH-4 (Af1) and MO-1 (B1-b1) were identical with the common rearrangement in sub-lineages B1-b1, -b2 and -d; and the sporadic rearrangement (5-bp deletion spanning nt 218 to 222) in CH-17 (SC-e) was identical to the common rearrangement in sub-lineage SC-f.

Discussion

We showed that isolates belonging to most lineages and sub-lineages had archetypal TCRs, that is, identical, or almost identical, with the CY TCR (Yogo et al., 1990), with a few nucleotide mismatches but without any rearrangements (Fig. 1). This finding demonstrates that the ancestral JCV had an archetypal TCR and that this configuration has essentially been conserved during the evolution of JCV, providing support for the view that JCV strains carrying archetypal TCRs, or those slightly deviating from it, circulate in the human population (Yogo et al., 1990; Yogo and Sugimoto, 2001).

Additionally, we confirmed that TCR rearrangements occurred in several isolates belonging to various lineages and sub-lineages. We classified these TCR rearrangements into two categories, sporadic rearrangements found in rare isolates and common rearrangements identified in all, or essentially all, isolates belonging to particular lineages or sub-lineages. Interestingly, TCR changes identical with four of the six common rearrangements occurred as sporadic rearrangements. This observation suggests that sporadic and common rearrangements are not independent, but that the former may have been transformed into the latter in the course of JCV evolution.

The question then arose as to how TCRs with common rearrangements became the major TCR species, with the other TCRs, including archetypal ones, eliminated from a population of JCV. Common rearrangements might have provided a selective advantage because of a higher growth ability. This possibility is unlikely, however, since the same TCR rearrangements found as common rearrangements in some lineages or sub-lineages occurred as sporadic rearrangements (i.e., occurred only rarely) in others. Therefore, an alternative explanation is needed for the shift from sporadic to common TCR rearrangements.

We consider that the implications of the obtained results are best interpreted on the basis of a close relationship between JCV and human populations (Sugimoto et al., 1997; Yogo et al., 2004). As for the origin and migration of modern humans, Ramachandran et al. (2005) proposed a model of a serial founder effect with a single origin in sub-Saharan Africa, and recent genetic studies have provided substantial support for this model (Li et al., 2008; Jakobsson et al., 2008). This model holds that in the course of human migrations, new population was frequently formed by small numbers of individuals. Since JCV co-migrated with human populations (Sugimoto et al., 1997; Stoner et al., 2000), JCV strains in the parental population would have been transmitted to the new population. If it can be assumed that the number of individuals who founded the new population was small, only a single strain may have been transmitted to the new population. The transmitted JCV strain may have carried a variant TCR with a sporadic rearrangement, and may have evolved into a new lineage or sub-lineage with a common rearrangement in the course of the expansion of the host population.

Sporadic rearrangements were detected at higher rates in two lineages (EU-c and Af1) and three sub-lineages (MY-g, SC-b and -e). EU-c is the oldest lineage among the three lineages belonging to super-lineage A (Sugimoto et al., 2002b), and Af1 is the only lineage belonging to super-lineage C, possibly representing the ancient type of JCV (Pavesi, 2003). It seems reasonable that sporadic rearrangements accumulated in these old lineages. However, because of the small sample sizes (two to eight) in the lineages or sub-lineages in which the incidence of sporadic rearrangements was high (Table 1), further analysis with larger numbers of isolates is needed.

The TCR rearrangements detected in complete JCV genomes directly cloned from the urine of non-immunocompromised individuals (Figs. 1 and 2) were all simple rearrangements, presenting a striking contrast to the complex TCR rearrangements detected in JCV isolates from the brain and cerebrospinal fluid of PML patients (Yogo and Sugimoto, 2001). This is not surprising, because polyomavirus TCR rearrangement may differently occur depending on tissues where polyomaviruses replicate. Indeed, Gosert et al. (2008) recently reported that BK polyomavirus (a human polyomavirus closely related to JCV) undergoes TCR rearrangement more frequently in plasma than in urine samples from renal transplant recipients. In addition, it should be noted that JCV variants with PML-type TCRs persist only within single hosts and never return to the human population (Yogo and Sugimoto, 2001; this study).

In summary, we detected both common and sporadic TCR rearrangements. The observation that several common rearrangements in some lineages or sub-lineages also occurred as sporadic rearrangements in other lineages or sub-lineages suggested that sporadic rearrangements occasionally became common ones with the evolution of JCV. We explained this finding based on the host-linked evolution of JCV. In addition, this study has shown that the archetypal configuration of the JCV TCR has essentially been conserved in the course of JCV evolution.

Materials and methods

Sequence data

Two hundred and ninety-eight TCR sequences of JCV were derived from complete genomes directly cloned from the urine of non-immunocompromised individuals. The origins of isolates, including DDBJ/EMBL/GenBank accession numbers, are shown in Supplementary Table 1. Numbers of isolates analyzed are shown in Table 1 for each JCV lineage or sub-lineage. The classification of the isolates used in this study was confirmed by a neighbor-joining phylogenetic analysis based on complete coding sequences (Supplementary Fig. 1).

Detection of rearrangements

TCR sequences were aligned using CLUSTAL W (Thompson et al., 1994). Deletions and duplications were readily identified as gaps in the aligned sequences.

Statistical analysis

Statistical analysis was performed using the chi-square test with a Yates correction or with a Fisher exact test using the statistical

software package SPSS. The significance level was set at 5%. All statistical analyses were performed using numbers of strains, rather than percentages.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.virol.2008.07.016.

References

Agostini, H.T., Ryschkewitsch, C.F., Stoner, G.L., 1996. Genotype profile of human polyomavirus JC excreted in urine of immunocompetent individuals. J. Clin. Microbiol. 34, 159–164.

Agostini, H.T., Deckhut, A., Jobes, D.V., Girones, R., Schlunck, G., Prost, M.G., Frias, C., Pérez-Trallero, E., Ryschkewitsch, C.F., Stoner, G.L., 2001. Genotypes of JC virus in East, Central and Southwest Europe. J. Gen. Virol. 82, 1221–1231.

Ault, G.S., Stoner, G.L., 1993. Human polyomavirus JC promoter/enhancer rearrangement patterns from progressive multifocal leukoencephalopathy brain are unique derivatives of a single archetypal structure. J. Gen. Virol. 74, 1499–1507.

Chesters, P.M., Heritage, J., McCance, D.J., 1983. Persistence of DNA sequences of BK virus and JC virus in normal human tissues and in diseased tissues. J. Infect. Dis. 147, 676–684.

Cui, X., Wang, J.C., Deckhut, A., Joseph, B.C., Eberwein, P., Cubitt, C.L., Ryschkewitsch, C.F., Agostini, H.T., Stoner, G.L., 2004. Chinese strains (Type 7) of JC virus are Afro-Asiatic in origin but are phylogenetically distinct from the Mongolian and Indian strains (Type 2D) and the Korean and Japanese strains (Type 2A). J. Mol. Evol. 58, 568–583.

Frisque, R.J., Bream, G.L., Cannella, M.T., 1984. Human polyomavirus JC virus genome. J. Virol. 51, 458–469.

Gosert, R., Rinaldo, C.H., Funk, G.A., Egli, A., Ramos, E., Drachenberg, C.B., Hirsch, H.H., 2008. Polyomavirus BK with rearranged noncoding control region emerge in vivo in renal transplant patients and increase viral replication and cytopathology. J. Exp. Med. 205, 841–845.

Guo, J., Kitamura, T., Ebihara, H., Sugimoto, C., Kunitake, T., Takehisa, J., Na, Y.Q., Al-Ahdal, M.N., Hallin, A., Kawabe, K., Taguchi, F., Yogo, Y., 1996. Geographical distribution of the human polyomavirus JC virus types A and B and isolation of a new type from Ghana. J. Gen. Virol. 77, 919–927.

Iida, T., Kitamura, T., Guo, J., Taguchi, F., Aso, Y., Nagashima, K., Yogo, Y., 1993. Origin of JC polyomavirus variants associated with progressive multifocal leukoencephalopathy. Proc. Natl. Acad. Sci. U. S. A. 90, 5062–5065.

Jakobsson, M., Scholz, S.W., Scheet, P., Gibbs, J.R., VanLiere, J.M., Fung, H.C., Szpiech, Z.A., Degnan, J.H., Wang, K., Guerreiro, R., Bras, J.M., Schymick, J.C., Hernandez, D.G., Traynor, B.J., Simon-Sanchez, J., Matarin, M., Britton, A., van de Leemput, J., Rafferty, I., Bucan, M., Cann, H.M., Hardy, J.A., Rosenberg, N.A., Singleton, A.B., 2008. Genotype, haplotype and copy-number variation in worldwide human populations. Nature. 451, 998–1003.

Jeong, B.H., Lee, K.H., Choi, E.K., Kim, K., Kim, Y.S., 2004. Genotyping of the JC virus in urine samples of healthy Korean individuals. J. Med. Virol. 72, 281–289.

Kato, A., Kitamura, T., Sugimoto, C., Ogawa, Y., Nakazato, K., Nagashima, K., Hall, W.W., Kawabe, K., Yogo, Y., 1997. Lack of evidence for the transmission of JC polyomavirus between human populations. Arch. Virol. 142, 875–882.

Kato, A., Kitamura, T., Takasaka, T., Tominaga, T., Ishikawa, A., Zheng, H.-Y., Yogo, Y., 2004. Detection of the archetypal regulatory region of JC virus from the tonsil tissue of patients with tonsillitis and tonsilar hypertrophy. J. Neurovirol. 10, 244–249.

Kitamura, T., Aso, Y., Kuniyoshi, N., Hara, K., Yogo, Y., 1990. High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. J. Infect. Dis. 161, 1128–1133.

Kitamura, T., Kunitake, T., Guo, J., Tominaga, T., Kawabe, K., Yogo, Y., 1994. Transmission of the human polyomavirus JC virus occurs both within the family and outside the family. J. Clin. Microbiol. 32, 2359–2363.

Kunitake, T., Kitamura, T., Guo, J., Taguchi, F., Kawabe, K., Yogo, Y., 1995. Parent-to-child transmission is relatively common in the spread of the human polyomavirus JC virus. J. Clin. Microbiol. 33, 1448–1451.

Li, J.Z., Absher, D.M., Tang, H., Southwick, A.M., Casto, A.M., Ramachandran, S., Cann, H.M., Barsh, G.S., Feldman, M., Cavalli-Sforza, L.L., Myers, R.M., 2008. Worldwide human relationships inferred from genome-wide patterns of variation. Science 319, 1100–1104.

Loeber, G., Dörries, K., 1988. DNA rearrangements in organ-specific variants of polyomavirus JC strain GS. J. Virol. 62, 1730–1735.

Major, E.O., 2001. Human polyomavirus, In: Knipe, D.M., Howley, P.M., et al. (Eds.), Fields Virology, 4th ed. Lippincott Williams & Wilkins, Philadelphia, pp. 2175–2196.

Martin, J.D., King, D.M., Slauch, J.M., Frisque, R.J., 1985. Differences in regulatory sequences of naturally occurring JC virus variants. J. Virol. 53, 306–311.

Matsuda, M., Jona, M., Yasui, K., Nagashima, K., 1987. Genetic characterization of JC virus Tokyo-1 strain, a variant oncogenic in rodents. Virus Res. 7, 159–168.

Padgett, B.L., Walker, D.L., 1973. Prevalence of antibodies in human sera against JC virus, an isolate from a case of progressive multifocal leukoencephalopathy. J. Infect. Dis. 127, 467–470.

Padgett, B.L., Walker, D.L., ZuRhein, G.M., Eckroade, R.J., Dessel, B.H., 1971. Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. Lancet 297, 1257–1260.

Pavesi, A., 2003. African origin of polyomavirus JC and implications for prehistoric human migrations. J. Mol. Evol. 56, 564–572.

Ramachandran, S., Deshpande, O., Roseman, C.C., Rosenberg, N.A., Feldman, M.W., Cavalli-Sforza, L.L., 2005. Support from the relationship of genetic and geographic distance in human populations for a serial founder effect originating in Africa. Proc. Natl. Acad. Sci. U. S. A. 102, 15942–15947.

Stoner, G.L., Jobes, D.V., Fernandez Cobo, M., Agostini, H.T., Chima, S.C., Ryschkewitsch, C.F., 2000. JC virus as a marker of human migration to the Americas. Microbes Infect. 2, 1905–1911.

Sugimoto, C., Kitamura, T., Guo, J., Al-Ahdal, M.N., Shchelkunov, S.N., Otova, B., Ondrejka, P., Chollet, J.Y., El-Safi, S., Ettayebi, M., Grésenguet, G., Kocagöz, T., Chaiyarasamee, S., Thant, K.Z., Thein, S., Moe, K., Kobayashi, N., Taguchi, F., Yogo, Y., 1997. Typing of urinary JC virus DNA offers a novel means of tracing human migrations. Proc. Natl. Acad. Sci. U. S. A. 94, 9191–9196.

Sugimoto, C., Hasegawa, M., Kato, A., Zheng, H.-Y., Ebihara, H., Taguchi, F., Kitamura, T., Yogo, Y., 2002a. Evolution of human *Polyomavirus* JC: implications for the population history of humans. J. Mol. Evol. 54, 285–297.

Sugimoto, C., Hasegawa, M., Zheng, H.-Y., Demenev, V., Sekino, Y., Kojima, K., Honjo, T., Kida, H., Hovi, T., Vesikari, T., Schalken, J.A., Tomita, K., Mitsunobu, Y., Ikegaya, H., Kobayashi, N., Kitamura, T., Yogo, Y., 2002b. JC virus strains indigenous to northeastern Siberians and Canadian Inuits are unique but evolutionally related to those distributed throughout Europe and Mediterranean areas. J. Mol. Evol. 55, 322–335.

Suzuki, M., Zheng, H.-Y., Takasaka, T., Sugimoto, C., Kitamura, T., Beutler, E., Yogo, Y., 2002. Asian genotypes of JC virus in Japanese-Americans suggest familial transmission. J. Virol. 76, 10074–10078.

Thompson, J.D., Higgins, D.G., Gibson, T.J., 1994. CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. Nucleic Acids Res. 22, 4673–4680.

Tominaga, T., Yogo, Y., Kitamura, T., Aso, Y., 1992. Persistence of archetypal JC virus DNA in normal renal tissue derived from tumor-bearing patients. Virology 186, 736–741.

Yogo, Y., Sugimoto, C., 2001. The archetype concept and regulatory region rearrangement. In: Khalili, K., Stoner, G.L. (Eds.), Human Polyomaviruses: Molecular and Clinical Perspectives. John Wiley & Sons, New York, pp. 127–148.

Yogo, Y., Kitamura, T., Sugimoto, C., Ueki, T., Aso, Y., Hara, K., Taguchi, F., 1990. Isolation of a possible archetypal JC virus DNA sequence from nonimmunocompromised individuals. J. Virol. 64, 3139–3143.

Yogo, Y., Iida, T., Taguchi, F., Kitamura, T., Aso, Y., 1991. Typing of human polyomavirus JC virus on the basis of restriction fragment length polymorphisms. J. Clin. Microbiol. 29, 2130–2138.

Yogo, Y., Sugimoto, C., Zheng, H.-Y., Ikegaya, H., Takasaka, T., Kitamura, T., 2004. JC virus genotyping offers a new paradigm in the study of human populations. Rev. Med. Virol. 14, 179–191.

Zheng, H.-Y., Kitamura, T., Takasaka, T., Chen, Q., Yogo, Y., 2004. Unambiguous identification of JC polyomavirus strains transmitted from parents to children. Arch. Virol. 149, 261–273.