JC Virus Strains Indigenous to Northeastern Siberians and Canadian Inuits Are Unique But Evolutionally Related to Those Distributed Throughout Europe and Mediterranean Areas

Chie Sugimoto,1 Masami Hasegawa,2 Huai-Ying Zheng,1,3 Vladimir Demenev,4 Yoshiharu Sekino,5 Kazuo Kojima,6 Takeo Honjo,7 Hiroshi Kida,8 Tapani Hovi,9 Timo Vesikari,10 Jack A. Schalken,11 Kyoichi Tomita,3 Yukari Mitsuobu,1 Hiroshi Ikegaya,12 Nobuyoshi Kobayashi,1 Tadaichi Kitamura,3 Yoshiaki Yogo1

1 Laboratory of Viral Infection, Department of Microbiology and Immunology, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
2 Department of Prediction and Control, The Institute of Statistical Mathematics, 4-6-7 Minami-Azabu, Minato-ku, Tokyo 106-8569, Japan
3 Department of Urology, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
4 Department of Public Health, Administration of Khabarovsk Territory, Khabarovsk, Russia
5 The Great Journey, 1-6 Wakaba, Shinjuku-ku, Tokyo 160-0011, Japan
6 The Last Great Expedition on the Earth, 2-454 Kurashiki, Higashiyamato, Tokyo 207-0032, Japan
7 Himalayan Veterinary Hospital, 2-43-11 Mitsuhi, Musashimurayama, Tokyo 208-0021, Japan
8 Laboratory of Microbiology, Department of Disease Control, Graduate School of Veterinary Medicine, Hokkaido University, Kita 18, Nishi 9, Kita-ku, Sapporo 060-0818, Japan
9 Department of Virology, National Public Health Institute, Mannerheimintie, 166, 00380 Helsinki, Finland
10 Department of Virology and Vaccine Research, University of Tampere Medical School, 33101 Tampere, Finland
11 Urological Research Laboratory, University Hospital Nijmegen, Nijmegen, The Netherlands
12 Department of Forensic Medicine, The Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract. Human polyomavirus JC virus (JCV) isolates around the world are classified into more than 10 geographically distinct genotypes (designated as subtypes). Evolutionary relationships among JCV subtypes were recently examined, and the following pattern of JCV evolution was indicated. The ancestral JCV first divided into three superclusters, designated Types A, B, and C. A split in Type A generated two subtypes, EU-a and -b, containing mainly European and Mediterranean isolates. The split in Type B generated Af 2 (the major African subtype), Bi-c (a minor European subtype), and various Asian subtypes. Type C generated a single subtype (Afl), consisting of isolates derived from western Africa. In this study, JCV isolates prevalent among northeastern Siberians and Canadian Inuits were evaluated in the context of the above-described pattern of JCV evolution. The Siberian/Arctic JCV isolates were classified as belonging mainly to Type A, based on the result of a preliminary phylogenetic analysis. We then examined, using the whole-genome approach, the phylogenetic relationships among worldwide Type A isolates. In neighbor-joining and maximum-likelihood analyses, Type A JCVs worldwide consistently diverged into three subtypes, EU-a, -b, and -c, with high bootstrap probabilities. EU-c was constructed only by northeastern Siberian isolates, derived mainly from Nanais living in the lower Amur River region, and was shown to have been generated by the first
split in Type A. Most Siberian/Arctic isolates derived from Chukchis, Koryaks, and Canadian Inuits formed a distinct cluster within the EU-a subtype, with a high bootstrap probability. Based on the present findings, we discuss ancient human migrations, accompanied by Type A JCVs, across Asia and to Arctic areas of North America.

Key words: JC virus (JCV) — Complete DNA sequences — JCV evolution — JCV types — Siberians — Europeans — Population history — Human migration.

Introduction

JC virus (JCV) is a member of the Polyomaviridae family. Its genome is a single molecule of covalently closed, circular, superhelical double-stranded DNA about 5100 bp long (Cole and Conzen 2001). JCV is ubiquitous in the human population, although it is known to be the etiological agent of progressive multifocal leukoencephalopathy (PML) (Padgett et al. 1971). Primary infection with this virus usually occurs asymptotically during childhood (Padgett and Walker 1973; Walker and Padgett 1983). JCV persists in the renal tissue of most adults, who excrete progeny viruses in the urine (Chesters et al. 1983; Tominaga et al. 1992; Kitamura et al. 1990, 1997). JCV is usually transmitted from parents to children during long-term cohabitation (Kunitake et al. 1995; Yogo et al. 2000) but is rarely transmitted between human populations (Kato et al. 1997).

JCV isolates in the world were classified into more than 10 groups (designated as subtypes) according to the results of phylogenetic analysis of a 610-bp region (IG region) of the viral genome (Sugimoto et al. 1997; Guo et al. 1998). Each JCV subtype occupies a unique domain in the Old World (Sugimoto et al. 1997; Guo et al. 1998). The evolutionary relationships among JCV subtypes were recently examined (Sugimoto et al. 2002) using the whole-genome approach, with which a highly reliable phylogeny of JCV isolates can be reconstructed (Jobes et al. 1998; Hatwell and Sharp 2000), and the following pattern of JCV evolution was indicated. The ancestral JCV first divided into three superclusters, designated Types A, B, and C. A split in Type A generated two subtypes, EU-a and -b, containing mainly European and Mediterranean isolates. The first split in Type B generated A12 (the major African subtype). Subsequent splits in Type B generated B1-c (a minor European subtype) and all seven Asian subtypes (B1-a, -b, and -d, B2, MY, CY, and SC). Type C generated a single subtype (Af1), consisting of isolates derived from western Africa.

The geographic distributions of JCV subtypes (Sugimoto et al. 1997; Guo et al. 1998) indicated a close correlation between JCV subtypes and human populations. Indeed, Asian subtypes of JCV were detected in Native Americans and Pacific Island populations (Agostini et al. 1997b; Sugimoto et al. 2000; Ryschkewitsch et al. 2000; Stoner et al. 2000), which is consistent with the Asian origin of these native populations. Therefore, we considered that the identification of JCV genotypes indigenous to northeastern Siberians and Arctic populations in North America would provide insights into the origin of these populations. We report here that a novel subtype belonging to Type A and a unique cluster within subtype EU-a occur in northeastern Siberians and Canadian Inuits. Based on the present findings, we discuss ancient human migrations, accompanied by Type A JCVs, across Asia and to Arctic areas of North America.

Materials and Methods

Urine Samples

We collected 19 to 36 urine samples from Nanais, Chukchis, and Koryaks in northeastern Siberia, Inuits in Arctic areas of Canada, and various tribes living in the Kolyma basin. Sites of urine collection are shown in Fig. 1. All urine donors were at least 25 years old and were natives of each region. The donors were either healthy volunteers or general patients. In addition, urine samples were collected from general patients in Finland (Tampere, Helsinki), The Netherlands (Amsterdam), and the Russian Federation (Khabarovsk). The donors were at least 50 years old and were natives of each region. The donors in Khabarovsk were all Slavs. In addition, we used a large number of urine samples collected previously at various sites in Europe and the Mediterranean (Sugimoto et al. 1997).

DNA Analysis

The viral DNA was extracted from the urine as described previously (Kitamura et al. 1990). The 610-bp IG region was amplified by PCR using primers P1 and P2 (Kunitake et al. 1995) and Pwo DNA polymerase with proofreading activity (Roche Diagnostics Corporation, Mannheim, Germany). The IG region encompasses the 3’-terminal regions of both the T-antigen and the VP1 genes and was previously established as a region of the JCV genome that contains abundant type-determining sites (Ault and Stoner 1992). The IG region was sequenced with an autossequencer (ABI377; Perkin-Elmer, Foster City, CA) according to the protocol provided by the company. Entire JCV DNA clones were cloned into pUC19 at the unique BamHI site as described previously (Yogo et al. 1991). The resultant complete JCV DNA clones were prepared using a QIA-GEN Plasmid Maxi kit (QIAGEN GmbH, Hilden, Germany). Purified plasmids were sequenced as described (Sugimoto et al. 2002).

Phylogenetic Analysis

The noncoding regulatory region of the JCV genome was excluded from phylogenetic analysis, as this region is hypervariable, espe-