Two distinct genotypes (MY-x and MX) of JC virus previously identified in Hokkaido Ainu

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Abstract Genotyping the urinary JC virus (JCV) DNA is a useful means to gain new insights into the origin of ethnic groups. We recently detected thirteen JCV isolates from the Ainu, an indigenous population living on Japan's northernmost island (Hokkaido). Based on phylogenetic analysis, these isolates were classified into five genotypes: two (MX and MY-x) were first identified in the Ainu, two (EU-a/Arc and EU-c) are prevalent in northeastern Siberians and an Arctic tribe, and one (MY-b) is widespread among Hondo Japanese, i.e. contemporary Japanese excluding the Ainu. Although these findings have several potential implications for the development of the modern Ainu, further studies are required to reach a definite conclusion. In this report, an isolate in a forensic subject whose ethnic origin was Ainu belonged to the MX genotype and two isolates recently identified in South Koreans and grouped as Native American isolates belonged to the MY-x genotype. The present findings suggest that the MX genotype of JCV is unique to the Ainu, whereas MY-x is spread among some Northeast Asian populations.

Key words: Ainu, JC virus, genotype, MX, MY-x

Introduction

JC virus (JCV) is a member of the *Polyomaviridae* family. Its genome is a single molecule of covalently closed, circular double-stranded DNA about 5100 bp in length (Cole and Conzen, 2001). Although JCV causes progressive multifocal leukoencephalopathy (PML) in immunocompromised patients (Walker, 1985), it is ubiquitous in the human population; it infects children asymptomatically, then persists in renal tissue throughout life (Padgett and Walker, 1973; Chesters et al., 1983; Tominaga et al., 1992; Kitamura et al., 1997). In most adults, renal JCV is not latent, but instead replicates and its progeny are excreted into urine (Kitamura et al., 1990, 1994; Agostini et al., 1996). JCV strains around the world can be classified into more than ten major genotypes, with each genotype occupying a unique geographical domain (Sugimoto et al., 1997; Yogo et al., 2004). Analysis of JCV genotypes has thus provided new insights into the origins of various ethnic groups throughout the world (e.g. Kitamura et al., 1998; Guo et al., 2001; Saruwatari et al., 2002; Miranda et al., 2004; Takasaka et al., 2004; Yogo et al., 2004).

Using phylogenetic analysis, Yogo et al. (2003) recently

analyzed thirteen JCV isolates from the Ainu, an indigenous population living on Hokkaido, the northernmost island of Japan, and classified them into five genotypes: two (MX and MY-x) were first identified in the Ainu, two (EU-a/Arc and EU-c) were prevalent in northeastern Siberians and an Arctic tribe, and one (MY-b) was widespread among Hondo Japanese (i.e. contemporary Japanese, excluding the Ainu). Although two new genotypes were recognized in Yogo et al.'s (2003) study, the data size was too small for them to draw definite conclusions about the ethnic distribution of these genotypes. In the present study, we performed a detailed phylogenetic analysis of three unique JCV isolates, one identified by ourselves in an Ainu subject and two detected by Cui et al. (2004) in Koreans living in Seoul, South Korea. The latter two isolates were described as Type 2A2, which is characteristic of Native Americans (Cui et al., 2004).

Materials and Methods

Subject

A 70-year-old male Ainu who was born in Makubetsu, southern Hokkaido, and died of pneumonia was the subject of this study. A medico-legal autopsy was performed at his family's request. His ethnic origin was found to be Ainu according to interviews with the family.

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Table 1. JCV isolates whose complete DNA sequences were used for the phylogenetic analysis

Genotype	Isolate	Geographic origin (ethnic origin)	Accession no. ¹	Reference
Afl	#601	USA	AF015537	Agostini et al. (1998c)
Afl	GH-1	Ghana	AB038252	Kato et al. (2000)
Afl	GH-2	Ghana	AB038253	Kato et al. (2000)
Afl	GH-3	Ghana	AB048545	Sugimoto et al. (2002a)
Afl	GH-4	Ghana	AB048546	Sugimoto et al. (2002a)
EU-a	G2	Germany	AB038251	Kato et al. (2000)
EU-a	N2	Netherlands	AB048574	Sugimoto et al. (2002a)
EU-a	SW-3	Sweden	AB048575	Sugimoto et al. (2002a)
EU-a	UK-2	UK	AB048576	Sugimoto et al. (2002a)
EU-a	IT-5	Italy	AB048568	Sugimoto et al. (2002a)
EU-a	#123	USA	AF015527	Agostini et al. (1998a)
EU-a	#124	USA	AF015526	Agostini et al. (1998a)
EU-a	Mad-1	USA	J02226	Frisque et al. (1984)
EU-a/JK ²	AT-2	Japan	AB048569	Sugimoto et al. (2002a)
EU-a/JK	AT-4	Japan	AB048570	Sugimoto et al. (2002a)
EU-a/JK	HR-5	Japan	AB048572	Sugimoto et al. (2002a)
EU-a/JK	HR-13	Japan	AB048571	Sugimoto et al. (2002a)
EU-a/JK	SD-9	Japan	AB048573	Sugimoto et al. (2002a)
EU-a/JK	SK-6	South Korea	AB183152	Yogo et al. (2004)
EU-a/Arc	ES-1	Canada (Inuit)	AB074578	Sugimoto et al. (2002b)
EU-a/Arc	ES-3	Canada (Inuit)	AB074579	Sugimoto et al. (2002b)
EU-a/Arc	KO-2	Siberia (Koryak)	AB074585	Sugimoto et al. (2002b)
EU-a/Arc	KO-3	Siberia (Koryak)	AB074586	Sugimoto et al. (2002b)
EU-a/Arc	KO-5	Siberia (Koryak)	AB074587	Sugimoto et al. (2002b)
EU-a/Arc	AN-12	Japan (Ainu)	AB092586	Yogo et al. (2003)
EU-b	GR-3	Greece	AB048563	Sugimoto et al. (2002a)
EU-b	MR-7	Morocco	AB048564	Sugimoto et al. (2002a)
EU-b	N25	Netherlands	AB048565	Sugimoto et al. (2002a)
EU-b	SP-1	Spain	AB048566	Sugimoto et al. (2002a)
EU-b	UK-1	UK	AB048567	Sugimoto et al. (2002a)
EU-b	#402	USA	AF015528	Agostini et al. (1998a)
EU-c	AM-5	Siberia (Nanai)	AB074576	Sugimoto et al. (2002b)
EU-c	AM-7	Siberia (Nanai)	AB074577	Sugimoto et al. (2002b)
EU-c	AM-18	Siberia (Nanai)	AB074575	Sugimoto et al. (2002b)
EU-c	SI-1	Siberia	AB074589	Sugimoto et al. (2002b)
EU-c	SI-7	Siberia	AB074590	Sugimoto et al. (2002b)
EU-c	AN-3	Japan (Ainu)	AB092579	Yogo et al. (2003)
EU-c	AN-5	Japan (Ainu)	AB092581	Yogo et al. (2003)
EU-c	AN-11	Japan (Ainu)	AB092585	Yogo et al. (2003)
Af2	#308	Tanzania	U73500	Agostini et al. (1997)
Af2	#311	USA (African American)	U73501	Agostini et al. (1997)
Af2	#312	USA (African American)	U73502	Agostini et al. (1997)
Af2	ET-3	Ethiopia	AB048547	Sugimoto et al. (2002a)
B1-a	ML-1	Malaysia	AB048548	Sugimoto et al. (2002a)
B1-a	C2	Taiwan	AB048549	Sugimoto et al. (2002a)
B1-a	CB-2	China	AB048550	Sugimoto et al. (2002a)
B1-b	MO-3	Mongolia	AB048551	Sugimoto et al. (2002a)
B1-b	MO-5	Mongolia	AB048552	Sugimoto et al. (2002a)
B1-b	SL-2	Sri Lanka	AB048553	Sugimoto et al. (2002a)
B1-b	#230	USA (African American)	AF015536	Agostini et al. (1998b)
B1-c	N4	Netherlands	AB048554	Sugimoto et al. (2002a)
B1-c	GS/K	Germany	AF004349	Loeber and Dörries (1988)
B1-c	GS/B	Germany	AF004350	Loeber and Dörries (1988)
B1-c	#223	USA (African American)	AF015532	Agostini et al. (1998b)
B1-c	#227	USA (European American)	AF015533	Agostini et al. (1998b)
B1-d	SA-3	Saudi Arabia	AB048555	Sugimoto et al. (2002a)
B1-d	SA-5	Saudi Arabia	AB048556	Sugimoto et al. (2002a)
B2	IN-6	India	AB048557	Sugimoto et al. (2002a)
B2	MU-3	Mauritius	AB048558	Sugimoto et al. (2002a)
B2	MU-9	Mauritius	AB048559	Sugimoto et al. (2002a)
CY	CY	Japan	AB038249	Kato et al. (2000)
CY	Tky-2a	Japan	AB038255	Kato et al. (2000)
CY	CB-3	Japan	AB048560	Sugimoto et al. (2002a)
CY	MO-1	Mongolia	AB048561	Sugimoto et al. (2002a)
CY	MO-6	Mongolia	AB048562	Sugimoto et al. (2002a)

Table 1. (continued)

Genotype	Isolate	Geographic origin (ethnic origin)	Accession no. ¹	Reference
MX	AN-9	Japan (Ainu)	AB092584	Yogo et al. (2003)
MX	AN-13	Japan (Ainu)	AB092587	Yogo et al. (2003)
MX	ANF	Japan (Ainu)	AB185020	This study
MY-a	Aic-1	Japan	AB081005	Zheng et al. (2003)
MY-a	AT-8	Japan	AB048577	Sugimoto et al. (2002a)
MY-a	JP-7	Japan	AB081016	Zheng et al. (2003)
MY-a	YI	Japan	AB081030	Zheng et al. (2003)
MY-b	Tokyo-1	Japan	AF030085	Agostini et al. (1998b)
MY-b	Tky-1	Japan	AB038254	Kato et al. (2000)
MY-b	HR-7	Japan	AB048578	Sugimoto et al. (2002a)
MY-b	MY	Japan	AB038250	Kato et al. (2000)
MY-b	SK-1	South Korea	AB081028	Zheng et al. (2003)
MY-b	SK-4	South Korea	AB081029	Zheng et al. (2003)
MY-b	AN-4	Japan (Ainu)	AB092580	Yogo et al. (2003)
MY-b	AN-6	Japan (Ainu)	AB092582	Yogo et al. (2003)
MY-b	AN-8	Japan (Ainu)	AB092583	Yogo et al. (2003)
MY-c	#224	USA (Hispanic)	AF015529	Agostini et al. (1998b)
MY-c	ME-5	Mexico (Tarahumalan)	AB081021	Zheng et al. (2003)
MY-c	ME-14	Mexico (Tarahumalan)	AB081018	Zheng et al. (2003)
MY-c	ME-16	Mexico (Tarahumalan)	AB081019	Zheng et al. (2003)
MY-c	GU-8	Guatemala (Mayan)	AB081015	Zheng et al. (2003)
MY-d	#225	USA (Navaho)	AF015530	Agostini et al. (1998b)
MY-d	#226	USA (Navaho)	AF015531	Agostini et al. (1998b)
MY-e	GU-4	Guatemala (Mayan)	AB081014	Zheng et al. (2003)
MY-e	GU-15	Guatemala (Mayan)	AB081011	Zheng et al. (2003)
MY-e	GU-21	Guatemala (Mayan)	AB081012	Zheng et al. (2003)
MY-e	GU-25	Guatemala (Mayan)	AB081013	Zheng et al. (2003)
MY-e	ME-8	Mexico (Tarahumalan)	AB081022	Zheng et al. (2003)
MY-f	PE-1	Peru (Andean)	AB081023	Zheng et al. (2003)
MY-f	PE-11	Peru (Andean)	AB081024	Zheng et al. (2003)
MY-f	PE-12	Peru (Andean)	AB081025	Zheng et al. (2003)
MY-f	PE-16	Peru (Andean)	AB081026	Zheng et al. (2003)
MY-f	PE-21	Peru (Andean)	AB081027	Zheng et al. (2003)
MY-g	#228	USA (Navaho)	AF015534	Agostini et al. (1998b)
MY-g	#229	USA (European American)	AF015535	Agostini et al. (1998b)
MY-g	CN-1	Canada (Beaver/Dene Tha')	AB081007	Zheng et al. (2003)
MY-g	CN-13	Canada (Beaver/Dene Tha')	AB081006	Zheng et al. (2003)
MY-g	CN-15	Canada (Beaver/Dene Tha')	AB081008	Zheng et al. (2003)
MY-g	CN-25	Canada (Beaver/Dene Tha')	AB081009	Zheng et al. (2003)
MY-g	CN-28	Canada (Beaver/Dene Tha')	AB081010	Zheng et al. (2003)
MY-x	AN-1	Japan (Ainu)	AB092578	Yogo et al. (2003)
MY-x	255A	South Korea	AY121910	Cui et al. (2004)
MY-x	256A	South Korea	AY121911	Cui et al. (2004)
MY	ME-4	Mexico (Tarahumalan)	AB081020	Zheng et al. (2003)
MY	ME-12	Mexico (Tarahumalan)	AB081017	Zheng et al. (2003)
SC	CW-2	China	AB048579	Sugimoto et al. (2002a)
SC	ID-1	Indonesia	AB048580	Sugimoto et al. (2002a)
SC	ML-6	Malaysia	AB048581	Sugimoto et al. (2002a)
SC	MO-11	Mongolia	AB048582	Sugimoto et al. (2002a)
2E	#233	New Britain (Tolai)	AF281605	Jobes et al. (2001)
2E	#234	Guam (Chamorro)	AF281606	Jobes et al. (2001)
8A	#801	PNG (Highlander)	AF281623	Jobes et al. (2001)
8A	#802	PNG (Highlander)	AF281624	Jobes et al. (2001)
8B	#803	PNG (Highlander)	AF281625	Jobes et al. (2001)
8B	#804	PNG (Highlander)	AF281626	Jobes et al. (2001)

¹ GSDB, DDBJ, EMBL, and NCBI accession numbers.² EU-a/Arc has been renamed EU-a/JK (Yogo et al., 2004).

Figure 1. Neighbor-joining (NJ) phylogenetic tree relating 118 complete JCV DNA sequences. A phylogenetic tree was constructed from complete sequences, excluding regulatory sequences, using the NJ method. The phylogenetic tree was visualized using the TREEVIEW program (Page, 1996). The tree was rooted using Af1 as the outer group, as this genotype probably represents the ancestral type (Pavesi, 2003). The symbols for sequences are shown in Table 1. The number at each node in the tree indicates the bootstrap probability (BP, %) obtained from 1000 replicates (only values >70% are shown for major clusters). Superclusters (Types A, B, and C), genotypes (Af1, Af2, EU-a, EU-b, EU-c, B1-a, B1-b, B1-c, B1-d, B2, CY, MX, MY, 2E, 8A, and 8B), intra-EU-a subgroups (EU-a/Arc and EU-a/JK), and intra-MY subgroups (MY-a to MY-g and MY-x) are indicated. Isolates from the Ainu (Yogo et al., 2003; this study) and from Koreans (Cui et al., 2004) are shown in white on black backgrounds.

DNA extraction and analysis

About 5 ml of urine was collected from the subject's bladder and was used as the source for our extraction of viral DNA, as described by Kitamura et al. (1990). A 610-bp IG region was amplified by means of polymerase chain reaction (PCR) using the P1 and P2 primers (Kunitake et al., 1995). The entire JCV DNA was cloned into pUC19 at the unique *Bam*HI site, as described by Yogo et al. (1991), and the resultant clone, which carried the entire JCV DNA, was sequenced as described by Sugimoto et al. (2002a).

Reported complete DNA sequences of JCV

The complete JCV DNA sequences reported previously and used in this study are shown in Table 1, along with their GSDB, DDBJ, EMBL, and NCBI accession numbers.

Phylogenetic Analysis

The non-coding regulatory region of the JCV genome was excluded from our phylogenetic analysis, as this region is hypervariable, especially in JCV isolates derived from the brains of patients with PML (Yogo and Sugimoto, 2001). DNA sequences were aligned using the CLUSTAL W program (Thompson et al., 1994) with a gap-opening penalty of 15.00 and a gap-extension penalty of 6.66. To evaluate the phylogenetic relationships among DNA sequences, we used the neighbor-joining (NJ) method (Saitou and Nei, 1987) in CLUSTAL W. Divergences were estimated using Kimura's two-parameter method (Kimura, 1980). To assess the confidence limit of the branching patterns of the NJ tree, bootstrap probabilities (BPs) were estimated using 1000 bootstrap replicates (Felsenstein, 1985) in CLUSTAL W. BPs greater than 70% were considered to be significant (Hillis and Bull, 1993). A phylogenetic tree was then visualized using the TREEVIEW program (Page, 1996).

Results

As the urine sample from the Ainu subject gave positive amplification in the PCR process, we attempted to establish complete clones of the JCV DNA from the urine. We obtained a complete JCV DNA clone, which we designated ANF. We then sequenced this clone completely. Cui et al. (2004) recently reported various JCV isolates in Asia, including China, South Korea, and India. Among these isolates, two from Seoul (255A and 256A) attracted our attention because despite their Asian origin, they were described as a genotype (Type 2A2) formerly considered to be characteristic of Native Americans (Cui et al., 2004). We constructed an NJ phylogenetic tree from the complete DNA sequences of ANF, 255A, and 256A, together with 118 complete sequences that had been collected from around the world, including ten detected in the Ainu (Yogo et al., 2003). Based on the resulting tree (Figure 1), we conclude that ANF and two isolates (AN-9 and AN-13) that had previously been detected in the Ainu (Yogo et al., 2003) formed a distinct clade (designated MX), with a high bootstrap probability (100%). In contrast, the Korean isolates (255A and 256A) together with an isolate (AN-1) from an Ainu formed another distinct clade (MY-x) with a 100% BP (Figure 1). MY-x and the other MY subgroups (MY-a to MY-g) consti-

tuted a superclade, designated MY. As previously shown (Yogo et al., 2003), the MX and MY grouping has been demonstrated with a significantly high BP (83%; Figure 1).

Discussion

Yogo et al. (2003) detected MY-x and MX in only one or a few subjects. Therefore, the ethnic distribution of these genotypes required further study. In the present study, we demonstrated the presence of the MX genotype in a forensic subject whose origin was Ainu. MX was previously detected at two distant sites (Asahikawa and Shiraoi) on Hokkaido (Yogo et al., 2003). In the present study, we detected MX in a subject from another site on Hokkaido (i.e. Makubetsu), which suggests that the MX genotype of JCV is widespread among the Ainu, albeit at a lower frequency.

We found that two isolates from Seoul belonged to MY-x, a subgroup within genotype MY (Yogo et al., 2003). These isolates were previously described as belonging to the Native American subgroup of MY (named Type 2A2; Cui et al., 2004), but the result of our analysis suggests that this classification should be revised. Although MY-x was distributed in two distinct human populations (i.e. the Ainu and Koreans), further division of the MY-x isolates was not demonstrated. This suggests that peoples carrying the MY-x genotype migrated to the Korean Peninsula and Hokkaido relatively recently (i.e. not earlier than 10000 years ago).

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