Sequence Identity between the Genomes of Humans and Viruses

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Key Words

Virus-human interactions • Viral diseases • Human genome sequence • Virus genome sequence • Short sequence identity • Basic local alignment search tool

Abstract

Objective: People exposed to viruses usually do not develop diseases. Viruses cause diseases; however, most of the pathologic effects of these diseases are not caused directly by the viruses but by the side effects of the immune response. It is possible that sequence identity may exist between viruses and humans and may be biologically relevant to the infection of virus. The aim of this study was to find out whether sequence identity exists between viruses and humans. **Methods:** BLAST searches of virus genome sequences against human genome were performed using the resources of the National Center for Biotechnology Information (NCBI). **Results:** All the viruses that were compared to humans contain different numbers of short identical regions to the human genome. Each identical region was 20–30 nt and some were found at multiple sites within the human genome. **Conclusion:** A new role of the virus in the relationship between viruses and humans was taken into account. We assume that viruses have brought their sequence into the human genome in the long past history of

human-virus interaction. In the process, viruses play roles as carriers to transfer external sequence information into the human genome.

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Introduction

The relationship between viruses and humans is still not completely understood. There are many viruses on earth, but not all of them cause diseases. When exposed to the same virus, some people get sick, but most remain healthy. Viruses cause diseases; however, most of the pathologic effects of these diseases are not caused directly by the viruses but by the side effects of the immune response. Viruses only aim to replicate themselves but not to kill the host. In contrast, human beings try to eradicate all disease-causing viruses. Unfortunately, they have failed. The long-term interaction of humans and viruses may result in a balance. Viruses are possibly not just pathogens. Thus, we speculate that a sequence identity exists between genomes of viruses and humans. The publication of the human genome and large numbers of virus genome sequences enables us to conduct an assessment of identical sequences between humans and viruses [1].

Table 1. Algorithm parameters

Program	blastn
Word size	11
Expect value	1
Hitlist size	100
Match/mismatch scores	1, -4
Gap costs	5, 2
Low complexity filter	yes
Filter string	L; R -d repeat/repeat_9606; m
Genetic code	1

Methods

BLAST search of several virus genomes against the genome of humans was performed with the resources of the National Center for Biotechnology Information (NCBI) (http://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Nucleotides&PROGRAM=blastn&MEGABLAST=on&BLAST_PROGRAMS=megaBlast&PAGE_TYPE=BlastSearch&SHOW_DEFAULTS=on&LINK_LOC=blasthome). On the web search page above, choose the database 'Human genomic plus transcript' and the program 'Somewhat similar sequences (blastn)'. The search parameters are shown in table 1. The GeneBank accession numbers of virus genomes are accessible on the web (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=Genome>). Readers can perform the alignments of all the viruses of interest with the method we introduced.

The following viruses were compared: human immunodeficiency virus 1 (HIV-1, GeneBank accession No. NC_001802), severe acute respiratory syndrome-associated coronavirus (SARS-CoV, NC_004718), human papillomavirus 16 (HPV-16, NC_001526), hepatitis B virus (HBV, NC_003977), hepatitis C virus (HCV, NC_009825), variola virus (NC_001611), adenovirus-1 (AC_000017), adenovirus 2 (NC_001405), adenovirus 9 (NC_010956), adenovirus 11 (AC_000015), adenovirus 17 (NC_002067), adenovirus 40 (NC_001454), adenovirus A (NC_001460), adenovirus E (NC_003266), B19 virus (NC_000883), Dengue virus type 1 (NC_001477), Dengue virus 2 (NC_001474), Dengue virus 3 (NC_001475), Dengue virus 4 (NC_002640), Japanese encephalitis virus (NC_001437), West Nile virus (NC_001563), yellow fever virus (NC_002031), hepatitis A virus (NC_001489), hepatitis delta virus (NC_001653), hepatitis E virus (NC_001434), human herpesvirus 1 (NC_001806), human herpesvirus 2 (NC_001798), human herpesvirus 3 (NC_001348), human herpesvirus 4 (NC_007605), human herpesvirus 5 (NC_001347), human herpesvirus 6 (NC_001664), human herpesvirus 7 (NC_001716), human herpesvirus 8 (NC_003409), HIV-2 (NC_001722), rabies virus (NC_001542), human parainfluenza virus 1 (NC_003461), human parainfluenza virus 2 (NC_003443), human parainfluenza virus 3 (NC_001796), rubella virus (NC_001545), simian virus 40 (NC_001669), influenza A virus, influenza B virus, influenza C virus, human coronavirus HKU1 (NC_006577), human papillomavirus type 6 (NC_001355), human papillomavirus type 18 (NC_001357), enterobacteria phage 13a (NC_011045), and tobacco mosaic virus (NC_001367).

Results

We compared large numbers of DNA virus and RNA virus genomes with the human genome database with the program BLAST [2]. These viruses included the oldest viruses (poxviruses, rabies virus) and newly discovered viruses (SARS-CoV, HIV), small viruses (HBV) and large viruses (variola virus). Unexpectedly, we found that all the viruses that had been compared to humans contain a different number of short regions identical to the human genome (100% identity). We only list the BLAST results of HIV-1, SARS-CoV, HCV, HPV-16, HBV and variola virus as representative RNA and DNA viruses due to space constraints (tables 2–7). According to the BLAST results, we found that a DNA virus or a virus with a larger genome often has more identical regions than an RNA virus. For a specific virus, different subtypes contained different numbers of identical regions.

Each of the identical regions was 20–30 nt and some were found at multiple sites within the human genome. Most of these identical regions were located in intergenic regions of the human genome, some were located in regions of human genes, and a few were located in noncoding regions. They were found in either the plus or minus orientation in the human genome. Interestingly, the lengths of these identical regions never exceed 30 nt and they were widespread on the human chromosomes. These short identical sequences were found to be quite unrelated to miRNA sequences [3].

Most of the human genes that contain identical sequences have functions that can be generally termed metabolism according to the Gene Ontology (GO) database [4]. They encode enzymes, binding proteins and transporters involved in DNA replication and cell metabolism.

Discussion

The publication of the human genome sequence has provided the opportunity to analyze host-virus interactions in a new way. In the current study, we investigate the possibility of sequence identity between the genomes of many viruses and humans. A previous study only compared the genomes of parvoviruses and their respective hosts [3]. They found several 17- to 26-nt identical sequences, and more importantly, the ontology of host genes in which identical regions were found highlighted several pathways or processes including the cytoskeleton,

Table 2. BLAST result of HCV

Name of region of sequence identity	HCV sequence nt	Sequence of identity	Human genes containing sequence, n	GeneBank accession No. of human genome	Features in part of human genome	E value
HCV-human-1	9122–9146	AAACCAAACCTCAAACCTCACTCCATT	1	NT_008984.17	FAT tumor suppressor homolog 3	0.038
HCV-human-2	2297–2319	AGATCCTCCCCTGCTCTTTCACC	1	NT_008046.15	intergenic region	0.61
HCV-human-3	2925–2947	AGACCTAGTATTTGACATCACAA	1	NT_004559.13	dynein, axonemal, heavy polypeptide 14	0.61
HCV-human-4	7238–7260	CTGTTCCCTCTCCCAGGAGGAAA	1	NT_034772.5	intergenic region	0.61

Table 3. BLAST result of HIV-1

Name of region of sequence identity	HIV sequence nt	Sequence of identity	Human genes containing sequence, n	GeneBank accession No. of human genome	Features in part of human genome	E value
HIV-1-human-1	3365–3388	AAATTATGGTACCAGTTAGAGAAA	1	NT_033899.7	intergenic region	0.15
HIV-1-human-2	7937–7960	ACCCCGAGGGGACCCGACAGGCC	1	NW_001838878.1	intergenic region	0.15
HIV-1-human-3	409–431	GAAAGAAAAAATATAAATTAAAA	1	NT_010783.14	intergenic region	0.6
HIV-1-human-4	3116–3138	ATTTATCAAGAGCCATTAAAAA	1	NT_010859.14	THO complex 1	0.6
HIV-1-human-5	8608–8630	ACTTTTAAAAAGAAAAGGGGGGA	1	NT_005403.16	intergenic region	0.6
HIV-1-human-6	3727–3749	AAATGAACAAGTAGATAAATTAG	1	NT_030059.12	intergenic region	0.6

Table 4. BLAST result of SARS-CoV

Name of region of sequence identity	SARS-CoV sequence nt	Sequence of identity	Human genes containing sequence, n	GeneBank accession No. of human genome	Features in part of human genome	E value
SARS-CoV-human-1	12251–15275	TAACATGCTTAGGATAATGGCCTCT	1	NT_022792.17	polypeptide N-acetylglucosaminyltransferase 17	0.12
SARS-CoV-human-2	3184–3207	GAGGAAGAAGAAGAGGAAGACTGG	1	NT_005403.16	intergenic region	0.49
SARS-CoV-human-3	15251–15274	TAACATGCTTAGGATAATGGCCTC	1	NT_008046.15	intergenic region	0.49

Table 5. BLAST result of HBV

Name of region of sequence identity	HBV sequence nt	Sequence of identity	Human genes containing sequence, n	GeneBank accession No. of human genome	Features in part of human genome	E value
HBV-human-1	2218–2240	CTGCCTTACTTTTGGAGAGAAA	1	NT_025741.14	intergenic region	0.21
HBV-human-2	1915–1936	GTATAAAGAATTGGAGCTTCT	1	NT_011362.9	protein tyrosine phosphatase, receptor type, T isoform 2 protein tyrosine phosphatase, receptor type, T isoform 1	0.83
HBV-human-3	2610–2631	AATGAAAAAAGGAGATTAAAT	1	NT_033927.7	intergenic region	0.83

Table 6. BLAST result of variola virus

Name of region of sequence identity	Variola virus sequence nt	Sequence of identity	Human genes containing sequence, n	GeneBank accession No. of human genome	Features in part of human genome	E value
Variola virus-human-1	105044-105071	GAGGATGATGATGAAAGAGGAAGATG	1	NT_024524.13	intergenic region	0.012
Variola virus-human-2	133978-134004	AAATTTTCTCTTAAAAATGTTTCT	1	NT_028405.11	intergenic region	0.048
Variola virus-human-3	26644-26669	TAAATTAATTTTATTAAATTAAT	1	NT_007592.14	leucine-rich repeat, containing 16	0.19
Variola virus-human-4	160783-160808	TAAATATCTTTAATAACAGAGTTTAAT	1	NT_009237.17	intergenic region	0.19
Variola virus-human-5	14356-14381	GTTTCTATATCTATATCTACATCTAT	1	NT_019546.15	intergenic region	0.19
Variola virus-human-6	55389-55413	AATGTTTCTTACATATTTTCTCT	1	NT_019546.15	protein tyrosine phosphatase, receptor type, Q	0.19
Variola virus-human-7	61183-61207	TAGTATATCCATACAATGGAACTACT	5	NT_007933.14	reelin isoform b, reelin isoform a	0.76
Variola virus-human-8	61183-61207	TAGTATATCCATACAATGGAACTACT	5	NT_006713.14	dimethylglycine dehydrogenase precursor	0.76
Variola virus-human-9	61183-61207	TAGTATATCCATACAATGGAACTACT	5	NT_006576.15	intergenic region	0.76
Variola virus-human-10	61183-61207	TAGTATATCCATACAATGGAACTACT	5	NT_011757.15	intergenic region	0.76
Variola virus-human-11	61183-61207	TAGTATATCCATACAATGGAACTACT	5	NT_005403.16	intergenic region	0.76
Variola virus-human-12	135901-135925	ATATTAGTATGTTATATATTATATA	1	NT_009714.16	intergenic region	0.76
Variola virus-human-13	76610-76634	CTGTGGAATAAAAAATAAACCAAGGAT	1	NT_010498.15	chromodomain helicase DNA binding protein 9	0.76
Variola virus-human-14	26651-26675	ATTTTTTATTAAATTAATTAATTAA	1	NW_001838972.2	intergenic region	0.76
Variola virus-human-15	18844-18868	CATATACACATTTTAATAAAAAATAAT	1	NT_034772.5	SEC24-related gene family, member A	0.76
Variola virus-human-16	15692-15716	TATTTTATGTTATTTTGTTAAAAA	1	NT_009952.14	glypican 5	0.76

Table 7. BLAST result of HPV-16

Name of region of sequence identity	HPV-16 sequence nt	Sequence of identity	Human genes containing sequence, n	GeneBank accession No. of human genome	Features in part of human genome	E value
HPV16-human-1	2363-2387	TTTTGTAAATCTAAAGCCATTTT	1	NT_010799.14	slingshot 2	0.032
HPV16-human-2	1899-1921	TTACAACATAGTTTAAATGATTG	1	NT_008583.16	protein kinase, cGMP-dependent, type 1 isoform 1 protein kinase, cGMP-dependent, type 1 isoform 2	0.51
HPV16-human-3	6696-6718	ACATATAAAAAATACTAACTTTAA	1	NT_011362.9	protein tyrosine phosphatase, receptor type, T isoform 2 protein tyrosine phosphatase, receptor type, T isoform 1	0.51

cell adhesion and Wnt signaling. They assumed that the sequence identity is relevant to persistent infection of parvoviruses.

All of the significant hits had an E value <1. Specially, the BLAST hit of human herpesvirus 1 had an E value of 6e-04. A search result of chance matches could be excluded.

A certain degree of nucleotide similarity may be due to conserved kinase, polymerase and nucleic acid binding proteins between humans and viruses, which could be classified into orthologs. It is estimated that over 8% of the human genome is made up of endogenous retroviruses that may contribute to the sequence identity [5].

It is interesting that the phenomenon of sequence identity is universal among all the viruses. HIV might bring their sequences into the human genome by integration [6]; however, this cannot explain the sequence identity of other RNA viruses. For a virus' lack of reverse transcriptase (for example, HCV), it is possible that some parts of transcribed human genomes moved from humans to viral genomes. Herpesvirus gene homologs had been found in the human genome [7]. It is believed that large DNA viruses (herpesviruses and poxviruses) 'acquire' these genes from humans for their own good by mechanisms of immune evasion [8–10]. This may contribute to short regions of sequence identity but still could not explain the phenomenon of other DNA viruses. A

model is needed to explain how the viral sequences were transferred to the host genome.

Why the human genome sequence regions are 100% identical to the viral sequences needs to be investigated further. Presumably, any sequence will deteriorate over time unless some outside force requires it to maintain a conserved base sequence and this outside force would allow a putative function to be established. Viruses may use the identical regions for their own benefits during the long time of evolution.

We have developed the hypothesis that viruses introduced short sequences into the human genome during the long-term history of virus-human interaction. The hypothesis is based on the fact that one identical region of the virus genome was found at multiple sites within the human genome. In the case of the variola virus, 5 different regions of the human genome contain sequences identical to nucleotide 61183–61207 of the virus genome (table 6). In this process, viruses play roles as carriers to transfer exogenous sequence information into humans, not just pathogens.

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