Review

# Genetic Diversity and Evolution of Human Rotaviruses Based on Whole Genome

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**Abstract** | Group A rotaviruses (RVA) are a major cause of severe viral diarrhea in infants and children. Although studies on the genetic diversity of the antigenically important RVA VP7- and VP4- protein encoding genes are important for vaccine development or judging the efficacy of existing RVA vaccines, they do not always provide conclusive information on the overall and complex genetic makeup of RVAs, as the remaining 9 RVA gene segments are also susceptible to the forces governing RVA genetic diversity. Whole genomic analysis of RVAs has revolutionized the study of RVA genomics, providing a plethora of conclusive and vital data on the overall genetic diversity, true origin and complex evolutionary patterns of human RVA strains. In this review, we have summarized and discussed the significance of recent research outcomes obtained from whole genomic analysis of common and unusual human RVAs.

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## Introduction

Rotavirus A (RVA) is the most common cause of severe viral gastroenteritis in infants and young children worldwide, causing approximately 453,000 deaths each year (Tate et al., 2012). Rotavirus belongs to the genus Rotavirus within the family Reoviridae. The rotavirus genome is composed of eleven segments of double-stranded RNA (Estes and Kapikian, 2007). These RNA segments encode six structural proteins (VP1-VP4, VP6 and VP7) and six nonstructural proteins (NSP1-NSP6) (Estes and Kapikian, 2007). The RVA outer capsid proteins VP7 and VP4 contain neutralization antigens, and by neutralization assays, have been classified into G and P serotypes, respectively (Estes and Kapikian, 2007). Apart from these serotypes, G and P genotypes based on genetic diversity of the VP7 and VP4 genes, respectively, have been defined, and at least 27 G types and 37 P types have been discriminated so far (Matthijnssens et al., 2011a; Trojnar et al., 2013). In human RVAs, G1, G2, G3, G4, G9, and G12 combined with P[4], P[6], and P[8] are frequently detected throughout the world, with G1P[8] being the most prevalent (Gentsch et al., 1996; Matthijnssens et al., 2009a; Santos and Hoshino, 2005). Currently, two oral live human RVA vaccines, RotarixTM (a monovalent vaccine manufactured by GlaxoSmithKline Biologicals, Belgium) and RotaTeqTM (a pentavalent vaccine manufactured by Merck & Co, USA), containing VP7 and VP4 of major G and P genotypes are available globally (Glass et al., 2013). Epidemiological surveillance of G and P genotypes are of great significance to judge the efficacy of the rotavirus vaccines as well as to understand the influence exerted by these vaccines on wild RVA strains.

Genetic diversity of rotaviruses is governed by at least


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four mechanisms; point mutations, reassortment, rearrangement, and intragenic recombination (Ghosh and Kobayashi, 2011). Among these, reassortment, which is an exchange/substitution of RNA segments between different rotavirus strains, contributes to the maximum genetic diversity of RVAs. Reassortment events often result in generation of RVA strains with novel constellation of RNA segments, thereby playing a major role in the genetic evolution of rotaviruses. All the eleven gene segments of RVAs are susceptible to reassortment events and other mechanisms of genetic diversity, such as accumulation of point mutations.

**Table 1:** *Genotypes assigned to the 11 gene segments of RVA strains*

| RVA gene | Genotype | Nucleotide sequence identity cut-off value (%)[a] | No. of genotypes[b] | Common genotypes in humans |
|---|---|---|---|---|
| VP7, | G | 80 | 27 | G1-G4, G9, G12 |
| VP4 | P | 80 | 37 | P[4], P[6], P[8] |
| VP6 | I | 85 | 17 | I1, I2 |
| VP1 | R | 83 | 9 | R1, R2 |
| VP2 | C | 84 | 9 | C1, C2 |
| VP3 | M | 81 | 8 | M1, M2 |
| NSP1 | A | 79 | 18 | A1, A2 |
| NSP2 | N | 85 | 10 | N1, N2 |
| NSP3 | T | 85 | 12 | T1, T2 |
| NSP4 | E | 85 | 15 | E1, E2 |
| NSP5 | H | 91 | 11 | H1, H2 |

[a]Nucleotide sequence identity cut-off value used to assign a RVA gene segment to one of the genotypes reported so far, or to a new RVA genotype. [b]RVA genotypes reported so far.

Therefore, to obtain conclusive data on the overall genetic diversity and evolution of RVAs, information on their whole genome, i.e., sequence data of all the 11 RNA segments, is indispensable. In 2008, the RCWG (Rotavirus classification working group) proposed a whole genome-based genotyping system for classification of RVAs in which all the 11 RVA gene segments (VP7-VP4-VP6-VP1-VP2-VP3-NSP1-NSP2-NSP3-NSP4-NSP5 genes) are assigned to respective genotypes (Gx-P[x]-Ix-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx, respectively (where x denotes the genotype number)) (Matthijnssense et al., 2008a). Introduction of the RCWG genotyping scheme resulted in generation of a plethora of data on whole genomes of human and animal RVAs, providing conclusive and vital insights into the overall genetic makeup, complex evolutionary patterns, reassortment events and interspecies transmission of RVAs. Genotype numbers of individual RNA segments identified so far are listed in Table 1. In this review, we have summarized and discussed the significance of recent research outcomes obtained from whole genomic analysis of human RVAs.

## Wa-like genogroup and DS-1-like genogroup

Applying the whole genome-based genotyping system, most human RVA strains have been classified into at least two major genogroups, i.e., Wa-like genogroup and DS-1-like genogroup, with genotype constellations G1/3/4-P[8]-I1-R1-C1-M1-A1-N1-T1-H1-H1 and G2-P[4]-I2-R2-C2-M2-A2-N2-T2-H2-H2, respectively (Matthijnssens et al., 2008a). Human RVA strains belonging to the Wa-like genogroup and DS-1-like genogroup were found to share several genotypes with those of porcine and bovine RVAs, respectively, indicating a common origin of the Wa-like human RVAs and porcine strains, and of DS-1-like human and bovine RVA strains (Matthijnssens et al., 2008a). Despite sharing several genotypes with those of porcine and bovine RVAs, strains of these two human RVA genogroups were found to be phylogenetically distinct from those of animal RVAs within the same genotype (Matthijnssens et al., 2008a). The Wa-like and DS-1-like genogroups are believed to be highly stable genetically, and are subjected to little genetic alterations. These genogroups are considered to have preferred gene constellations, which may be related to the functional fitness of all the 11 viral proteins, allowing them to spread, adapt and persist in human populations worldwide (Heiman et al., 2008). However, phylogenetic analyses of the whole genomes of strains belonging to these common genogroups have revealed that dynamic genetic evolutions do occur frequently among human RVAs, primarily within the genogroups.

McDonald et al. (2009) analyzed the whole genomes of 51 G3P[8] human RVA strains circulating in a single location in the US from 1974 to 1991, and found co-circulating Wa-like genogroup strains belonging to genetically distinct RVA clades (allele constellations), i.e., G3P[8] rotaviruses with different intra-genotype phylogenetic lineages for all the 11 RNA segments. Among these clades, a single clade appeared as a major clade after more than a decade, probably due to acquisition of fitness advantage after reassortment with

unidentified RVA strain(s). A subsequent study in the US analyzed the whole genomes of several co-circulating Wa-like genogroup G1P[8], G3P[8] and G12P[8] RVA strains during a period of five years, and reported the occurrence of intra-genogroup reassortment among these RVAs (McDonald et al., 2012). More recently, a large-scale whole genome-based study on G3P[8] human RVA strains collected from China over a period of 12 years revealed intra-genogroup reassortment events with co-circulating strains over the years (Wang et al., unpublished data). Interestingly, most of these reassortment events involved genes encoding the nonstructural proteins (Wang et al., unpublished data). Thus, among the RVAs of the Wa-like genogroup, reassortment occurs commonly, often generating co-circulating RVAs with different allelic constellations. However, only those with a higher fitness advantage become the prevalent strain in a population. In contrast to the Wa-like genogroup, evolutionary patterns for the DS-1 genogroup over a long-time period has not yet been well studied, although the whole genomes of several strains from different countries have been analyzed so far (Bányai et al., 2011; Chen et al., 2008; Heiman et al., 2008; Ghosh et al., 2011a, d; Jere et al., 2011). Thus, it is remains to be determined as to whether the DS-1-like genogroup exhibit similar evolutionary patterns as RVAs of the Wa-like genogroup.

## AU-1-like genogroup

By RNA-RNA hybridization, most of the human RVAs have been classified into at least two major genogroups, designated as Wa-like and DS-1-like, and one minor genogroup, represented by strain RVA/Human-tc/JPN/AU-l/1982/G3P3[9] (Nakagomi et al., 1989; Nakagomi and Nakagomi, 1991). AU-1-like RVAs have been detected occasionally in humans, and the whole genomes of only a few of these RVAs have been sequenced so far (Ghosh and Kobayashi, 2011; Ghosh et al., 2012b; Matthijnssens et al., 2011b; Wang et al., 2013). To date, strain AU-1 is the sole representative of the typical AU-1-like genotype constellation (G3-P[9]-R3-C3-M3-A3-N3-T3-E3-H3), whilst a few human RVA strains possessing other genotypes on an AU-1-like genotype backbone have also been reported (Ghosh and Kobayashi, 2011; Ghosh et al., 2012b; Matthijnssens et al., 2011a, b; Rahman et al., 2007; Wang et al., 2013). Recently, two Chinese human RVA G3P[9] strains (strains RVA/Human-tc/CHN/L621/2006/G3P[9] and RVA/Human-wt/CHN/E2451/2011/ G3P[9]) were found to possess a canine/feline-like H6 NSP5 genotype on an AU-1-like genotype constellation (Wang et al., 2013). Whole genomic analysis of a G12P[9] RVA strain (strain RVA/Human-tc/THA/T152/1998/G12P[9]) from Thailand revealed a predominantly AU-1-like genotype backbone, except for the VP7, NSP1 and NSP5 genes which belonged to the G12, A12 and H6 genotypes, respectively (Matthijnssens et al., 2008a, b; Rahman et al., 2007). Human RVA G1P[9] strain RVA/Human-tc/JPN/K8/1977/G1P[9] exhibited a G1-P[9]-I1-R3- C3-M3-A1-N1-T3-E3-H3 genotype constellation, providing evidence for reassortment events involving acquisition of four Wa-like genes, possibly from G1P[8] RVAs, by an AU-1-like P[9] strain (Ghosh et al., 2012b). The AU-1-like human RVAs are believed to have originated from interspecies transmission and multiple reassortment events involving feline/canine RVAs (Ghosh and Kobayashi, 2011; Matthijnssens et al., 2011b; Nakagomi et al., 1990; Wang et al., 2013).

## Intergenogroup reassortment events

Although most human RVA strains exhibit a RVA strain Wa-like or DS-1-like genotype constellation, RVAs possessing both Wa-like and DS-1-like genotypes have been reported sporadically in humans (Ghosh et al., 2011a, 2013a, 2013b; Ghosh and Kobayashi, 2011; Heylen et al., 2013; Kuzuya et al., 2013; Matthijnssens et al., 2008b, 2011a; Matthijnssens and Van Ranst, 2012; Tran et al., 2013) (Table 2). In addition, evidence for intergenogroup reassortment events involving Wa-like or DS-1-like and AU-1-like strains have been obtained (Ghosh et al., 2012b). However, it is believed that RVA strains belonging to different genogroups do not readily exchange their genome segments except for the outer capsid coding genes, and therefore, strains arising from intergenogroup reassortment events are likely to be selected against in nature (Ghosh and Kobayashi, 2011; Heiman et al., 2008; Matthijnssens and Van Ranst, 2012; McDonald et al., 2009, 2012). The low rate of detection of RVAs with mixed genotype constellations corroborates this hypothesis. On the other hand, it has been also hypothesized that a high frequency of co-circulating Wa-like and DS-1-like strains might facilitate intergenogroup reassortment events, as evident from recent studies where intergenogroup reassortants derived from Wa-like and DS-1-like human RVAs were shown to spread rapidly, persist over longer periods of time and become relevant

**Table 2:** *Complete genotype constellations of selected human RVA strains representing the Wa-like, DS-1-like and AU-1-like genogroups, intergenogroup reassortants, animal-to-human interspecies transmission*

| Strain | Genotypes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | VP7 | VP4 | VP6 | VP1 | VP2 | VP3 | NSP1 | NSP2 | NSP3 | NSP4 | NSP5 |
| **Wa-like genogroup** | | | | | | | | | | | |
| RVA/Human-tc/USA/Wa/1974/G1P1A[8] | G1 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| RVA/Human-tc/BGD/MMC71/2005/G1P[8] | G1 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| RVA/Human-tc/USA/P/1974/G3P1A[8] | G3 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| RVA/Human-wt/USA/DC827/1978/G4P[8] | G4 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| RVA/Human-tc/USA/WI61/1983/G9P1A[8] | G9 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| RVA/Human-wt/BGD/Dhaka25-02/2002/G12P[8] | G12 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| **DS-1-like genogroup** | | | | | | | | | | | |
| RVA/Human-tc/USA/DS-1/1976/G2P1B[4] | G2 | P[4] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human-wt/CHN/TB-Chen/1996/G2P[4] | G2 | P[4] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| **AU-1-like genogroup** | | | | | | | | | | | |
| RVA/Human-tc/JPN/AU-1/1982/G3P3[9] | G3 | P[9] | I3 | R3 | C3 | M3 | A3 | N3 | T3 | E3 | H3 |
| RVA/Human-wt/CHN/E2451/2011/G3P[9] | G3 | P[9] | I3 | R3 | C3 | M3 | A3 | N3 | T3 | E3 | H6 |
| RVA/Human-tc/THA/T152/1998/G12P[9] | G12 | P[9] | I3 | R3 | C3 | M3 | A12 | N3 | T3 | E3 | H6 |
| **Intergenogroup reassortants (Wa x DS-1) and (Wa x AU-1)** | | | | | | | | | | | |
| RVA/Human-tc/VEN/M37/1982/G1P2A[6] | G1 | P[6] | I1 | R1 | C1 | M1 | A1 | N1 | T2 | E1 | H1 |
| RVA/Human-tc/JPN/K8/1977/G1P[9] | G1 | P[9] | I1 | R3 | C3 | M3 | A1 | N1 | T3 | E3 | H3 |
| RVA/Human-tc/KEN/AK26/1982/G2P[4] | G2 | P[4] | I2 | R2 | C2 | M2 | A2 | N1 | T2 | E2 | H2 |
| RVA/Human-wt/USA/6212/2003/G3P[3] | G3 | P[3] | I3 | R1 | C2 | M3 | A9 | N2 | T3 | E3 | H6 |
| RVA/Human-wt/IND/Mani-253/2007/G4P[4] | G4 | P[4] | I1 | R1 | C1 | M2 | A8 | N1 | T1 | E1 | H1 |
| RVA/Human-tc/IDN/57M/1980/G4P[10] | G4 | P[10] | I1 | R1 | C1 | M1 | A1 | N1 | T2 | E1 | H2 |
| RVA/Human-tc/PHL/L26/1987/G12P[4] | G12 | P[4] | I2 | R2 | C2 | M1/2 | A2 | N1 | T2 | E2 | H1 |
| RVA/Human-wt/Matlab13-03/2003/G12P[6] | G12 | P[6] | I1 | R1 | C1 | M1 | A1 | N1 | T2 | E1 | H1 |
| **Strains derived from animal to human interspecies transmision and/or animal-human reassortment events Artiodactyl/bovine-to-human** | | | | | | | | | | | |
| RVA/Human-tc/ISR/Ro8059/1995/G6P[1] | G6 | P[1] | 12 | R2 | C2 | M2 | A3 | N2 | T6 | E2 | H3 |
| RVA/Human-wt/SVN/SI-R56/07/2007/G6P[11] | G6 | P[11] | 12 | R2 | C2 | M2 | A13 | N2 | T6 | E2 | H3 |
| RVA/Human-wt/HUN/Hun5/1997/G6P[14] | G6 | P[14] | 12 | R2 | C2 | M2 | A11 | N2 | T6 | E2 | H3 |
| RVA/Human-tc/KEN/B12/1987/G8P[1] | G8 | P[1] | I2 | R2 | C2 | M2 | A3 | N2 | T6 | E2 | H3 |
| RVA/Human-tc/IDN/69M/1980/G8P4[10] | G8 | P[10] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human-wt/JPN/KF17/2010/G6P[9] | G6 | P[9] | I2 | R2 | C2 | M2 | A3 | N2 | T3 | E3 | H3 |



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|---|---|---|---|---|---|---|---|---|---|---|---|
| RVA/Human-tc/GBR/A64/1987/G10P11[14] | G10 | P[14] | I2 | R2 | C2 | M2 | A3 | N2 | T6 | E2 | H3 |
| **Porcine-to-human** | | | | | | | | | | | |
| RVA/Human-wt/ARG/Arg4605/2006/G4P[6] | G4 | P[6] | I1 | R1 | C1 | M1 | A8 | N1 | T7 | E1 | H1 |
| RVA/Human-tc/CHN/R479/2004/G4P[6] | G4 | P[6] | I5 | R1 | C1 | M1 | A1 | N1 | T7 | E1 | H1 |
| RVA/Human-wt/JPN/Ryukyu-1120/2011/G5P[6] | G5 | P[6] | I5 | R1 | C1 | M1 | A8 | N1 | T1 | E1 | H1 |
| RVA/Human-wt/CMR/6784/ARN/2000/G5P[7] | G5 | P[7] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| RVA/Human-wt/BEL/BE2001/2009/G9P[6] | G9 | P[6] | I5 | R1 | C1 | M1 | A8 | N1 | T7 | E1 | H1 |
| RVA/Human-tc/THA/Mc323/1989/G9P[19] | G9 | P[19] | I5 | R1 | C1 | M1 | A8 | N1 | T1 | E1 | H1 |
| RVA/Human-wt/KOR/CAU12-2/2012/G11P[25] | G11 | P[25] | I12 | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 |
| **Feline/canine-to-human** | | | | | | | | | | | |
| RVA/Human-tc/ISR/Ro1845/1985/G3P[3] | G3 | P[3] | I3 | R3 | C2 | M3 | A9 | N2 | T3 | E3 | H6 |
| RVA/Human-tc/USA/HCR3A/1984/G3P[3] | G3 | P[3] | I3 | R3 | C2 | M3 | A9 | N2 | T3 | E3 | H6 |
| RVA/Human-wt/ITA/PAI58/1996/G3P[9] | G3 | P[9] | I2 | R2 | C2 | M2 | A3 | N2 | T6 | E2 | H3 |
| **Lapine-to-human** | | | | | | | | | | | |
| RVA/Human-wt/BEL/B4106/2000/G3P[14] | G3 | P[14] | I2 | R2 | C2 | M3 | A9 | N2 | T6 | E5 | H3 |
| **Simian-to-human** | | | | | | | | | | | |
| RVA/Human-tc/KEN/B10/1987/G3P[2] | G3 | P[2] | I16 | R8 | C5 | M5 | A5 | N5 | T5 | E13 | H5 |

(Banyai et al., 2011; Doan et al., 2012; Kuzuya et al., 2013). Large-scale whole genome studies may be required to obtain conclusive data on the frequency and stability of RVA strains derived from intergenogroup reassortment events.

## Interspecies transmission and animal-human reassortment events

Humans are vulnerable to infection with animal RVAs, especially in developing and underdeveloped countries where people live in close proximity to livestock and other animals under extreme unhygienic conditions (Cook et al., 2004; Martella et al., 2010). Whole genomic analyses of several human RVA strains have yielded a plethora of conclusive data on animal-to-human interspecies transmission of RVAs, often coupled with complex reassortment events (Table 2). Evidences for interspecies transmission of RVAs to humans from a wide variety of animal host species, such as artiodactyls (ruminants and camelids), cats, dogs, pigs, rabbits and even wildlife (monkeys), have been obtained so far (Degiuseppe et al., 2013; Doan et al., 2013; Ghosh et al., 2011b, c, 2012a; Ghosh and Kobayashi, 2011; Komoto et al., 2013; Martella et al., 2010; Matthijnssens et al., 2006, 2008b, 2009b, 2011a, b; Mukherjee et al., 2013; Steyer et al., 2013; Tsugawa and Hoshino, 2008; Zeller et al., 2012). Following animal-to-human interspecies transmission events, many a time animal RVAs have been found to reassort with human RVAs, generating progeny viruses possessing both animal and human RVA genes (Afrad et al., 2013; Delogu et al., 2013; Dong et al., 2013; Ghosh et al., 2011d; Ghosh and Kobayashi, 2011; Matsushima et al., 2012; Matthijnssens et al., 2011a; Matthijnssens and Van Ranst, 2012; Mukherjee et al., 2012; Than et al., 2013a, b; Yamamoto et al., 2011). On the other hand, reassortants derived from RVAs of more than one animal host species have also been shown to infect humans (Ghosh and Kobayashi, 2011; Matthijnssens et al., 2011a, b; Mukherjee et al., 2012; Wang et al., 2010). Barring a few exceptions, animal-like RVA strains have failed to spread efficiently and persist in the human population, indicating that a specific genotype/genomic constellation of the 11 RVA gene segments might influence the host range restriction of RVA strains (Matthijnssens and Van Ranst, 2012).

## Conclusions

Whole genomic analysis of human and animal RVA has revolutionized the study of RVA genomics, providing a plethora of conclusive and vital data on the overall genetic diversity, true origin and evolutionary patterns of common and uncommon human RVA strains, such as the presence of stable genetic constellations in common human RVAs, evidence fointragenogroup reassortment events and selection of the most fit allelic constellation within a RVA genogroup, intergenogroup reassortment events, and animal-to-human interspecies transmission and reassortment events. However, barring a few exceptions, most whole genome-based studies so far are limited


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to a few RVA strains. Large-scale whole genome sequencing of hundreds of co-circulating RVA strains from humans and animals might be required to gain a proper understanding of the complex genodynamics of RVAs in a population.

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