Circulation of a novel human respiratory syncytial virus Group B genotype during the 2014–2015 season in Catalonia (Spain)

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Abstract

Human respiratory syncytial virus (HRSV) is one of the most common viral aetiological agents in the youngest population. In the present study a novel HRSV-B BA genotype is first described based on the phylogenetic analysis of the coding hypervariable region 2 sequences of G protein from strains detected during the 2014–2015 season. Among all strains detected in the last season, 44% belonged to this new genotype. Therefore, it highlights the importance of a continuous HRSV surveillance to monitor the emergence and spread of new genotypes or variants with genetic changes that may affect antigenic and tropism features.

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Introduction

Human respiratory syncytial virus (HRSV) is the most common respiratory pathogen and the main cause of lower respiratory tract infections among infants and young children. Primary infection usually occurs in the first years of childhood, although re-infections are common throughout life [1]. It is also recognized as a significant respiratory pathogen among immunosuppressed and elderly patients. HRSV exhibits a clear pattern of seasonality, and epidemics are usually reported in the late autumn and winter in temperate regions, and during the rainy season in tropical regions [2]. HRSV is classified in the genus *Pneumovirus* belonging to the Paramyxoviridae family. Its genome is a non-segmented negative-strand RNA of approximately 15 000 nucleotides that contains ten genes encoding 11 proteins [3]. The envelope of the virus contains two major glycoproteins, G and F, which play an essential role in the virus attachment and entry to the host cell. Antigenic and genetic differences lead to classification of HRSV into two different groups, HRSV-A and HRSV-B, which co-circulate every season with one being predominant. Based on the hypervariable region 2 (HVR-2) located in the C-terminal domain of the G protein, at least 12 genotypes (GA1–GA7 [4,5], SAA1 [6], NA1 and NA2 [7], CB-A [8] and ON1 [9]) for HRSV-A and 22 genotypes (GB1–GB4 [5,10], URU1 and URU2 [11], SAB1–SAB3 [10], BA1–BA12 [12] and CB-B [13]) for HRSV-B have been described. In the present study, we report the circulation of a novel HRSV-B genotype circulating in Catalonia (Spain) during the 2014–2015 season.

Materials and Methods

Respiratory specimens from patients with suspicion of acute respiratory tract infection attending the Hospital Universitari Vall d'Hebron in Barcelona were collected from October 2014 to April 2015 for virological diagnosis. All laboratory-confirmed HRSV samples were typed as HRSV-A or HRSV-B, and phylogenetic analysis and molecular characterization of a random representative sampling of HRSV-B strains were performed as previously described [14].

Results

A total of 5189 specimens from 3683 patients were collected, of which 448 (9%) from 409 (11%) patients were laboratory-confirmed for the different HRSV groups: HRSV-A (145; 35%)

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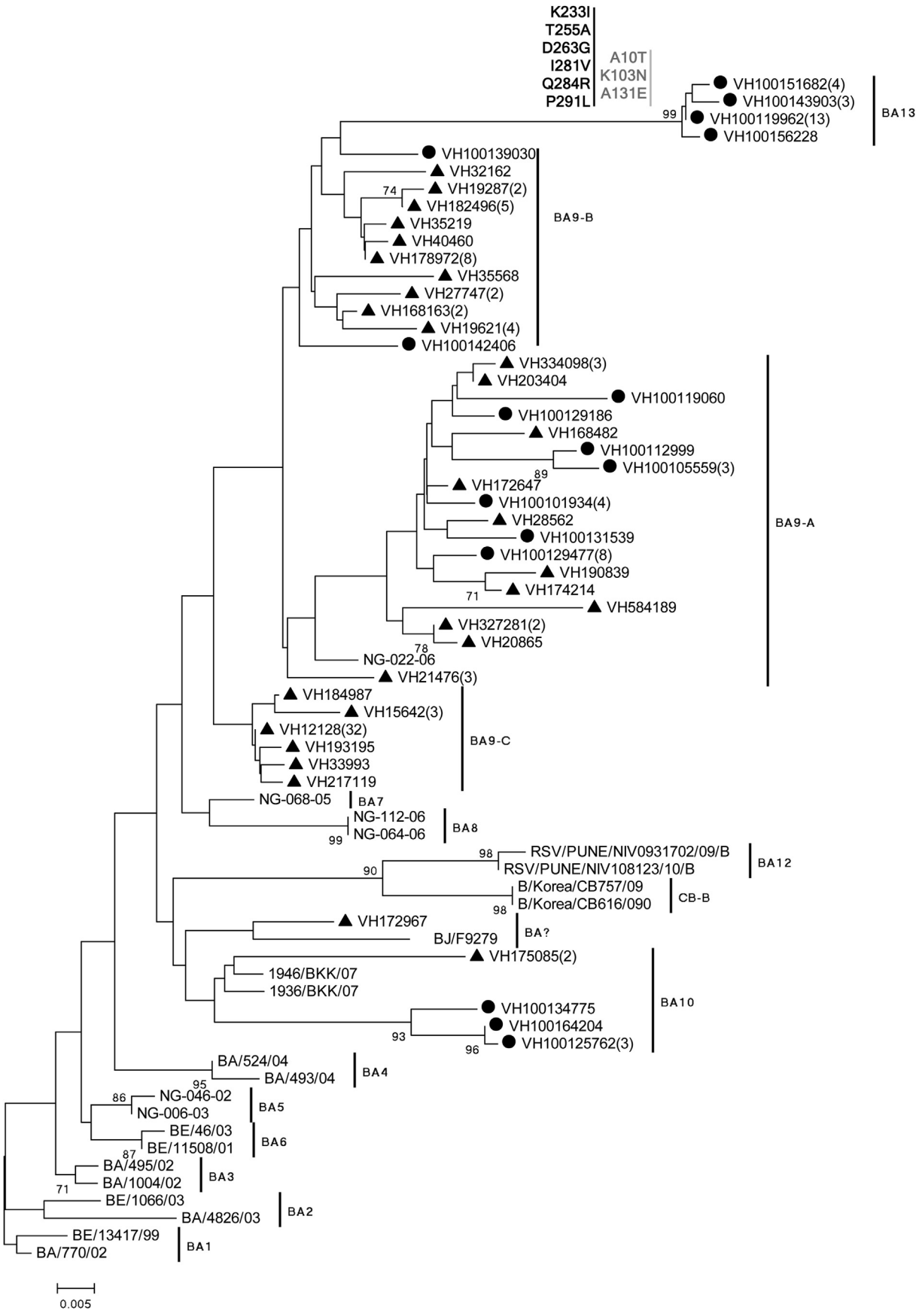

and HRSV-B (256; 63%). In addition, two (<1%) samples were HRSV-A/B co-infections, and six (1%) could not be typed. Complete HVR-2 sequences from 48 HRSV-B specimens were sequenced and studied (Fig. 1), of which 22 (46%) belonged to BA9 genotype and five (10%) to BA10. The remaining 21 (44%) sequences clustered together with a bootstrap value of 100% showing a maximum pairwise distance (p-distance) between members of 0.006 and an average divergence within group (p-distance) of 0.004 base differences per site. Therefore, according to the criterion used to define novel genotypes by Venter *et al*. [10], because these sequences clustered together with a bootstrap value over 70% and showed a maximum intragroup p-distance <0.07, they would belong to a novel genotype not previously described, which is named in this study as BA13 to follow on from the nomenclature used so far. This novel genotype also belongs to the BA genetic group, because it carries the 60-nucleotide duplication in the HVR-2 that characterizes it. Moreover, it shows the lowest genetic distance to BA9 sequences, more particularly to BA9-B (mean p-distance 0.0475 base differences per site). The whole predicted G protein of strains belonging to the novel genotype is defined by some key amino acid substitutions relative to the first described BA sequences, which were found in the cytoplasmic domain (A10T), in HVR-1 (K103N and A131E) and in HVR-2 (K233I, T255A, D263G, I281V, Q284R and P291L). In spite of the high similarity between strains within this novel genotype, the possibility that they formed part of a nosocomial outbreak was ruled out because the corresponding respiratory samples were collected from patients attending seven different hospital wards during a 4-month period.

Discussion

The co-circulation of both HRSV groups has been reported in Catalonia during the last two seasons with a great predominance of HRSV-B [14]. Among the HRSV-B group, BA has been the most prevalent genotype. After its emergence in 1999 in Buenos Aires (Argentina) [15], the BA genotype spread worldwide and became predominant in most countries—showing over time a great diversification into at least 13 different genotypes (from BA1 to BA12 and CB-B) [16]. The BA genotype is defined by a common 60-nucleotide duplication in the HVR-2 that is also carried by all circulating HRSV-B strains characterized in this study throughout the 2014–2015 season in Catalonia, including those strains belonging to the novel genotype. As we recently reported in Catalonia [14], BA9 was the predominant HRSV-B genotype during the 2013–2014 season, distinguishing up to three genetic subgroups (BA9-A, BA9-B and BA9-C). During the 2014–2015 season, strains belonging to BA9-A and BA10 genotypes remained similar to or slightly evolved from strains of the previous season. However, almost half of the characterized sequences fell within the novel genotype that we describe in this study, which have probably evolved from 2013–2014 BA9-B strains because they showed the lowest genetic distance compared to each other. These results reinforce the idea that the predicted viral G protein sequence is continuously evolving, acquiring sometimes amino acid substitution that might result in the appearance of novel genotypes over time. These substitutions might also result in new antigenic features that help the virus to spread among the population season after season. This genetic diversity would be driven by the host immune response, which acts as an evolutionary selective pressure. Furthermore, these changes in the antigenic features become a challenge in the development of future vaccines to prevent infection. For the next HRSV vaccine to be most effective, its antigen recognition should be the highest possible. Therefore, the present study reports the identification of a novel BA genotype in Catalonia during the last season and highlights the importance of continuous monitoring of the genetic diversity of circulating HRSV strains worldwide.

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Transparency Declaration

The authors declare no conflict of interest.

FIG. 1. Phylogenetic tree of BA genotypes based on HVR-2 sequences from HRSV-B strains. The sequences of the present study are marked with black points and sequences previously studied from 2013–2014 season are marked in black triangles. Sequences were previously collapsed to haplotypes, and the numbers of represented sequences are shown in brackets. Amino acid mutations within the HVR-2 and in other G protein domains are marked in black and in grey, respectively.

Ethical approval

Institutional Review Board approval (PRAG78/2014) was obtained from the Hospital Universitari Vall d'Hebron Clinical Research Ethics Committee.

References

[1] Faghihloo E, Yavarian J, Jandaghi NZ, Shadab A, Azad TM. Genotype circulation pattern of human respiratory syncytial virus in Iran. Infect Genet Evol 2014;22:130–3.

[2] de-Paris F, Beck C, de Souza Nunes L, Machado AB, Paiva RM, da Silva Menezes D, et al. Evaluation of respiratory syncytial virus group A and B genotypes among nosocomial and community-acquired pediatric infections in southern Brazil. Virol J 2014;11(1):36.

[3] Tapia LI, Shaw CA, Aideyan LO, Jewell AM, Dawson BC, Haq TR, et al. Gene sequence variability of the three surface proteins of human respiratory syncytial virus (HRSV) in Texas. PLoS One 2014;9(3):e90786.

[4] Peret TC, Hall CB, Hammond GW, Piedra PA, Storch GA, Sullender WM, et al. Circulation patterns of group A and B human respiratory syncytial virus genotypes in 5 communities in North America. J Infect Dis 2000;181(6):1891–6.

[5] Peret TC, Hall CB, Schnabel KC, Golub JA, Anderson LJ. Circulation patterns of genetically distinct group A and B strains of human respiratory syncytial virus in a community. J Gen Virol 1998;79(Pt 9):2221–9.

[6] Agenbach E, Tiemessen CT, Venter M. Amino acid variation within the fusion protein of respiratory syncytial virus subtype A and B strains during annual epidemics in South Africa. Virus Genes 2005;30(2):267–78.

[7] Shobugawa Y, Saito R, Sano Y, Zaraket H, Suzuki Y, Kumaki A, et al. Emerging genotypes of human respiratory syncytial virus subgroup A among patients in Japan. J Clin Microbiol 2009;47(8):2475–82.

[8] Baek YH, Choi EH, Song MS, Pascua PN, Kwon HI, Park SJ, et al. Prevalence and genetic characterization of respiratory syncytial virus (RSV) in hospitalized children in Korea. Arch Virol 2012;157(6):1039–50.

[9] Eshaghi A, Duvvuri VR, Lai R, Nadarajah JT, Li A, Patel SN, et al. Genetic variability of human respiratory syncytial virus A strains circulating in Ontario: a novel genotype with a 72 nucleotide G gene duplication. PLoS One 2012;7(3):e32807.

[10] Venter M, Madhi SA, Tiemessen CT, Schoub BD. Genetic diversity and molecular epidemiology of respiratory syncytial virus over four consecutive seasons in South Africa: identification of new subgroup A and B genotypes. J Gen Virol 2001;82(Pt 9):2117–24.

[11] Blanc A, Delfraro A, Frabasile S, Arbiza J. Genotypes of respiratory syncytial virus group B identified in Uruguay. Arch Virol 2005;150(3):603–9.

[12] Choudhary ML, Anand SP, Wadhwa BS, Chadha MS. Genetic variability of human respiratory syncytial virus in Pune, Western India. Infect Genet Evol 2013;20:369–77.

[13] Almajhdi FN, Farrag MA, Amer HM. Group B strains of human respiratory syncytial virus in Saudi Arabia: molecular and phylogenetic analysis. Virus Genes 2014;48(2):252–9.

[14] Gimferrer L, Campins M, Codina MG, Martín MeC, Fuentes F, Esperalba J, et al. Molecular epidemiology and molecular characterization of respiratory syncytial viruses at a tertiary care university hospital in Catalonia (Spain) during the 2013–2014 season. J Clin Virol 2015;66:27–32.

[15] Trento A, Viegas M, Galiano M, Videla C, Carballal G, Mistchenko AS, et al. Natural history of human respiratory syncytial virus inferred from phylogenetic analysis of the attachment (G) glycoprotein with a 60-nucleotide duplication. J Virol 2006;80(2):975–84.

[16] Dapat IC, Shobugawa Y, Sano Y, Saito R, Sasaki A, Suzuki Y, et al. New genotypes within respiratory syncytial virus group B genotype BA in Niigata, Japan. J Clin Microbiol 2010;48(9):3423–7.