Mumps Virus Genotyping: Basis and Known Circulating Genotypes

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Abstract: Although mumps virus (MV) is considered antigenically monotypic, twelve different genotypes of MV based on genetic variation in the SH gene (A to L) are currently recognised by the WHO. Both dominance of a single genotype and co-circulation of different genotypes in the same geographical area, as well as temporal replacement of genotypes have been described in different countries. The different histories of genotype importation, variations in vaccine coverage and the use of different vaccine strains in each country results in a complex picture that could be the cause of the different geographical patterns of mumps virus genotype circulation observed in different countries. Lack of full cross-protection between different genotypes has been reported and has been suggested as a cause of vaccine failure, especially for vaccine strains belonging to genotype A, which is genetically distant to the remaining genotypes that include most of the currently circulating wild strains. Finally, a differential ability to invade the neural system has been suggested for some particular strains belonging to genotype D.

Keywords: Mumps, molecular epidemiology, genotypes.

INTRODUCTION

Mumps is a highly transmissible but usually benign disease characterized by fever and swelling of the salivary glands. It is distributed worldwide and in the absence of vaccination is a childhood disease. However, in some cases, clinical complications can arise such as bilateral orchitis or self-limited meningitis. More serious complications such as encephalitis, deafness, sexual male sterility, and pancreatitis may occur but these are rare [1].

Mumps is caused by Mumps virus (MV), which belongs to the genus Rubulavirus of the subfamily Paramyxovirinae in the family Paramyxoviridae (Order Mononegavirales). Other important human pathogens belonging to the same genus are the human Parainfluenza virus 2 and the human Parainfluenza virus 4. MV is antigenically monotypic which in principle allows commercial vaccines to protect against all circulating strains. Thus, mumps vaccination has been incorporated into the regular immunization schedule of many countries, usually along with measles and rubella vaccines in a triple formulation. These vaccines have enabled the WHO to establish global strategies for the advanced control of measles and rubella leading to an elimination target in some regions. However, in contrast to rubella and measles, secondary vaccine failure occurs frequently in the case of mumps and circulation of MV within highly vaccinated populations has been frequently reported [2-7].

Twelve different genotypes of MV based on genetic variation in the SH gene are currently recognised by the WHO [8-10]. Altough all of them are considered to be the same serotype, lack of full cross-protection between different genotypes has been reported [11] and has been suggested as a cause of vaccine failure. However, other reports did not find this lack of cross reaction among different genotypes [12]. Also, it has been suggested that different genotypes may differ in their ability to invade the neural system and cause disease [13, 14] although this is not universally accepted to be the case.

Previous experience with elimination programmes for other vaccine-preventable diseases as measles, rubella or polio suggests that genotyping is an important tool for epidemiological surveillance [15], since it makes it possible to trace the patterns of viral circulation. Recently, the WHO has recommended genotyping for monitoring circulating MV genotypes in the context of surveillance programmes and has provided the first standardization protocols.

This has led to a series of molecular epidemiology studies which providing data on MV genotype distribution [10, 16-29].

In the present manuscript we review these studies which demonstrate the usefulness of MV genotyping for the epidemiological surveillance of MV.

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METHODS OF MUMPS VIRUS GENOTYPING

The WHO recommended a standardized scheme for MV genotyping established by an international group of experts in a Weekly Epidemiological Record published in 2005 [15]. It is based on sequence analysis of the so-called small hydrophobic (SH) gene. Standard nomenclature for strains (country code, year, strain and genotype) and criteria for establishing new mumps genotypes were also proposed. The following steps are required.

1. Sequencing of the 316 nucleotides of the SH gene to detect strains that diverge more than 5% from reference strains.
2. Identification of at least 2 identical strains (to avoid technical error).
3. Submission of sequence data to public databases such as GenBank, together with the strain name and data source.

A subsequent article published the same year by the same group [8] provided a table listing the reference strains for genotypes A to L, as well as for three possible new genotypes. Interestingly, one of these potential new genotypes includes the vaccine strains L-Zagreb and Leningrad-3, that remain unassigned. A new genotype (M) has been proposed for strains circulating in Brazil in 2006-2007 [30]. Although no specific procedures for sequence analysis were described, the authors use Neighbour-Joining analysis with Kimura 2p model and 1000 replications for bootstrapping. A similar tree containing the reference sequences is shown in Fig. (**1**).

Finally, different subgenotypes have been described for genotypes D (D1, D2), G (G1, G2) and H (H1, H2) [10] which are widely reported in the literature.

MUMPS VIRUS GENOTYPE DISTRIBUTION

Data about mumps genotypes are available in reports from different European countries such as Belarus [31],

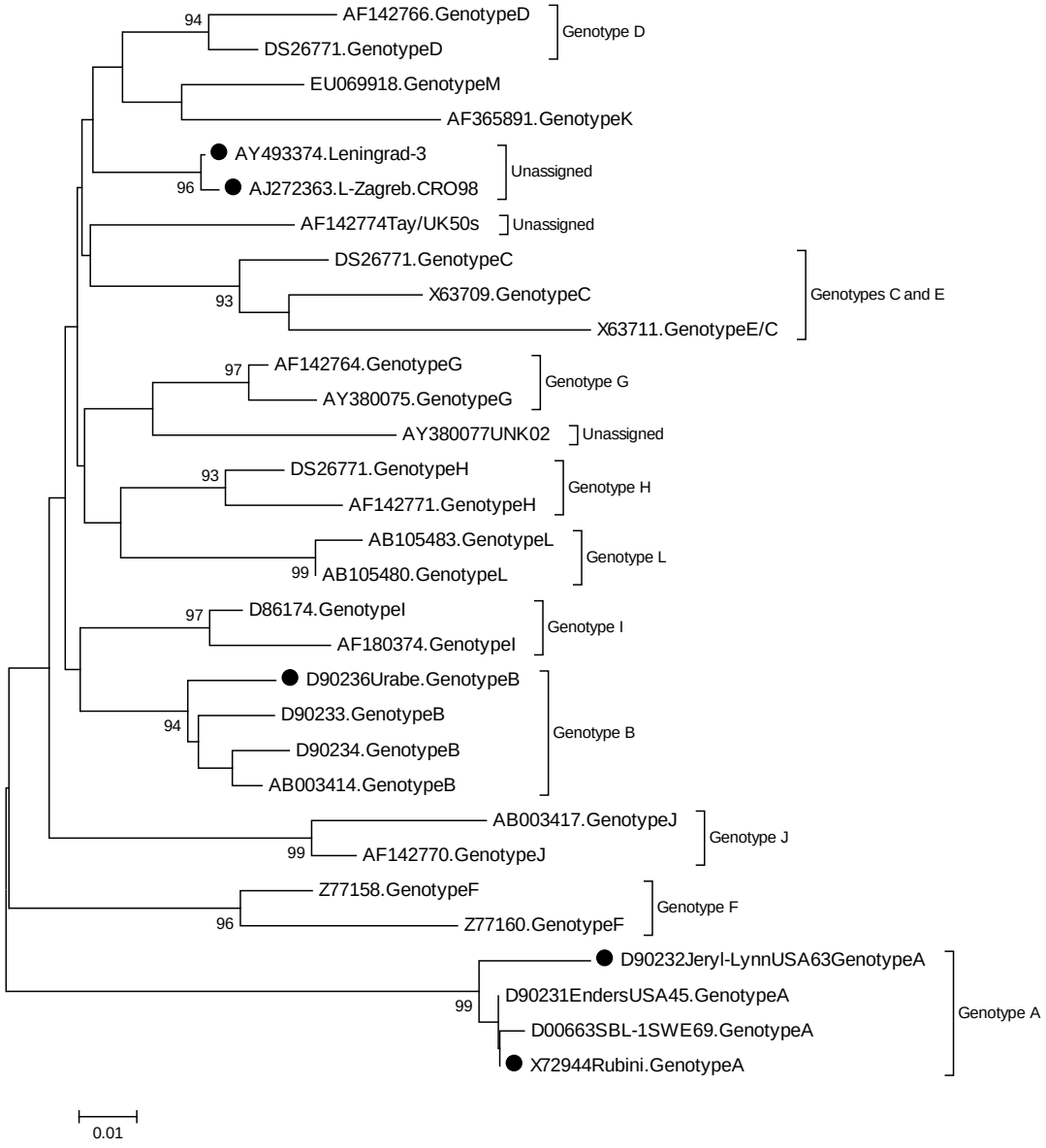

Fig. (1). Phylogenetic relationships of the SH sequences of the reference strains for mumps genotyping. Sequences of the most used vaccines are marked with dots.

Croacia [32], Denmark [24], Ireland [33], Lithuania [14], Portugal [5], Russia [16], Spain [22, 34], Sweden [13, 35], Switzerland [29] United Kingdom [19, 20] as well as from Argentina [10], Brazil [30] and Canada [36] in America, and China [27], Japan [17, 23, 25, 37], and South Korea [18, 38] in Asia. Additional data are available as unpublished sequences in Gene Bank. Since all these data were collected at different times, comparisons are sometimes difficult to make since there was little standardization on genotype nomenclature before 2005. Furthermore, articles reporting large sets of data show temporal changes in the dominant genotype, as well as co-circulation of several genotypes in the same or in neighbouring countries. On the other hand, there is evidence of simultaneous circulation of the same dominant genotype in remote countries as was the case with genotype G1 in Croacia [32], Spain, United Kingdom [19, 20] and Canada [36] during 2006. The different histories of genotype importation, variations in vaccine coverage and the use of different vaccine strains in each country result in a complex picture that could explain the different geographical patterns of mumps virus genotype circulation described in different countries. Collaborative studies analyzing the genotype circulation in wider areas are needed to obtain a more accurate picture.

An unpublished series of data from Spain show that genotype H1 was dominant between 1999 and 2003 and was replaced by G1 after a "silent" period of two years with very little mumps circulation. Genotype G1 seemed to cause an increase of mumps between 2006 and 2009 with outbreaks occurring in many regions within Spain as well as in Canada, United States, The Netherlands, United Kingdom and Croacia. Genotype D1 co-circulated during 2001 and 2002 along with the dominant genotype H1. Four additional genotypes (C, G2, H2, and J) were found which caused not only sporadic cases, but also local outbreaks, although they failed to establish wider circulation compared to G1 or H1. This suggests a differential capacity of different genotypes to establish circulation among vaccinated populations.

MUMPS VIRUS GENOTYPES AND VACCINES

Currently used vaccines contain different strains belonging to different genotypes. Strains Jerryl Lynn and Rubini belong to genotype A, while Urabe is genotype B. Strains L-Zagreb and Leningrad-3 remain unclassified in the table of reference strains (Fig. **1**).

The sequence of the SH genomic region is not only useful for genotyping, but also allows vaccine strains and wild strains within the same genotype to be distinguished. As it is crucial for characterizing post-vaccination cases of either mumps or meningitis, this is another important use of mumps virus genotyping.

MUMPS GENOTYPES AND VACCINE FAILURE

Although mumps virus is considered monotypic, lack of full cross-protection between different genotypes has been suggested as a cause of vaccine failure. Jerryl-Lynn and Rubini vaccine strains belong to genotype A which is genetically distant from the other genotypes as shown in Fig. (**1**). Wild strains belonging to the A genotype used to be dominant before vaccination , but nowadays most MV wild strains belong to other genotypes. The genetic distance between genotype A vaccine strains and non-A wild strains has been proposed to be a determinant factor in vaccine failure. Other vaccine strains such as Urabe which belongs to genotype B and the unassigned Leningrad-3 and L-Zagreb strains are more similar to most wild strains (Fig. **1**). The poor efficiency of the genotype A Rubini vaccine strain is well documented and has therefore been discarded for use [39]. It is currently not clear whether the Urabe, L-Zagreb and Leningrad-3 vaccines are more effective than the Jerryl Lynn one [39]. On the other hand, non-A vaccines have been more frequently associated with post vaccination meningitis [39] and are considered less safe. Additional studies are needed to obtain a better balance between efficiency and safety in order to establish the best future strategy for achieving optimal vaccine efficacy.

Data from neutralization experiments are still unclear since it has been reported that pre-existing naturally acquired antibodies may fail to neutralise a particular wild genotype A strain, although not wild genotype D [11]. Important differences in cross-neutralization titres among genotypes A, C, D, G, H and I have also been reported [12]. Another study [40] on two particular MV strains selected because they are genetically very distant (genotype A Enders, and genotype D Lo1), showed significant differences in neutralisation titres obtained for each strain using a collection of human sera found to be positive for MV antibodies by ELISA. Despite the observed differences, the authors did not conclude that MV was not monotypic, but suggested that the failure of achieving antibody protection could be due to low antibody titres. Additional studies are needed on genotype cross neutralization as well as on the ability of antibodies induced by different vaccine strains to neutralise different genotypes, in order to establish if genetic variation can lead to vaccine failure.

MUMPS VIRUS GENOTYPES AND NEUROTROPISM

Meningitis and more rarely encephalitis are the most common complications of mumps. Some reports also suggest a differential neurovirulence of some genotypes. A study from Sweden [13] reported the occurrence of genotypes C and D, but not genotype A, in the spinal fluid of patients with meningitis. However, genotype A can be detected in non complicated mumps cases collected at the same suggesting lower neurovirulence for this genotype. A particular strain (ODATE-1) from Japan seemed to exhibit an unusual high neurovirulence during an epidemic in Japan [41]. Additional studies are needed to establish the differential ability of different MV genotypes to invade the central nervous system and to dtermine the molecular determinants of neurovirulence. The lack of a suitable experimental model of neurological MV infections is a serious impediment for achieving these goals.

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