



# The Basic Knowledge of Varicella Zoster Virus (VZV) Molecular Genetic Testing

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## Abstract

VZV is unique among the herpes viruses in its transmission by inhalation of aerosolized virus particles. Infection via the respiratory route increases the opportunity for rapid spread of the virus through susceptible populations and exposure of those already latently infected.

The genotyping of VZV helps to better understand differences in properties of individual wild type and/or vaccine VZV strains; inform about pathogenic potential of individual VZV strains and help to detect mutations in functionally important gene and analyze their effects on phenotype.

**Keywords:** Varicella-zoster virus; Herpes zoster; Molecular genetic; Genotyping

## Introduction

Varicella zoster virus (VZV) is a highly contagious human pathogen. It is easily transmitted within families school classmates and other groups by airborne particles and droplets in exhaled air, or, on a closer contact, by the fluid from blisters or sores. Virus can be also transmitted indirectly by contact with clothing and other items exposed to fresh drainage from open sores. Patients are contagious up to five days before and five days after the appearance of their rash. When sores have crusted over, the patient is usually no longer contagious [1,2].

VZV causes varicella (chickenpox) on primary infection, during which a lifelong latent infection is established [3]. Chickenpox is characterized by one to two days of low grade fever, general weakness, prodromal malaise, pharyngitis, rhinitis and a rash, which is often the first sign of the disease [4,5]. Rarely, patient may experience the VZV infection and disease without rash. The rash of chickenpox is typically very itchy Shinjoh and Takahashi et al. [6] and develops in crops with raised red spots appearing first, progressing to blisters that burst and create open sores, before crusting over [7,8]. The process usually starts on the scalp, then involves the trunk, and finally spreads centrifugally to the arms and legs. Less commonly the lesions can be found in the mucosa of the oropharynx and vagina [9,10]. Any area of skin that is irritated (eczema, diaper rash, sunburn) could be seriously affected by the rash of VZV Kaushik et al. [11]. In adults, complications are more frequent in pregnant women, with negative consequences for the fetus and the newborns, and in immunocompromised people, with an increased risk of mortality [12-17].

A lifelong latent infection is established during the first exposure and can reactivate, typically after age fifty, to cause herpes zoster (HZ, shingles) [18-20]. In these cases lesions are localized and painful, often involving the trunk and following an area of dermatome. Herpes zoster occurs frequently in adults, but is not uncommon in immunocompromised and even normal children [21-23]. Some patients develop serious pain that lasts for months after the rash has healed, which is called post herpetic neuralgia (PHN) Gilden et al. [24].

Virus can be transmitted to susceptible persons suffering from either disease condition, although zoster carries a significantly lower risk of transmission. Varicella cases arising through transmission from zoster patients result in the reintroduction of strains, which first infected the individual decades earlier, and, as such, likely contribute to the genetic stability of VZV [25,26].

## VZV Epidemiology

The epidemiology of VZV infection varies geographically [27-29]. Varicella displays marked

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seasonality (peak in spring) in temperate climates, and infection is nearly ubiquitous by the age of 20. For no clear reasons, seasonality does not occur in tropical countries, and larger proportion of people enter adulthood uninfected by VZV [30,31]. In addition, several studies have demonstrated a distinctive geographic distribution of the major VZV genotypes aligning with cool versus warm climate regions of the globe [32,33]. It is unclear whether the strain distribution is actually driven by climate or/and other factors, such as immigration patterns Loparev et al. [30], Loparev et al. [34].

In Czech Republic the incidence of varicella ranges between 35,000 to 40,000 cases/year during last ten years (Epidat system, www.szu.cz). There were three incidence peaks in 1998, 2004 and 2007 years, when the incidence reached 50,000 cases/year. New cases always occur from January to June with a peak typically in May. An average of 6,000 cases of zoster annually during the last decade has been reported via Epidat system for Czech population. Czech women are affected about 1.4 times more often than men and the peak incidence of HZ is around 70 years of age.

VZV exhibits tropism for neural tissues and therefore neurologic complications, which can occur before or after the acute infection Sauerbrei and Wutzler et al. [35], are typical for VZV infection, Cerebellar ataxia is one possible benign VZV complication that is thought to be due to post infection demyelination. It is estimated to occur in 1 in 4000 cases among those younger than 15 years old. Ataxia, vomiting, altered speech, fever, vertigo and tremor are common symptoms, but resolution usually occurs within 2 to 4 weeks. Lee et al. [25], [36,37].

More serious complication of VZV is encephalitis, which occurs in 0.1 to 0.2 % of patients. Mortality has been estimated to range between 5 to 20 % and sequelae have been described in 15 % of survivors Saez-Llorens et al. [38].

Reye's syndrome is described in association with varicella, often with concomitant use of aspirin in children younger than 5 years. It begins in late stages of varicella with vomiting, restlessness, irritability, and progressive decrease in the level of consciousness, associated with progressive cerebral edema Malavige et al. [2].

Immunocompromised patients contracting VZV are at risk of more severe course of disease. They may develop severe skin eruptions with or without hemorrhage and healing even of the "typical" VZV cutaneous lesions takes three times longer than in the general population. These patients may also develop high fever and the virus also more often spreads to visceral organs causing hepatitis, pneumonitis, pancreatitis, and encephalitis. Bacterial super infections (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*) of the primary virus lesions, leading to bacteremia can develop.

Antiviral therapy significantly reduces morbidity and can reduce mortality. Rarely, varicella in early pregnancy (first 20 weeks) may result in congenital varicella syndrome (CVS). CVS occurs in 2% of infections and is characterized by unusual cutaneous defects, cicatricial skin scars, and atrophy of the extremities. The patients often have microcephaly, cortical atrophy, seizures, mental retardation, chorioretinitis, microphthalmia, or cataracts. Newborns, whose mothers develop varicella close to term, are in risk of neonatal varicella. These babies can be born with varicella lesions or develop lesions after birth, but they typically do not develop serious complications [39-41].

In addition herpes zoster can lead to a wide spectrum of serious health complications [42,43]. Zoster can affect the cornea causing iridocyclitis with secondary glaucoma (*herpes zoster ophthalmicus*) Eskiizmir et al. [19]. Postherpetic neuralgia may occur in as many as 25 to 50 % of patients older than 50 years. Almost 50 % of persons older than 50 suffer debilitating pain for more than 1 month [44,45]. Meningoencephalitis and encephalitis are described in patients with zoster as well Vandercam et al. [46].

Immunocompromised patients can experience a more severe form of the disease Tavazzi et al. [41]. Lesions form for up to 2 weeks after infection and scabbing occurs until 3 to 4 weeks into the course of the disease. Patients with lympho proliferative malignancies are at risk of cutaneous dissemination and visceral involvement, including pneumonitis, hepatitis, and meningoencephalitis Sutradhar et al. [47]. Eight to eleven percent of patients with HIV are infected with VZV. These patients can develop chronic herpes zoster, with formation of new lesions without the healing of the already existing ones.

Although rapid spread and a low mutation rate could both explain the low level of genetic diversity of VZV, the geographical distribution and relatedness of strains does suggest that the spread of VZV subsequent to the major human migrations has made a strong contribution to its geographic epidemiology Loparev et al. [30]. Rapid spread is possible, because VZV, uniquely among herpes viruses, is transmitted by aerosolization of virus, resulting in airborne epidemic infections. Geographic spread may be particularly rapid in warmer regions, where varicella occurs on average 10 years later in life. In this scenario, the disease is transmitted between individuals who are more mobile than the children, who otherwise account for the majority of infectious cases in more temperate climates Loparev et al. [30], Loparev et al. [48], Loparev et al. [34].

## VZV Genome

The virus has icosahedral symmetry and contains centrally located linear double-stranded DNA molecule 124,884 base pairs (bp) in length with surrounding envelope. The VZV genome has been considered to be stable [49,50]. The variability between individual strains is only ~ 0.1 % and is manifested as single nucleotide polymorphisms (SNP) [51,52]. The genome consists of a unique long region (UL, about 105,000 bp) flanked by an inverted repeat regions (terminal repeat long - TRL, internal repeat long - IRL) and unique short region (US, 5,232 bp) flanked by internal repeat (terminal repeat short - TRS and inverted repeat short - IRS, each 7,319 bp) [53-57].

## Basic Molecular Genetic Analysis of VZV Genome

Molecular genetic analysis of VZV strains greatly contributes to the characterization of VZV genotypic groups. Various methods have been utilized and reported for identifying and genotyping VZV strains LaRussa et al. [58], LaRussa et al. [8], Campsall et al. [59], Loparev et al. [30], Loparev et al. [34], Nagel et al. [60]. Early VZV typing efforts relied on DNA restriction fragment length polymorphism analysis (RFLP), an approach that was sufficiently powerful to demonstrate high degree of sequence conservation among VZV strains. Nevertheless, some intra-strain variation among wild-type isolates of VZV was observed Faga et al. [61], Norberg et al. [55], Parker et al. [62]. VZV DNA restriction fragment length polymorphism (RFLP) has been used to distinguish most wild-type VZV isolates from the Oka vaccine strain, using SNP located in ORF 38 (PstI site in many wild-type strains), ORF 54 (BglI site in Oka

LaRussa et al. [58], LaRussa et al. [8], Loparev et al. [30] and ORF 62 (SmaI site) Li and Zhu et al. [63].

Analysis utilizing this method also determined that wild type VZV strains isolated in the US and Japan have distinctive PstI and BglI RFLP profiles. Japanese isolates are PstI+, BglI+ or PstI-, BglI+, while most isolates from the US, UK, Europe, and eastern Australia isolates are PstI+, BglI- [64,65], Loparev et al. [34]. BglI+ strains, apart from those isolated in Japan, are common in tropical regions such as equatorial Africa, India, Bangladesh, China, Central America and northern Australia [36,37], Liu et al. [66]. An unusual PstI-, BglI-VZV strain was reported in Australia Loparev et al. [48], a strain that could represent either recombination between the dominant genotypes or point mutation in the ORF 38 locus.

The majority of already published genotyping efforts were directed to multi-SNP analysis and different SNPs were picked up by different researchers Carr et al. [49], Peters et al. [67], [33,34]. The method developed by Loparev et al, which utilizes the detection of SNPs in ORF 22, differentiated three major VZV genotypes - E (European), J (Japanese), and M (mosaic) - utilising only one amplicon (ORF 22) approach Loparev et al. [54], Loparev et al. [48], Loparev et al. [34], MacNail et al. [68], Norberg et al. [55], Peters et al. [67]. Four SNPs in ORF 22 are able to discriminate also between four mosaic strains, named M1, M2, M3 and M4. Studies have shown that strains of the M genotype prevailed in tropical regions, whereas E strains dominated in temperate longitudes and J genotype strains were the dominant genotype in Japan. In later studies, this approach was combined with PCR amplification of the ORF 21, ORF 22 and ORF 50 Loparev et al. [34]. Thus utilization of PCR amplifications of the ORF 21 502 bp target region, ORF 22 447 bp target region and ORF 50 514 bp target region led to further identification of the E1 and E2 genotypes.

Strains of the genotype E1 are usually more common in Europe and Australia than E2 strains Loparev et al. [48], Loparev et al. [34]. One hypothesis speculated Norberg et al. [55] that genotype E2 strains may have arisen more than a century ago in remote European colonies such as Australia and New Zealand through recombination events between E1 and tropical genotype M strains and effectively competed with the original tropical and imported E1 strains, establishing themselves in the population Loparev et al. [34]. Recombination events between E1 and J strains could also play a role in the appearance of genotype E2 strains. Alternatively, E2 strain might have emerged in Europe Loparev et al. [54] in those countries with E1 and M strains already in circulation, spreading afterwards to Australia and New Zealand. Recombinant variants of E2 could have been also selected by temperate climates to which increasing numbers of people migrated from warmer regions.

## Conclusion

The easiest way to discover even the least predicted variations in the VZV genome is undoubtedly possible only by full genome sequencing approach. However, this approach is relatively expensive and time consuming, which makes it unpractical especially for clinical laboratories. Furthermore, a relatively large quantity of experimental material is needed, which is not always available. This makes the approach of genotyping selected short amplicons with their subsequent bioinformatic analyses a valid and practical method for the epidemiological studies. These are important for tracking changes in VZV epidemiology, with increasing significance especially now during the time of introduction of new vaccination programmes both for varicella and zoster in European countries.

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