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# Structural and functional modeling of viral protein 5 of Infectious Bursal Disease Virus

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ABSTRACT

Infectious Bursal Disease (IBD) is an acute, highly contagious and immunosuppressive disease of young chicken. The causative virus (IBDV) is a bi-segmented, double-stranded RNA virus. The virus encodes five major proteins, viral protein (VP) 1–5. VPs 1–3 have been characterized crystallographically. Albeit a rise in the number of studies reporting successful heterologous expression of VP5 in recent times, challenging the notion that rapid death of host cells overexpressing VP5 disallows obtaining sufficiently pure preparations of the protein for crystallographic studies, the structure of VP5 remains unknown and its function controversial. Our study describes the first 3D model of IBD VP5 obtained through an elaborate computational workflow. Based on the results of the study, IBD VP5 can be predicted to be a structural analog of the leucine-rich repeat (LRR) family of proteins. Functional implications arising from structural similarity of VP5 with host Toll-like receptor (Tlr) 3 also satisfy the previously reported opposing roles of the protein in first abolishing and later inducing host-cell apoptosis.

## 1. Introduction

Infectious Bursal Disease (IBD) is one of the economically most important and common diseases of poultry. It is an acute, highly contagious and immunosuppressive viral disease of young chicken, characterized by the destruction of dividing lymphoid cells in the bursa of Fabricius causing cytolysis leading to immunosuppression, in addition to losses due to impaired growth and death, and excessive condemnations of carcasses because of skeletal muscle hemorrhages (Eterradossi and Saif, 2013).

IBD is caused by a virus (IBDV) of the genus *Avibirnavirus* of *Birnaviridae* family. The family *Birnaviridae* is represented by non-enveloped, icosahedral viruses having a double-stranded RNA genome with two segments A and B. Five major viral proteins (VP) have been identified in IBDV and they are generally referred to as VP 1–5. The smaller genome segment B, about 2.8 kb in size, encodes the RNA-dependent RNA polymerase, VP1. Genome segment A, about 3.2 kb in size, encodes a bicistronic mRNA containing two largely overlapping open reading frames (ORFs), A1 and A2. The larger ORF, A2, encodes a polyprotein in the form N-pVP2-VP4-VP3-C that is autoproteolytically cleaved by the viral protease, VP4, to form VP2, VP3, and VP4. VP2 and 3 are structural proteins occurring in the viral capsid. ORF A1 encodes a 17 kDa, non-structural VP5, which occurs only in infected cells (Eterradossi and Saif, 2013). Earlier results suggest two factors that may have discouraged obtaining sufficient amounts of the purified protein as required for crystallographic studies: first, VP5 may not always be expressed by the virus in cell culture, and second, heterologous overexpression of the protein causes the death of the host cells. Notwithstanding the first factor, lately, there has been an increase in the number of studies that report expression of VP5 in cell culture (Mendez et al., 2017). Nevertheless, the structure of IBD VP5 remains unknown and its function is controversial. VP5 is non-essential for virus replication *in vitro* (Mundt et al., 1997) or *in vivo* (Yao et al., 1998) but necessary for viral release from infected cells (Wu et al., 2009). VP5 is known to prevent apoptosis of the infected host cell during early stages (Liu and Vakharia, 2006) by interacting with the p85α subunit of the phosphatidylinositol 3-kinase (PI3K) (Wei et al., 2011) but promote apoptosis in later stages by interacting with voltage-dependent anion channel 2 polypeptide (VDAC2) (Li et al., 2012).

In the present communication, we utilize a combination of several computational methods to derive a structural and functional model of IBD VP5.

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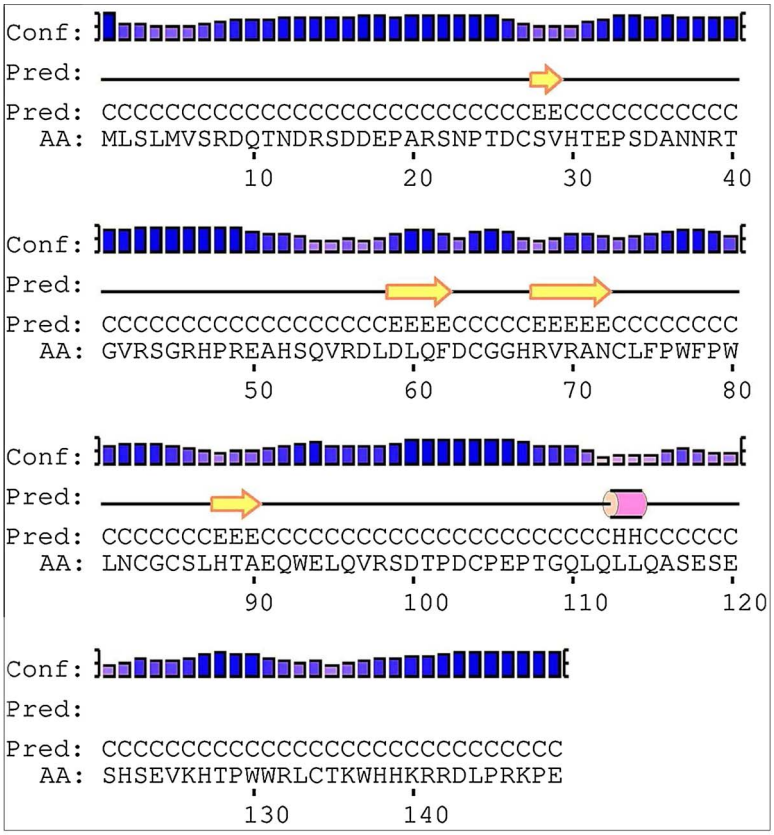
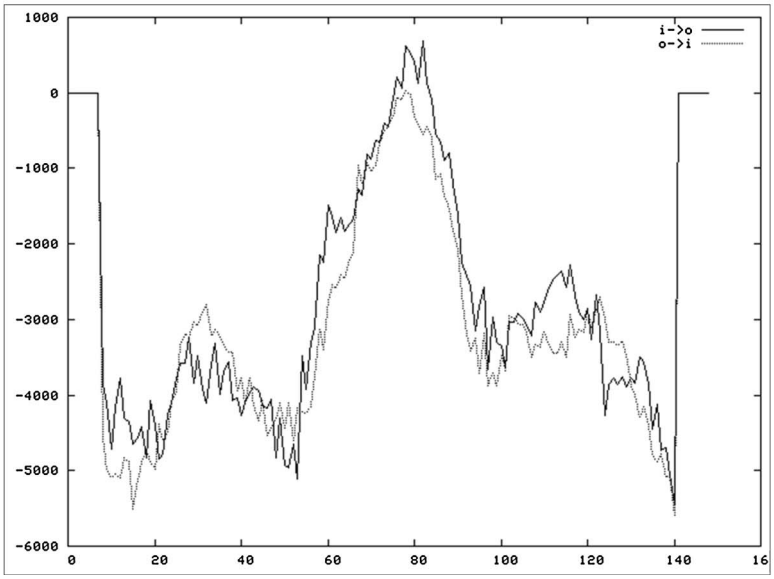



*a.*




*b.*

**Fig. 1.** *a.* Predicted secondary structure of IBD VP5 by PsiPred; random coils are represented as line (C), helices are represented as cylinders (H) and strands are represented as arrows (E) along the target sequence. Conf, Confidence of prediction, Pred; predicted secondary structure; AA, target sequence. *b.* Transmembrane topology of VP5; The propensity of IBD VP5 to exist as a transmembrane domain is plotted along its sequence; amino acids 67–82 are predicted to exist as a transmembrane domain with high confidence.

## 2. Materials and methods

### 2.1. Sequence retrieval and prediction of secondary structure

The amino acid sequence of VP5 (Accession: AEP25096.1) (Wang et al., 2011) was retrieved from GenBank (Benson et al., 2007), and PSIPRED *v*3.3 (Buchan et al., 2013) was used to predict the secondary structure of VP5.

### 2.2. Prediction of tertiary structure

The amino acid sequence of VP5 was queried in delta-BLAST (Domain Enhanced Lookup Time Accelerated – Basic Local Alignment Search Tool) (Boratyn et al., 2012) with default parameters against the Protein Data Bank (PDB). Delta-BLAST failed to identify any template suitable for the comparative modeling of the protein. Hence, *ab initio* and fold recognition modeling were resorted to; the sequence of VP5 was submitted to IntFold2 (Buenavista et al., 1851), QUARK (Xu and