Bornaviruses

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Article Contents

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Borna disease virus **(BDV) is a nonsegmented negative-strand ribonucleic acid (RNA) virus that is unique among viruses of the order *Mononegavirales* in its genomic organisation, nuclear localisation for replication and transcription, splicing and neurotropism. Most reports of natural infection have described outbreaks in horses and sheep in central Europe; however, the virus appears to be distributed worldwide and has the potential to infect many, if not all, warm-blooded hosts, causing disorders of the central, peripheral and autonomic nervous systems. In horses and sheep BDV is associated with fatal meningoencephalitis. In parrots and related exotic birds the recently characterised avian Bornavirus (ABV) may also infect the central nervous system; however, disease is typically manifest as a wasting disease due to autonomic nervous system infection and impaired peristalsis in the gastrointestinal tract. Whether bornaviruses infect humans remains controversial.**

Classification

Borna disease virus (BDV) is the prototype of the family *Bornaviridae*, genus *Bornavirus*, within the nonsegmented negative-strand ribonucleic acid (RNA) viruses (order *Mononegavirales*). Bornaviruses appear to be distributed worldwide and have the potential to infect most, if not all, warm-blooded hosts. Bornaviruses are similar in genomic organisation to other nonsegmented, negative-stranded (NNS) RNA viruses; however, their genomes ($\sim$8.9 kb) are substantially smaller than those of *Rhabdoviridae* (approximately 11–15 kb), *Paramyxoviridae* ($\sim$16 kb) or *Filoviridae* ($\sim$19 kb), and bornaviruses are distinctive in their nuclear localisation of replication and transcription. Although this feature is shared with the plant nucleorhabdoviruses, it is unique among animal viruses of the order *Mononegavirales*. Genome organisation and gene expression are remarkable for overlap of open reading frames (ORFs), transcriptional units and transcriptional signals; readthrough of transcriptional termination signals and differential use of translational initiation codons. There is a precedent for use of each of these strategies by the *Mononegavirales*. However, the concurrent use of such a diversity of strategies for the regulation of gene expression is unique among the known NNS RNA viruses. Furthermore, bornaviruses use the cellular splicing machinery to generate some of their messenger RNAs (mRNAs). Although splicing is also found in *Orthomyxoviridae* (segmented, negative-strand RNA viruses), it is unprecedented in *Mononegavirales*. **See also**: Filoviruses; Rhabdoviruses; RNA Virus Genomes

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Taxonomy

Order: *Mononegavirales*
Family: *Bornaviridae*
Genus: *Bornavirus*

Derivation of name

The name Borna refers to the city of Borna, Germany, the site of an equine epidemic in 1895–1896 that disabled the Saxon cavalry.

Physicochemical and physical characteristics

Virion M_r and the $S_{20,w}$ are not known for BDV and ABV. Partially purified BDV infectious particles have a buoyant density of 1.16–1.22 g mL^{-1} in caesium chloride, 1.22 g mL^{-1} in sucrose and 1.13 g mL^{-1} in renografin. Virions are stable at 37°C and lose only minimal infectivity after 24 h incubation in the presence of serum. Virus infectivity is rapidly lost by heat treatment at 56°C, exposure to pH 5.0, organic solvents, detergents, chlorine, formaldehyde or ultraviolet radiation (Ludwig *et al*., 1988).

Genome

BDV genomic sequences have been reported for three virus isolates, strain V, HE/80 and No/98 (Briese *et al*., 1994; Cubitt *et al*., 1994; Nowotny *et al*., 2000); whereas strain V and HE/80 sequences are approximately 95% identical at the nucleotide level, No/98 sequence differs by more than

15% from the other two isolates. The BDV genome consists of a single molecule of a linear, negative-stranded, nonpolyadenylated RNA comprised of approximately 8900 nucleotide (nt) (M_r of approximately 3×10^6). The genome is compact, 99.4% of its nucleotides are transcribed into subgenomic RNAs. Only 54 of 8910 bases (BDV strain V) are not found in primary viral transcripts. These bases represent the trailer region at the 5′ end of the genome (**Figure 1**). The region between the 3′ end of the genome and the first base of the first transcriptional unit is 42 nt long and has a high adenosine/uridine content of 64% with an adenosine to uridine ratio of approximately 1:2, similar to 3′-leader sequences of other *Mononegavirales*. Extracistronic sequences are found at the 3′ (leader) and 5′ (trailer) termini of the BDV genome that are complementary and may be aligned to form a terminal panhandle. The genome organisation of ABV is similar to that of BDV; however, sequence conservation at the nucleotide level is less than 70% (<80% at the amino acid level) (Honkavuori *et al*., 2008; Kistler *et al*., 2008; Rinder *et al*., 2009).

Proteins

Six major ORFs are present in the BDV antigenomic sequence (Briese *et al*., 1994; Cubitt *et al*., 1994; **Figure 1**). These ORFs code for polypeptides with predicted M_r of 40 kDa (p40), 23 kDa (p23), 10 kDa (p10), 16 kDa (p16), 57 kDa (p57) and 180 kDa (p190). Based on positions of gene sequences in the viral genome, relative abundance in infected cells, and biochemical and sequence features, these polypeptides are predicted to correspond to the nucleoprotein (N, p40), phosphoprotein (P, p23), matrix protein (M, p16), glycoprotein (G, p57) and L-polymerase (L, p190) found in other *Mononegavirales*. BDV p10 (X protein) does not have a clear homologue in other NNS RNA viral systems (Wehner *et al*., 1997). The X protein may mediate nuclear shuttling of viral gene products such as unspliced RNAs or ribonucleoprotein particles. It also appears to be involved in regulation of the viral polymerase (Schneider *et al*., 2003). *N* contains a nuclear localisation signal (NLS) as well as a nuclear export signal (NES) and is present in BDV in two isoforms (p40 and p38) that differ in length at the *N*-terminus. The functional significance of the different isoforms is unknown. Although the additional 13 amino acids present in the 40-kDa isoform include the NLS, the 38-kDa isoform may enter the nucleus through its interaction with P. P is an acidic polypeptide (predicted pI of 4.8), with a high serine–threonine content (16%). Its phosphorylation at serine residues is mediated by both protein kinase Cε (PKCε) and casein kinase II (Schwemmle *et al*., 1997; Prat *et al*., 2009). As with phosphoproteins of other *Mononegavirales*, P forms a central structural unit in the assembly of the active polymerase complex. P contains an NLS, binds to N, L and X, and may contribute to nuclear localisation of X and the 38-kDa isoform of N. The 16-kDa polypeptide is a putative matrix protein. The ORF for p57 directs the synthesis of a glycoprotein of 94-kDa, a polypeptide that can be processed by the subtilisin-like endoprotease furin (Richt *et al*., 1998). Both GP-94 and its *C*-terminal cleavage product GP-43 are associated with BDV infectious particles and are proposed to function in early events in infection. Incorporation of the *N*-terminal cleavage product GP-51 may also occur. The ORF of BDV complementary to the 5′ half of the genome (L, p190) is fused to a small upstream ORF by RNA splicing to generate a continuous ORF with a coding capacity of 190 kDa in the 6.1 and 6.0 kb transcripts (**Figure 1**). The deduced amino acid sequence from this ORF includes motifs that are conserved among NNS RNA virus L-polymerases.

Structure

Spherical, enveloped particles ranging in diameter from 40 to 190 nm have been identified by electron microscopy in extracts from BDV infected cultured cells (Zimmermann *et al*., 1994) or after induction of infected cultured cells with *n*-butyrate (Kohno *et al*., 1999). Particles of 90–100 nm or more contain a 50–60 nm electron-dense core and are presumed to represent infectious virions. Smaller particles are proposed to be defective interfering particles. Glycoprotein spikes of 7 nm have been visualised and budding was observed from spike-containing membrane regions of *n*-butyrate induced BDV infected cells. Virions in infected organ tissues have not been identified. **See also**: Virus Structure

Replication

Replication and transcription of the BDV NNS RNA genome occur in the nucleus of infected cells (Briese *et al*., 1992). Although this strategy is also found in some plant rhabdoviruses, it is a unique feature among animal NNS RNA viruses. For influenza virus, a segmented negative-strand RNA virus of animals, the nuclear localisation of transcription has been linked to a cap-snatching mechanism whereby cellular RNAs are used to prime viral transcription. This is not the case with BDV, as sequences at the 5′ end of the BDV mRNAs are homogeneous and genome-encoded (Schneemann *et al*., 1994). Instead, nuclear localisation of transcription in BDV appears to reflect a requirement for the cellular splicing machinery to process some of its primary subgenomic RNA transcripts. Replication of its negative-strand RNA genome is facilitated, as in other NNS RNA viruses, by the synthesis of a full-length positive-strand copy of the viral genome (antigenome) that serves as template for new negative-strand progeny genomes.

Transcription of the BDV genome results in the synthesis of at least four primary, 5′-capped and 3′-polyadenylated RNAs with apparent chain lengths of 0.8 kb, 1.2 kb, 2.8 kb and 7.1 kb (**Figure 1**). A fifth, leader-containing RNA of 1.9 kb initiates at the extreme 3′ end of the genome, is not capped and lacks polyadenylation at its 3′-end (T2 in **Figure 1**). Similar to other *Mononegavirales*, sequential and polar transcription results in a gradient whereby expression

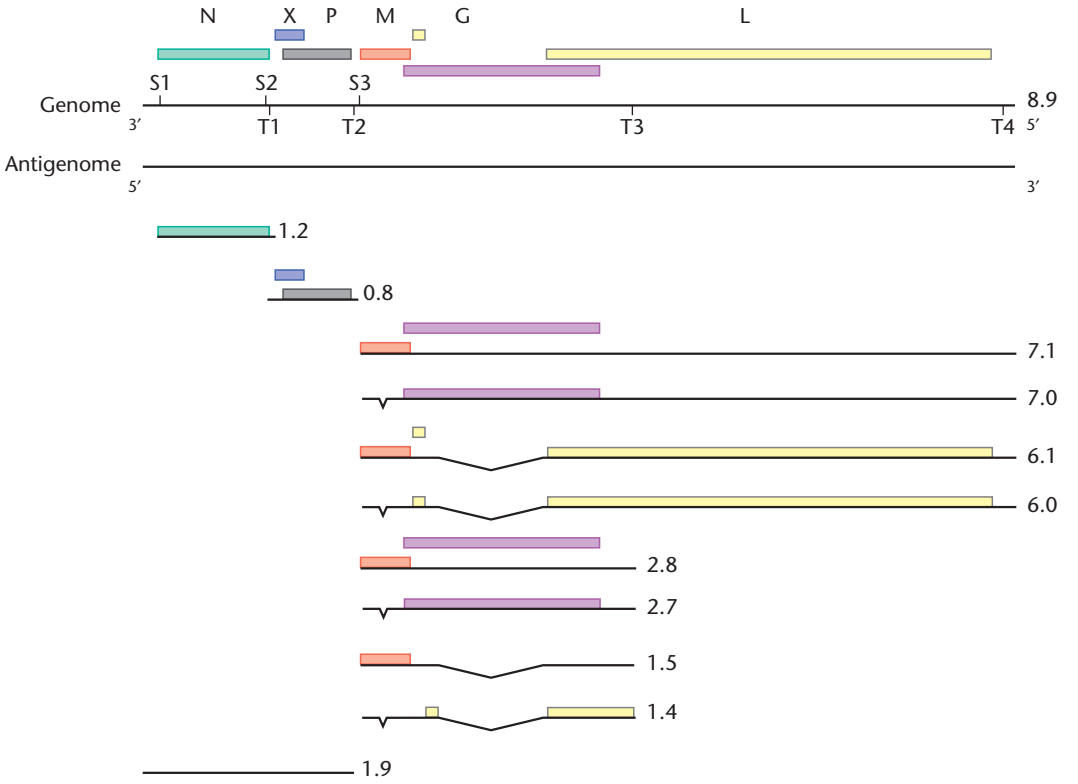

Figure 1 Genomic organisation and transcriptional map of *Borna disease virus* (BDV) strain V. Six major open reading frames (N, X, P, M, G and L) are represented above the BDV genome. Transcriptional start (S) and termination sites (T) used to generate RNA transcripts for expression of these proteins are indicated on the genomic strand (3′–5′, negative-strand genome). At least 10 different transcripts ranging in length from 0.8 to 7.1 kb (numerals to the right) are generated as shown below the full-length positive-strand copy of the genome (5′–3′, antigenome). The shorter transcripts below the 7.1 and 2.8 kb transcripts are derived by RNA splicing within the M or G open reading frames. The 1.9 kb transcript (1.9) is considered to represent a leader RNA rather than messenger RNA because it initiates at the extreme 3′ end of the BDV genome and is not capped or polyadenylated.

of BDV transcripts decreases with distance from the 3′-terminus. The six major ORFs (N, X, P, M, G and L) are expressed from only three transcription units. The first transcription unit (1.2 kb) is monocistronic and encodes the N protein. The second transcription unit (0.8 kb) is bicistronic and encodes the X and P proteins. The third transcription unit (2.8 or 7.1 kb RNA) is tricistronic and encodes the M, G and L proteins. The transcription start signals (S) are comprised of a semiconserved uridine-rich motif that is partially copied into the respective transcripts (Schneemann *et al*., 1994). This motif appears to be specific for bornaviruses, in that similar sequences are not present at the gene start sites of previously described *Mononegavirales*. Each termination site consists of 6–7 uridine residues preceded by an adenosine residue. This consensus sequence is reminiscent of the transcriptional termination–polyadenylation signals in known *Mononegavirales*, and it seems likely that polyadenylation of bornaviral transcripts also occurs by polymerase stuttering on the repetitive uridine residues.

An unusual feature of the bornavirus genome organisation is the positioning of transcriptional termination and initiation signals at gene junctions (Briese *et al*., 1994; Schneemann *et al*., 1994; Honkavuori *et al*., 2008; Kistler *et al*., 2008). Other than in filo-, rhabdo- and paramyxoviruses, where transcriptional termination–polyadenylation sites are usually separated from the next transcription initiation site by an intergenic region, the BDV transcriptional initiation site for the 0.8 kb RNA (S2 in **Figure 1**) is located 18 nt upstream of the termination site of the 1.2 kb RNA (T1 in **Figure 1**). A similar organisation has been observed in the paramyxovirus respiratory syncytial virus (RSV), where the transcriptional initiation site for the polymerase gene is located 68 nt upstream of the transcription termination site of the preceding 22 K gene. This arrangement has been proposed to serve as a mechanism for attenuation of transcription of the RSV polymerase gene. However, the 1.2 kb and the 0.8 kb RNAs are the most abundant RNAs in BDV-infected cells, implying that the overlap does not significantly affect transcription of the 0.8 kb RNA. It is possible that the degree of attenuation is a function of the length by which the two transcriptional signals are separated. If so, a stretch of 18 nt may not be sufficient to cause a noticeable decrease in transcription of the 0.8 kb RNA. Two nucleotides separate the second from the third transcription unit of BDV. However, the transcriptional initiation signal for the 2.8/7.1 kb RNAs (S3 in **Figure 1**) extends upstream across these

two bases into the termination signal of the 0.8 kb RNA (T2 in **Figure 1**), such that T2 is part of S3. The overlap of these domains does not appear to interfere with their recognition by the BDV polymerase, because termination and initiation occur efficiently at this gene junction. It is not clear how the BDV polymerase recognises the overlapping transcription signals as separate functional entities. **See also**: Respiratory Syncytial Virus

Several polycistronic BDV RNAs arise by readthrough at termination site T3 (**Figure 1**). Although transcriptional readthrough is not uncommon in *Mononegavirales*, it is usually considered to be aberrant, without known biological significance. In contrast, transcriptional readthrough is an essential feature of the molecular biology of bornaviruses. Only RNA transcripts resulting from readthrough at termination site T3 are capable of directing expression of the L protein (**Figure 1**). It is plausible that transcriptional readthrough may provide a mechanism for regulating BDV gene expression. For example, low-level readthrough at T3 would lead to decreased levels of L-polymerase, which should be needed only in catalytic amounts.

RNA splicing is another aspect that renders bornaviruses unique among the *Mononegavirales*. Two primary RNA transcripts of 2.8 and 7.1 kb originate at the third transcriptional start site of BDV that differ at their 3′ end due to use of alternative transcriptional termination sites (T3 or T4, **Figure 1**). Although the 2.8 kb transcript contains only the M and G ORFs, the 7.1 kb transcript contains in addition the L ORF. These primary transcripts are post-transcriptionally modified by differential splicing of two introns, intron 1 (94 nt, 1932–2025 nt, located within M ORF) and intron 2 (1.3 kb, 2410–3703 nt, located within G ORF) (**Figure 1**), to generate six additional RNAs (Schneider *et al*., 1994). Differential splicing of the two introns regulates expression of the M, G and L proteins. Splicing of intron 1 places the thirteenth amino acid (aa) residue of the M ORF in frame with a stop codon. Although this abrogates M expression, the resulting 13-aa minicistron facilitates G expression by ribosomal reinitiation. Splicing of intron 2 fuses 17 nt of upstream sequence (2393–2410 nt) containing an AUG to a continuous ORF comprising the remainder of the L coding sequence (3703–8819 nt). Whether splicing of intron 1 in the 6.0 kb transcript is essential for L expression is uncertain; however, preliminary data suggest that the 13-aa minicistron that facilitates G expression by ribosomal reinitiation also facilitates L expression. **See also**: Influenza Viruses

The mechanisms by which the bornavirus polymerase switches from synthesising subgenomic transcripts to full-length positive-strand RNAs, or from synthesis of full-length positive-strand RNAs to progeny negative-strand RNAs, are currently unknown. The intracellular site of virion assembly is unknown. **See also**: Measles Virus; Mumps Virus; Rhabdoviruses; RNA Plant and Animal Virus Replication

Recently, sequences homologous to BDV L, M and N sequences were found integrated into genomes of bats, lemurs, fish, elephants, rodents, squirrels, primates and man (Horie *et al*., 2010; Belyi *et al*., 2010). Some of these endogenous Borna-like (EBL) elements comprise full or partially truncated open reading frames flanked by viral regulatory initiation and termination sequences. Expression of the sequences as mRNA suggests they may have a functional role, perhaps in conferring resistance to infection (Horie *et al*., 2010; Belyi *et al*., 2010). There is evidence of multiple independent integration events. Although some, for example the BDV N-related EBLN-1, were introduced into primates before the divergence of marmoset and rhesus macaque approximately 40 million years ago, others, like TLS-EBLN in squirrels, were introduced more recently.

Epidemiology

Host range

Originally described as a fatal encephalitis in horses, Borna disease has also been reported in sheep, cattle, llamas, cats, dogs and ostriches (Lipkin and Briese, 2007). Because an even larger variety of species has been experimentally infected, including rabbits, birds and primates, it is predicted that the host range is likely to include all warm-blooded animals. There are no data concerning infection of species other than warm-blooded animals. Recently, viruses that are similar in genome organisation and immunologically cross reactive but considerably different in nucleic acid sequence have been implicated in proventricular dilatation disease (PDD), a fatal wasting disease of parrots, macaws and other exotic birds (Honkavuori *et al*., 2008; Kistler *et al*., 2008; Gray *et al*., 2010; Weissenbock *et al*., 2009).

Geographic range

Although there are reports of natural BDV infection in North America and Asia, classical Borna disease has not been confirmed outside of central Europe (Lipkin and Briese, 2007). Infection of birds with ABV has been confirmed in North America, Africa, Europe and Oceania.

Reservoirs and mechanisms for transmission

Neither the reservoir nor the mode of transmission for natural infection of BDV is known. An olfactory route for transmission has been proposed because intranasal infection is efficient and the olfactory bulbs of naturally infected horses show inflammation and oedema early in the course of disease (Ludwig *et al*., 1988). Reports of BDV nucleic acid and proteins in peripheral blood mononuclear cells also indicate a potential for haematogenous transmission. Experimental infection of neonatal rats results in virus persistence and is associated with the presence of viral gene products in saliva, urine and faeces. Such secreta/excreta are known to be important in transmission of other

pathogenic viruses (e.g. *Lymphocytic choriomeningitis virus*, hantaviruses). Thus, rats or other rodents have potential roles as natural reservoirs or vectors. Potential reservoirs for BDV in avians (Berg *et al*., 2001) or tree shrews (Hilbe *et al*., 2006) have been suggested. Vertical transmission of BDV has also been reported (Hagiwara *et al*., 2000). ABV is almost certainly transmitted via the fecal–oral route. Virus is present in high levels in cloacal swabs and guano of infected birds (Lierz *et al*., 2009; Rinder *et al*., 2009). **See also**: Hantaviruses

Human infection

Although there is consensus that humans are likely to be susceptible to BDV infection, the epidemiology and clinical consequences of human infection remain controversial. There have been no large controlled prevalence studies. Furthermore, methods for diagnosis of human infection are not standardised; thus, it is difficult to pursue meta-analysis. Most reports suggesting an association between BDV and human disease have focused on neuropsychiatric disorders, including unipolar depression, bipolar disorder or schizophrenia; however, BDV has also been linked to chronic fatigue syndrome, acquired immune deficiency syndrome (AIDS) encephalopathy, multiple sclerosis, motor neuron disease and brain tumours (glioblastoma multiforme) (**Table 1** and **Table 2**; Hatalski *et al*., 1997). The improbably broad spectrum of candidate disorders has led some investigators to propose that infection is ubiquitous and that elevation of serum antibody titres or the presence of viral transcripts in peripheral blood mononuclear cells or neural tissues in selected disorders reflects generalised (AIDS) or localised (glioblastoma multiforme) immunosuppression. **See also**: Acquired Immune Deficiency Syndrome (AIDS); Chronic Fatigue Syndrome; Motor Neuron Diseases; Schizophrenia

There are only infrequent reports where infectious virus has been isolated from humans. Methods used most commonly for serological diagnosis of infection include indirect immunofluorescence with infected cells and Western immunoblot or enzyme-linked immunosorbent assays (ELISAs) with extracts of infected cells or recombinant proteins. Infection may also be diagnosed through demonstration of BDV transcripts and proteins in tissues or peripheral blood mononuclear cells. BDV nucleic acids have been found in human brain by *in situ* hybridisation. However, most investigations with results indicating human infection of blood or brain have used nested reverse transcription–polymerase chain reaction (nRT–PCR), a method that is prone to artefacts due to inadvertent introduction of template from laboratory isolates or cross-contamination of samples. Amplification products representing bona fide isolates and those due to nRT–PCR amplification of low level contaminants cannot be readily distinguished by sequence analysis. Unlike other NNS RNA viruses, where the inherent low fidelity of viral RNA-dependent RNA polymerases results in sequence divergence of 10^3–10^4 per site per round of replication, BDV is characterised by extraordinary sequence conservation. Studies of N and P sequence from widely disparate BDV isolates revealed variability of up to 4.1% at the nucleotide level and 1.5% at the predicted amino acid level. Thus, similarities in sequence between putative new isolates and confirmed isolates cannot be used to exclude the former as artefacts. The extent to which sequence conservation in BDV represents enhanced polymerase fidelity or, more likely, selective environmental pressures is unknown. **See also**: Enzyme-linked Immunosorbent Assay

Clinical Features

Cells of many different lineages and species can be infected *in vitro* with BDV; however, virus production is more efficient in neural than nonneural cells. BDV is also neurotropic *in vivo*, with a particular predilection for neurons of the limbic system (Ludwig *et al*., 1988). Cells initially targeted in natural infection of horses and experimental infection of rats include neurons of the hippocampus and amygdala. The virus later spreads throughout the central nervous system (CNS) to infect astrocytes, Schwann cells and ependymal cells. Viral transport is presumably axonal and transsynaptic. Following intranasal infection, viral antigen is detected sequentially in olfactory receptor cells, olfactory nerve fibres, cells of the olfactory bulb and olfactory. In the hippocampus, viral antigen is localised in axon terminals, which form synaptic contacts with CA1 pyramidal cell dendrites before appearing in pyramidal cell bodies. Similar to rabies virus infection, it is likely that the spread of BDV infection within the CNS is mediated by ribonucleoprotein particles rather than enveloped virions (Gosztonyi *et al*., 1993; Ludwig *et al*., 1993; Clemente and de la Torre, 2007). **See also**: *Rabies Virus*

Clinical signs of BDV infection may be dramatic, subtle or inapparent, depending on the integrity and intensity of the host immune response to viral gene products. In adult immunocompetent animals (e.g. experimentally infected rats), BDV causes an immune-mediated multiphasic syndrome (Borna disease) that may include stereotyped motor behaviours, dyskinesias, dystonias, ataxia and paresis (Narayan *et al*., 1983). These rats have distinct disturbances in brain levels of catecholamine neurotransmitters, heightened sensitivity to dopamine agonists and altered levels of dopamine receptors in caudate-putamen (D_2 receptors) and nucleus accumbens (D_2 and D_3 receptors) (Solbrig *et al*., 1996). Furthermore, the administration of psychotropic drugs active in dopamine circuits suppresses some behavioural disturbances in these animals (e.g. hyperactivity and self-mutilation). In contrast to the robust disease observed in adult-infected rats, rats infected as neonates do not mount a cellular immune response to the virus and have a different syndrome, characterised by stunted growth, hyperactivity, subtle learning disturbances, altered taste preferences and abnormal responses to novel environments (ranging from excessive inhibition to excessive exploratory behaviour). Neonatal infection is

Table 1 Serum immunoreactivity to Borna disease virus in subjects with various diseases

	Prevalence			
Disease	Disease (%)	Control (%)	Assay	Reference
Psychiatric (various)	0.6 (4/694)	0 (0/200)	IFA	Rott *et al*. (1985) *Science* **228**: 755
	2 (13/642)	2 (11/540)	IFA	Bode *et al*. (1988) *Lancet* **ii**: 689
	4–7 (200–350/5000)	1 (10/1000)	WB/IFA	Rott *et al*. (1991) *Archives of Virology* **118**:143
	12 (6/49)		IFA	Bode *et al*. (1993) *Archives of Virology* **S7**: 159
	30 (18/60)		WB	Kishi *et al*. (1995) *FEBS Letters* **364**: 293
	14 (18/132)	1.5 (3/203)	WB	Sauder *et al*. (1996) *Journal of Virology* **70**: 7713
	24 (13/55)	11 (4/36)	IFA	Igata-Yi *et al*. (1996) *Nature Medicine* **2**: 948
	0 (0/44)	0 (0/70)	IFA/WB	Kubo *et al*. (1997) *Clinical and Diagnostic Laboratory Immunology* **4**: 189
	2.8 (35/1260)	1.1 (10/917)	ECLIA	Yamaguchi *et al*. (1999) *Clinical and Diagnostic Laboratory Immunology* **6**: 696
	9.8 (4/41)		IFA	Bachmann *et al*. (1999) *Journal of Neurovirology* **5**: 190
	15 (4/27)	0 (0/13)	IFA	Vahlenkamp *et al*. (2000) *Veterinary Microbiology* **76**: 229
	0 (0/89)	0 (0/210)	IFA/WB	Tsuji *et al*. (2000) *Journal of Medical Virology* **61**: 336
	5.5 (5/90)	0 (0/45)	WB (N^a)	Fukuda *et al*. (2001) *Journal of Clinical Microbiology* **39**: 419
	2.1 (17/816)		ECLIA	Rybakowski *et al*. (2001) *European Psychiatry* **16**: 191
	2.4 (23/946)	1.0 (4/412)	ECLIA	Rybakowski *et al*. (2002) *Medical Science Monitor* **8**: CR642 Rybakowski *et al*. (2001) *Psychiatria Polska* **35**: 819
	13 (11/87)	16 (45/290)	IFA	Lebain *et al*. (2002) *Schizophrenia Research* **57**: 303
	15 (26/171)	2 (1/50)	RLA	Matsunaga *et al*. (2005) *Clinical and Diagnostic Laboratory Immunology* **12**: 671
	23 (39/171)	0 (0/9)	WB	Matsunaga *et al*. (2005) *Clinical and Diagnostic Laboratory Immunology* **12**: 671
	29 (24/84)	20 (77/378)	RLA	Matsunaga *et al*. (2008) *Journal of Clinical Virology* **43**: 317
	67 (26/39)	22 (28/126)	CIC	Rackova *et al*. (2009) *Neuroendocrinol Letters* **30**: 414
Affective disorders	4.5 (12/265)	0 (0/105)	IFA	Amsterdam *et al*. (1985) *Archives of General Psychiatry* **42**: 1093
	4.2 (12/285)	0 (0/200)	IFA	Rott *et al*. (1985) *Science* **228**: 755
	38 (53/138)	16 (19/117)	WB (P^a)	Fu *et al*. (1993) *Journal of Affective Disorders* **27**: 61
	37 (10/27)		IFA	Bode *et al*. (1993) *Archives of Virology* **S7**: 159
	12 (6/52)	1.5 (3/203)	WB	Sauder *et al*. (1996) *Journal of Virology* **70**: 7713
	0–0.8 (0–1/122)	0 (0/70)	IFA/WB	Kubo *et al*. (1997) *Clinical and Diagnostic Laboratory Immunology* **4**: 189
	2.2 (1/45)	0 (0/45)	WB	Fukuda *et al*. (2001) *Journal of Clinical Microbiology* **39**: 419
	93 (26/28)	32 (21/65)	CIC	Bode *et al*. (2001) *Molecular Psychiatry* **6**: 481
	27 (9/33)	4 (1/25)	WB	Terayama *et al*. (2003) *Psychiatry Research* **120**: 201
	19 (25/129)	20 (77/378)	RLA	Matsunaga *et al*. (2008) *Journal of Clinical Virology* **43**: 317
	4.8 (5/104)	0 (0/42)	ELISA	Flower *et al*. (2008) *APMIS Supplement* **(124)**: 89
	0 (0/138)	0 (0/60)	IFA	Na *et al*. (2009) *Psychiatry Investigation* **6**: 306

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Schizophrenia	25 (1/4)		IFA	Bode *et al*. (1993) *Archives of Virology* **S7**: 159
	32 (29/90)	20 (4/20)	WB	Waltrip *et al*. (1995) *Psychiatry Research* **56**: 33
	17 (15/90)	15 (3/20)	IFA	Waltrip *et al*. (1995) *Psychiatry Research* **56**: 33
	14 (16/114)	1.5 (3/203)	WB	Sauder *et al*. (1996) *Journal of Virology* **70**: 7713
	20 (2/10)		WB	Richt *et al*. (1997) *Journal of Neurovirology* **3**: 174
	0–1 (0–2/167)	0 (0/70)	IFA/WB	Kubo *et al*. (1997) *Clinical and Diagnostic Laboratory Immunology* **4**: 189
	14 (9/64)	0 (0/20)	WB	Waltrip *et al*. (1997) *Schizophrenia Research* **23**: 253
	36 (24/67)	0 (0/26)	WB (P[a])	Iwahashi *et al*. (1997) *Acta Psychiatrica Scandinavica* **96**: 412
	12 (38/276)		WB	Chen *et al*. (1999) *Molecular Psychiatry* 4: 33
	10 (3/29)	23 (6/26)	IFA	Selten *et al*. (2000) *Medical Microbiology and Immunology* **189**: 55
	8.9 (4/45)	0 (0/45)	WB	Fukuda *et al*. (2001) *Journal of Clinical Microbiology* **39**: 419
	13 (11/87)	16 (45/290)	IFA	Lebain *et al*. (2002) *Schizophrenia Research* **57**: 303
	8.6 (10/116)	0 (0/54)	WB	Yang *et al*. (2003) *Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi* **1**: 85
	22 (7/32)	4 (1/25)	WB	Terayama *et al*. (2003) *Psychiatry Research* **120**: 201
	23 (21/91)	20 (77/378)	RLA	Matsunaga *et al*. (2008) *Journal of Clinical Virology* **43**: 317
	0 (0/60)	0 (0/60)	IFA	Na *et al*. (2009) *Psychiatry Investigation* **6**: 306
Childhood neuropschiatric disorder	56 (93/166)	51 (50/98)	CIC	Donfrancesco *et al*. (2008) *APMIS Supplement* **(124)**: 80
CFS	24 (6/25)		WB	Nakaya *et al*. (1996) *FEBS Letters* **378**: 145
	34 (30/89)		WB	Kitani *et al*. (1996) *Microbiology and Immunology* **40**: 459 Nakaya *et al*. (1997) *Nippon Rinsho* **55**: 3064
	0 (0/69)	0 (0/62)	WB	Evengard *et al*. (1999) *Journal of Neurovirology* **5**: 495
	100 (7/7)	33 (1/3)	WB	Nakaya *et al*. (1999) *Microbiology and Immunology* **43**: 679
	11 (7/61)	0 (0/73)	WB	Li *et al*. (2003) *Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi* **17**: 330
	21 (17/82)	0 (0/73)	WB	Li *et al*. (2005) *Zhonghua Yi Xue Za Zhi* **85**: 701
MS	13 (15/114)	2.3 (11/483)	IP/IFA	Bode *et al*. (1992) *Journal of Medical Virology* **36**: 309
	0 (0/50)		IFA	Kitze *et al*. (1996) *Journal of Neurology* **243**: 660
HIV-positive	7.8 (36/460)	2.0 (11/540)	IFA	Bode *et al*. (1988) *Lancet* **ii**: 689
HIV-early	8.1 (61/751)	2.3 (11/483)	IP/IFA	Bode *et al*. (1992) *Journal of Medical Virology* **36**: 309
HIV-LAP	14 (34/244)	2.3 (11/483)	IP/IFA	Bode *et al*. (1992) *Journal of Medical Virology* **36**: 309
Schisto/malaria	9.8 (19/193)	2.3 (11/483)	IP/IFA	Bode *et al*. (1992) *Journal of Medical Virology* **36**: 309
SSPE associated				
BDV antibody	22 (39/174)	23 (39/173[b])	ELISA	Güngör *et al*. (2005) *Pediatric Infectious Disease Journal* **24**: 833
Mental health care workers	9.8 (8/82)	2.9 (8/277)	WB	Chen *et al*. (1999) *Molecular Psychiatry* **4**: 33
Family of schizophrenic patients	12 (16/132)	2.9 (8/277)	WB	Chen *et al*. (1999) *Molecular Psychiatry* **4**: 33
Living near horse farms	15 (16/108)	1 (1/100)	ELISA	Takahashi *et al*. (1997) *Journal of Medical Virology* **52**: 330
Ostrich exposure	46 (19/41)	10 (4/41)	ELISA	Weisman *et al*. (1994) *Lancet* **344**: 1232
Veterinarians	0.7 (1/138)		IFA	Kinnunen *et al*. (2007) *Journal of Clinical Virology* **38**: 64

(*Continued*)

Table 1 Continued

Disease	Prevalence		Assay	Reference
	Disease (%)	Control (%)		
Suspected hanta-virus infection	0.2 (1/361)		IFA	Kinnunen *et al*. (2007) *Journal of Clinical Virology* **38**: 64
Alcohol and drug addiction	37 (15/41)	37 (47/126)	CIC	Rackova *et al*. (2010) *BMC Psychiatry* **10**: 70
Multitransfused	8.3 (14/168)	0 (0/42)	ELISA	Flower *et al*. (2008) *APMIS Supplement* **(124)**: 89
Pregnant women	0.9 (2/214)		ELISA	Flower *et al*. (2008) *APMIS Supplement* **(124)**: 89
Blood donors	2.3 (5/219)		ELISA	Flower *et al*. (2008) *APMIS Supplement* **(124)**: 89
Normal population	59 (1204/2101)		TELISA	Patti *et al*. (2008) *APMIS Supplement* **(124)**: 70
	37 (591/1588)		TELISA	Patti *et al*. (2008) *APMIS Supplement* **(124)**: 74
	50 (130/258)		TELISA	Patti *et al*. (2008) *APMIS Supplement* **(124)**: 77

Notes: CFS, chronic fatigue syndrome; CIC, circulating immune complexes; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; IFA, immunofluorescence assay; IP, immunoprecipitation; Lap, lymphadenopathy; MS, multiple sclerosis; RLA, radioligand assay; Schisto/malaria, schistosomiasis and malaria; SSPE, subacute sclerosing panencephalitis; TELISA, triple ELISA – CIC, Ab, Ag and WB, western immunoblot.

[a]Immuoreactivity to BDV N and P was measured and the higher prevalence is given.

[b]Epilepsy, headache, and cerebral palsy.

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Table 2 Borna disease virus nucleic acid in subjects with various diseases

		Prevalence			
Disease	Tissue	Disease (%)	Controls (%)	Divergence[a]	Reference
Psychiatric (various)	PBMC	67 (4/6)	0 (0/10)	0–3.6	Bode *et al*. (1995) *Nature Medicine* **1**: 232
	PBMC	37 (22/60)	6.5 (5/77)	4.2–9.3	Kishi *et al*. (1995) *FEBS Letters* **364**: 293
					Kishi *et al*. (1996) *Journal of Virology* **70**: 635
	PBMC-coculture	9.1 (3/33)	0 (0/5)	0.07–0.83	Bode *et al*. (1996) *Molecualr Psychiatry* **1**: 200
					de la Torre *et al*. (1996) *Virus Research* **44**: 33
	PBMC	1.9 (2/106)	0 (0/12)		Kubo *et al*. (1997) *Clinical and Diagnostic Laboratory Immunology* **4**: 189
	PBMC	0 (0/24)	0 (0/4)		Richt *et al*. (1997) *Journal of Neurovirology* **3**: 174
	PB	0 (0/159)			Lieb *et al*. (1997) *Lancet* **350**: 1002
	Blood	(1/1)			Planz *et al*. (1998) *Lancet* **352**: 623
	PBMC	4 (5/126)	2.4 (2/84)		Iwata *et al*. (1998) *Journal of Virology* **72**: 10044
	PBMC	20 (3/15)	0 (0/3)		Planz *et al*. (1999) *Journal of Virology* **73**: 6251
	PBMC	0 (0/81)			Kim *et al*. (1999) *Journal of Neurovirology* **5**: 196
	PBMC	0 (0/27)			Bachmann *et al*. (1999) *Journal of Neurovirology* **5**: 190
	CSF	0 (0/27)			Bachmann *et al*. (1999) *Journal of Neurovirology* **5**: 190
	PBMC	1.8 (1/56)	0.6 (1/173)		Tsuji *et al*. (2000) *Journal of Medical Virology* **61**: 336
	PBMC	37 (10/27)	15 (2/13)		Vahlenkamp *et al*. (2000) *Veterinary Microbiology* **76**: 229
	PBMC	1.1 (1/90)	0 (0/45)		Fukuda *et al*. (2001) *Journal of Clinical Microbiology* **39**: 419
	PBMC	33 (10/30)	13 (4/30)		Miranda *et al*. (2006) *Journal of Affected Disorder* **90**: 43
Affective disorders	PBMC	33 (1/3)	0 (0/23)		Sauder *et al*. (1996) *Journal of Virology* **70**: 7713
	PBMC	17 (1/6)	0 (0/36)		Igata-Yi *et al*. (1996) *Nature Medicine* **2**: 948
	PBMC	0 (0/9)			Richt *et al*. (1997) *Journal of Neurovirology* **3**: 174
	Brain	40 (2/5)	0 (0/10)		Salvatore *et al*. (1997) *Lancet* **349**: 1813.
	PBMC	4.1 (2/49)	2.4 (2/84)	0–5.1	Iwata *et al*. (1998) *Journal of Virology* **72**: 10044
	CSF	4.6 (3/65)	0 (0/69)	[Protein]	Deuschle *et al*. (1998) *Lancet* **352**: 1828
	PBMC	2.2 (1/45)	0 (0/45)		Fukuda *et al*. (2001) *Journal of Clinical Microbiology* **39**: 419
	PBMC	11 (6/53)	0 (0/32)		Wang *et al*. (2006) *Zhonghua Liu Xing Bing Xue Za Zhi* **27(6)**: 479
	PBMC	0 (0/138)	0 (0/60)		Na *et al*. (2009) *Psychiatry Investigation* **6**: 306
Schizophrenia	Brain	0 (0/3)	0 (0/3)		Sierra-Honigman *et al*. (1995) *British Journal of Psychiatry* **166**: 55
	CSF	0 (0/48)	0 (0/9)		Sierra-Honigman *et al*. (1995) *British Journal of Psychiatry* **166**: 55
	PBMC	0 (0/9)	0 (0/9)		Sierra-Honigman *et al*. (1995) *British Journal of Psychiatry* **166**: 55
	PBMC	64 (7/11)	0 (0/23)		Sauder *et al*. (1996) *Journal of Virology* **70**: 7713
	PBMC	10 (5/49)	0 (0/36)		Igata-Yi *et al*. (1996) *Nature Medicine* **2**: 948
	PBMC	0 (0/26)	0 (0/14)		Richt *et al*. (1997) *Journal of Neurovirology* **3**: 174
	Brain	53 (9/17)	0 (0/10)		Salvatore *et al*. (1997) *Lancet* **349**: 1813
	PBMC	9.8 (6/61)	0 (0/26)		Iwahashi *et al*. (1997) *Acta Psychiatrica Scandinavica* **96**: 412
	PBMC	3.9 (3/77)	2.4 (2/84)	0–5.1	Iwata *et al*. (1998) *Journal of Virology* **72**: 10044
	PBMC	14 (10/74)	1.4 (1/69)		Chen *et al*. (1999) *Molecular Psychiatry* **4**: 566

(*Continued*)

Table 2 Continued

Disease	Tissue	Prevalence		Divergence[a]	Reference
		Disease (%)	Controls (%)		
	Brain	25 (1/4)		[RNA, virus and protein]	Nakamura *et al*. (2000) *Journal of Virology* **74**: 4601
	PBMC	14 (4/29)	35 (9/26)		Selten *et al*. (2000) *Medical Microbiology and Immunology* **189**: 55
	PBMC	0 (0/45)	0 (0/45)		Fukuda *et al*. (2001) *Journal of Clinical Microbiology* **39**: 419
	PBMC	12 (3/25)		6.0–14	Nakaya *et al*. (1996) *FEBS Letters* **378**: 145 Kitani *et al*. (1996) *Microbiology and Immunology* **40**: 459
	PBMC	12 (7/57)	4.9 (8/172)		Nakaya *et al*. (1997) *Nippon Rinsho* **55**: 3064
	PBMC	0 (0/18)			Evengard *et al*. (1999) *Journal of Neurovirology* **5**: 495
	PBMC	0 (0/60)	0 (0/60)		Na *et al*. (2009) *Psychiatry Investigation* **6**: 306
	PBMC	44 (12/27)	15 (4/27)		Nunes *et al*. (2008) *Journal of Clinical Laboratory Analysis* **22**: 314
Schizoaffective	CSFMC	12 (6/52)	0 (0/32)		Wang *et al*. (2006) *Zhonghua Liu Xing Bing Xue Za Z*hi **27(6)**: 479
Viral encephalitis	PBMC	14 (6/43)	0 (0/98)	2.3–4.5	Wang *et al*. (2008) *Zhonghua Liu Xing Bing Xue Za Zhi* **29**: 1213
	PBMC	15 (6/40)	0 (0/46)		Li *et al*. (2009) *European Journal of Neurology* **16**: 399
	PBMC	10 (6/59)	0 (0/60)	4.7	Ma *et al*. (2009) *Zhonghua Liu Xing Bing Xue Za Zhi* **30**:1284
FMS	CSF	0 (0/18)	0 (0/6)		Wittrup *et al*. (2000) *Scandinavian Journal of Rheumatology* **29**: 387
CFS	PBMC	12 (3/25)		6.0–14	Nakaya *et al*. (1996) *FEBS Letters* **378**:145
Hippocampal	Brain	80 (4/5)			de la Torre *et al*. (1996) *Virus Research* **44**: 33
Sclerosis	Brain	15 (3/20)	0 (0/85)		Czygan *et al*. (1999) *Journal of Infectious Disease* **180**: 1695
Epilepsy	Brain	0 (0/106)			Hofer *et al*. (2006) *Journal of Clinical Virology* **36**:84
MS	CSF	11 (2/19)	0 (0/69)	[Protein]	Deuschle *et al*. (1998) *Lancet* **352**: 1828
	PBMC	0 (0/34)	0 (0/40)		Haase *et al*. (2001) *Annal of Neurology* **50**: 423
	PBMC	22 (2/9)	0 (0/98)	2.3–4.5	Wang *et al*. (2008) *Zhonghua Liu Xing Bing Xue Za Zhi* **29**: 1213
	PBMC	0 (0/9)	0 (0/46)		Li *et al*. (2009) *European Journal of Neurology* **16**: 399
Peripheral neuropathy	PBMC	0 (0/7)	0 (0/98)		Wang *et al*. (2008) *Zhonghua Liu Xing Bing Xue Za Zhi* **29**: 1213
	PBMC	0 (0/16)	0 (0/46)		Li *et al*. (2009) *European Journal of Neurology* **16**: 399
Parkinson disease	PBMC	0 (0/5)	0 (0/98)		Wang *et al*. (2008) *Zhonghua Liu Xing Bing Xue Za Zhi* **29**: 1213
HIV-infection	PBMC	13 (11/82)			Cotto *et al*. (2003) *Journal of Clinical Microbiology* **41**: 5577
Immunosuppressive treatment	PBMC	1.3 (1/80)			Cotto *et al*. (2003) *Journal of Clinical Microbiology* **41**: 5577
Multiple transfusions	PBMC	0.8 (1/127)	2 (2/200)		Lefrere *et al*. (2004) *Transfusion* **44**: 1396
Mental healthcare workers	PBMC	15 (7/45)	1.4 (1/69)		Chen *et al*. (1999) *Molecular Psychiatry* **4**: 566
Normal controls	PBMC		4.7 (8/172)		Kishi *et al*. (1995) *Medical Microbiology and Immunology* **184**: 135
	Brain		6.7 (2/30)		Haga *et al*. (1997) *Brain Research* **770**: 307
	PBMC		0 (0/100)		Davidson *et al*. (2004) *Vox Sanguinis* **86**: 148
	Plasma		0 (0/275[b])		Davidson *et al*. (2004) *Vox Sanguinis* **86**: 148

Notes: CFS, chronic fatique syndrome; CSF cerebrospinal fluid; PBMC, peripheral blood mononuclear cell; FMS, fibromyalgia syndrome and MS, multiple sclerosis.
[a]Divergence of P gene nucleotide sequence from Borna disease virus strain V and He/80.
[b]Plasma minipools of 91 individual samples.

associated with abnormal architecture in the cerebellum and hippocampus. Accumulating evidence suggests that these disturbances in cytoarchitecture are linked to alterations in expression of tissue factors, cytokines, neurotrophins and apoptosis-related products during critical periods of neural development (Hornig *et al*., 1999).

Interestingly, behavioural abnormalities, including hyperactivity, deficits in spatial memory and aggressiveness reminiscent of neonate rat infection or the infection of tree shrews, have recently been described in a transgenic mouse model in which the BDV P protein was expressed in glia cells (Kamitani *et al*., 2003). Animals expressing BDV P at high levels in their brains were characterised by reduced levels of brain-derived neurotropic factor (BDNF), serotonin (5-HT) receptors and decreased synaptic density in the absence of astrocytosis. These findings demonstrate that BDV gene products can directly interfere with neuronal function without inducing gross degenerative processes (Volmer *et al*., 2006; Prat *et al*., 2009).

Clinical features of ABV infection in birds include inflammation of the central, peripheral and autonomic nervous systems, in association with gastrointestinal dysfunction, ataxia and seizures (Gregory, 1998).

Control

No specific vaccine or antiviral therapy is established for BDV or ABV. Inoculation of a high dose of BDV attenuated by long-term culture in Madin–Darby canine kidney (MDCK) cells was found to result in amelioration of encephalitis in a rat model system; however, this approach has not been tested in other susceptible hosts. Immunisation of rats with recombinant vaccinia virus constructs expressing the BDV N gene resulted in earlier, more severe disease after challenge with infectious virus; however, protection in rats was recently reported using a parapoxvirus expression system for the BDV N gene. Ribavirin and Ara-C-related cytosine nucleosides may be of value. Although there is one report where BDV was found to be sensitive *in vitro* and *in vivo* to amantadine, three other reports found no antiviral activity *in vitro* or *in vivo* (Lipkin and Briese, 2007). **See also**: Antiviral Drugs

References

Belyi V, Levine AJ and Skalka AM (2010) Unexpected inheritance: multiple integrations of ancient bornavirus and ebolavirus/marburgvirus sequences in vertebrate genomes. *PLoS Pathogens* **6**: e1001030. doi:10.1371/journal.ppat.1001030.

Berg M, Johansson M, Montell H and Berg AL (2001) Wild birds as a possible natural reservoir of Borna disease virus. *Epidemiology Infection* **127**: 173–178.

Bode L, Dürrwald R, Rantam FA, Ferszt R and Ludwig H (1996) First isolates of infectious human Borna disease virus from patients with mood disorders. *Molecular Psychiatry* **1**: 200–212.

Briese T, de la Torre JC, Lewis A, Ludwig H and Lipkin WI (1992) Borna disease virus, a negative-strand RNA virus, transcribes in the nucleus of infected cells. *Proceedings of the National Academy of Sciences of the USA* **89**: 11486–11489.

Briese T, Schneemann A, Lewis AJ *et al*. (1994) Genomic organization of Borna disease virus. *Proceedings of the National Academy of Sciences of the USA* **91**: 4362–4366.

Clemente R and de la Torre JC (2007) Cell-to-cell spread of Borna disease virus proceeds in the absence of the virus primary receptor and furin-mediated processing of the virus surface glycoprotein. *Journal of Virology* **81**: 5968–5977.

Cubitt B, Oldstone C and de la Torre JC (1994) Sequence and genome organization of Borna disease virus. *Journal of Virology* **68**: 1382–1396.

Gosztonyi G, Dietzschold B, Kao M *et al*. (1993) Rabies and borna disease. A comparative pathogenetic study of two neurovirulent agents. *Laboratory Investigation* **68**: 285–295.

Gray P, Hoppes S, Suchodolski P *et al*. (2010) Use of avian bornavirus isolates to induce proventricular dilatation disease in conures. *Emerging Infectious Diseases* **16**: 473–479.

Gregory CR (1998) Progress in understanding proventricular dilatation disease. In: *Proceedings of the International Aviculturists Society*. Florida: Orlando.

Hagiwara K, Kamitani W, Takamura S *et al*. (2000) Detection of Borna disease virus in a pregnant mare and her fetus. *Veterinary Microbiology* **72**: 207–216.

Hatalski CG, Lewis AJ and Lipkin WI (1997) Borna disease. *Emerging Infectious Diseases* **3**: 129–135.

Hilbe M, Herrsche R, Kolodziejek J *et al*. (2006) Shrews as reservoir hosts of Borna disease virus. *Emerging Infectious Diseases* **12**: 675–677.

Honkavuori KS, Shivaprasad HL, Williams BL *et al*. (2008) Novel borna virus in psittacine birds with proventricular dilatation disease. *Emerging Infectious Diseases* **14**: 1883–1886.

Horie M, Honda T, Suzuki Y *et al*. (2010) Endogenous non-retroviral RNA virus elements in mammalian genomes. *Nature* **463**: 84–88.

Hornig M, Weissenbock H, Horscroft N and Lipkin WI (1999) An infection-based model of neurodevelopmental damage. *Proceedings of the National Academy of Sciences of the USA* **96**: 12102–12107.

Kamitani W, Ono E, Yoshino S *et al*. (2003) Glial expression of Borna disease virus phosphoprotein induces behavioral and neurological abnormalities in transgenic mice. *Proceedings of the National Academy of Sciences of the USA* **100**: 8969–8974.

Kistler AL, Gancz A, Clubb S *et al*. (2008) Recovery of divergent avian bornaviruses from cases of proventricular dilatation disease: identification of a candidate etiologic agent. *Virology Journal* **5**: 88.

Kohno T, Goto T, Takasaki T *et al*. (1999) Fine structure and morphogenesis of Borna disease virus. *Journal of Virology* **73**: 760–766.

Lierz M, Hafez HM, Honkavuori KS *et al*. (2009) Anatomical distribution of avian bornavirus in parrots, its occurrence in clinically healthy birds and ABV-antibody detection. *Avian Pathology* **38**: 491–496.

Lipkin WI and Briese T (2007) Bornaviridae. In: Knipe DM and Howley RM (eds) *Virology*, 5th edn, pp. 1829–1851. Philadelphia, PA, USA: Lippincott, Williams & Wilkins, a Wolters Kluwer Business.

Ludwig H, Bode L and Gosztonyi G (1988) Borna disease: a persistent virus infection of the central nervous system. *Progress in Medical Virology* **35**: 107–151.

Ludwig H, Furuya K, Bode L *et al*. (1993) Biology and neurobiology of Borna disease viruses (BDV), defined by antibodies, neutralizability and their pathogenic potential. *Archives of Virology Supplement* **7**: 111–133.

Narayan O, Herzog S, Frese K, Scheefers H and Rott R (1983) Behavioral disease in rats caused by immunopathological responses to persistent borna virus in the brain. *Science* **220**: 1401–1403.

Nowotny N, Kolodziejek J, Jehle CO *et al*. (2000) Isolation and characterization of a new subtype of Borna disease virus. *Journal of Virology* **74**: 5655–5658.

Prat CM, Schmid S, Farrugia F *et al*. (2009) Mutation of the protein kinase C site in borna disease virus phosphoprotein abrogates viral interference with neuronal signaling and restores normal synaptic activity. *PLoS Pathogens* **5**: e1000425.

Richt JA, Furbringer T, Koch A *et al*. (1998) Processing of the Borna disease virus glycoprotein gp94 by the subtilisin-like endoprotease furin. *Journal of Virology* **72**: 4528–4533.

Rinder M, Ackermann A, Kempf H *et al*. (2009) Broad tissue and cell tropism of avian bornavirus in parrots with proventricular dilatation disease. *Journal of Virology* **83**: 5401–5407.

Schneemann A, Schneider PA, Kim S and Lipkin WI (1994) Identification of signal sequences that control transcription of borna disease virus, a nonsegmented, negative-strand RNA virus. *Journal of Virology* **68**: 6514–6522.

Schneider PA, Schneemann A and Lipkin WI (1994) RNA splicing in Borna disease virus, a nonsegmented, negative-strand RNA virus. *Journal of Virology* **68**: 5007–5012.

Schneider U, Naegele M, Staeheli P and Schwemmle M (2003) Active borna disease virus polymerase complex requires a distinct nucleoprotein-to-phosphoprotein ratio but no viral X protein. *Journal of Virology* **77**: 11781–11789.

Schwemmle M, De B, Shi L, Banerjee A and Lipkin WI (1997) Borna disease virus P-protein is phosphorylated by protein kinase Cepsilon and casein kinase II. *Journal of Biological Chemistry* **272**: 21818–21823.

Solbrig MV, Koob GF, Joyce JN and Lipkin WI (1996) A neural substrate of hyperactivity in borna disease: changes in brain dopamine receptors. *Virology* **222**: 332–338.

Volmer R, Monnet C and Gonzalez-Dunia D (2006) Borna disease virus blocks potentiation of presynaptic activity through inhibition of protein kinase C signaling. *PLoS Pathogens* **2**: e19.

Wehner T, Ruppert A, Herden C *et al*. (1997) Detection of a novel Borna disease virus-encoded 10 kDa protein in infected cells and tissues. *Journal of Genetic Virology* **78**(Pt 10): 2459–2466.

Weissenbock H, Sekulin K, Bakonyi T, Hogler S and Nowotny N (2009) Novel avian bornavirus in a nonpsittacine species (Canary; Serinus canaria) with enteric ganglioneuritis and encephalitis. *Journal of Virology* **83**: 11367–11371.

Zimmermann W, Breter H, Rudolph M and Ludwig H (1994) Borna disease virus: immunoelectron microscopic characterization of cell-free virus and further information about the genome. *Journal of Virology* **68**: 6755–6758.

Further Reading

Bautista JR, Schwartz GJ, de la Torre JC, Moran TH and Carbone KM (1994) Early and persistent abnormalities in rats with neonatally acquired Borna disease virus infection. *Brain Research Bulletin* **34**: 31–40.

Dittrich W, Bode L, Ludwig H, Kao M and Schneider K (1989) Learning deficiencies in Borna disease virus-infected but clinically healthy rats. *Biological Psychiatry* **26**: 818–828.

Koprowski H and Lipkin WI (1995) Borna disease. *Current Topics in Microbiology and Immunology* **190**: 1–134.

Lipkin WI, Hornig M and Briese T (2001) Borna disease virus and neuropsychiatric disease – a reappraisal. *Trends in Microbiology* **9**: 295–298.

Lipkin WI, Travis GH, Carbone KM and Wilson MC (1990) Isolation and characterization of Borna disease agent cDNA clones. *Proceedings of the National Academy of Sciences of the USA* **87**: 4184–4188.

Sprankel H, Richarz K, Ludwig H and Rott R (1978) Behavior alterations in tree shrews induced by Borna disease virus. *Medical Microbiology and Immunology* **165**: 1–18.

Stitz L, Bilzer T, Richt JA and Rott R (1993) Pathogenesis of Borna disease. *Archives of Virology* **7**(suppl.): 135–151.

Zwick W (1939) Bornasche Krankheit und Enzephalomyelitis der Tiere. In: Gildemeister E, Haagen E and Waldmann O (eds) *Handbuch der Viruskrankheiten*, vol. 2, pp. 254–354. Jena: Fischer.