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Brief Communication

Structural analysis of a feline norovirus protruding domain

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ABSTRACT

Norovirus infects different animals, including humans, mice, dogs, and cats. Here, we show an X-ray crystal structure of a feline GIV.2 norovirus capsid-protruding (P) domain to 2.35 Å resolution. The feline GIV.2 P domain was reminiscent of human norovirus P domains, except for a novel P2 subdomain α-helix and an extended P1 subdomain interface loop. These new structural features likely obstructed histo-blood group antigens, which are attachment factors for human norovirus, from binding at the equivalent sites on the feline GIV.2 P domain. Additionally, an ELISA showed that the feline GIV.2 was antigenically distinct from a human GII.10 norovirus.

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Introduction

Human noroviruses (*Caliciviridae* family) are the dominant cause of outbreaks of gastroenteritis around the world. Human noroviruses are genetically and antigenically diverse (Hansman et al., 2006). Based on the capsid gene sequences, there are at least six main genogroups of noroviruses, which can be further subdivided into numerous genotypes. Most human noroviruses belong to genogroups I and II (GI and GII). Recently, a feline norovirus causing gastroenteritis in domestic cats was identified (Pinto et al., 2012). Genetic clustering placed the feline norovirus capsid sequence into GIV genotype 2 (GIV.2). Also belonging to GIV are lion, dog, and infrequently detected human noroviruses (Martella et al., 2007, 2009, 2011). Importantly, human norovirus genetic recombination appears to be a common event and the potential for zoonosis has been described in several studies (Bank-Wolf et al., 2010; Bull et al., 2005, 2007;Clarke and Lambden 1997; Eden et al., 2013; Humphrey et al., 1984; Mahar et al., 2013). These findings highlighted the importance of understanding the differences and similarities between animal and human noroviruses.

The X-ray crystal structure of human norovirus virus-like particles (VLPs) reveals two domains, a shell (S) domain and a protruding (P) domain (Prasad et al., 1999). The S domain forms a scaffold surrounding the viral RNA, whereas the P domain, which can be further subdivided into the P1 and P2 subdomains, likely contains the determinants for host recognition. The norovirus P domain can be expressed in *Escherichia coli* and this can form P dimers analogous to those on VLPs (Hansman et al., 2011). Studies with VLPs and/or P domains have shown that human, bovine, and canine noroviruses bind histo-blood group antigens (HBGAs) (Caddy et al., 2014; Hutson et al., 2002; Zakhour et al., 2009), whereas murine norovirus virions were found to interact with sialic acid (Taube et al., 2009). Little is known about the attachment factors or receptors for feline noroviruses. At least nine different HBGAs have been identified to bind to human norovirus. However, the relatively weak interaction, quality of reagents, and dissimilar ELISA formats have led to conflicting results concerning the specific HBGAs binding to different noroviruses (Caddy et al., 2014; Hansman et al., 2012; Lindesmith et al., 2012; Tan and Jiang 2010). In the study presented here, we show the X-ray crystal structure of a feline GIV.2 norovirus P domain and identified several novel structural features. We also found that the feline

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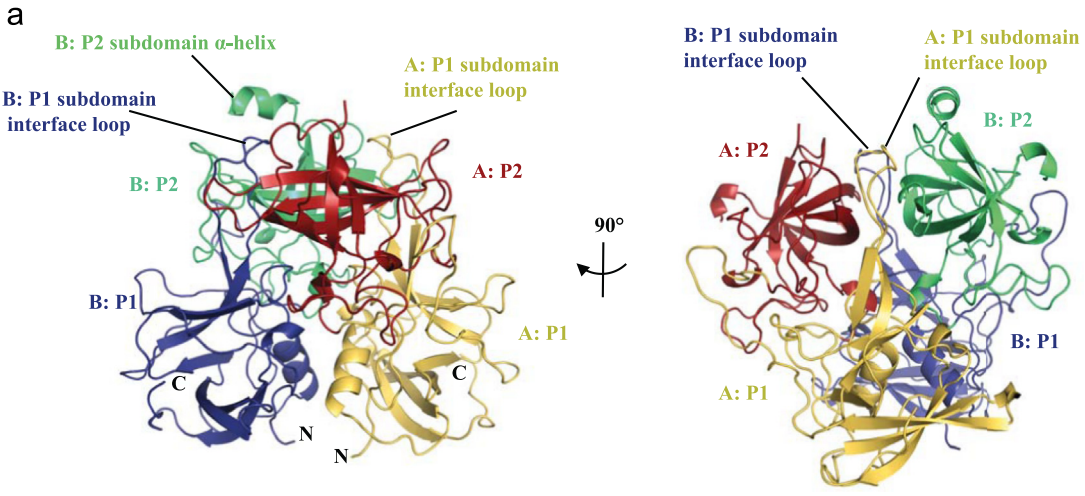
GIV.2 norovirus P domain was antigenically distinct from a human GII.10 P domain.

Results and discussion

In order to better understand the structural implications between animal and human norovirus capsids we solved the X-ray crystal structure of a recently identified feline GIV.2 norovirus P domain (Pinto et al., 2012). A single crystal of the feline GIV.2 P domain diffracted to 2.35 Å resolution (Fig. 1a). The structure was solved using molecular replacement with the GII.10 P domain as a search model (Hansman et al., 2011). Molecular replacement indicated a dimer in space group P21. Refinement of GIV.2 P domain led to an R_{work} value of 0.214 and R_{free}=0.268, with a well-defined electron density for most of the dimer (Table 1). Based on the GII.10 P domain structure, the GIV.2 P domain could be subdivided into P1 (224–277 and 438–569) and P2 (278–437) subdomains (Fig. 1). Analogous to other human noroviruses, the GIV.2 P1 subdomain contained an α-helix and seven β-strands, while the P2 subdomain contained six anti-parallel β-strands that formed a barrel-like structure. However, compared to the GII.10 capsid sequence, the feline GIV.2 P2 subdomain contained a large insertion between residues ~295 and 329 (Fig. 1b). The electron density of this insertion was disordered in chain A between residues 297 and 327 and in chain B between residues 297 and 319. Unfortunately, the disordered regions could not be modeled into the P domain structure. However, part of the insertion in chain B (residues 320–327) had clearly defined electron density and was found to be a short α-helix (Fig. 1a), although the α-helix had higher B-factors as compared to nearby residues and protein average, which suggested that the insertion was flexible. Interestingly, secondary structure prediction of the feline GIV.2 P domain indicated that the insertion actually formed a long α-helix structure (data not shown).

The location of the feline GIV.2 P2 subdomain α-helix corresponded to an extended loop on the GII.10 P2 subdomain (Fig. 2a)



b

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GIV.2     MKMASSDATPSSDGAGNLVPESQQEVLPLAPVAGAALAAPVVGQQNIIDPWIKENFVQAPQGEFTVSPKNSPGEVLVNLE   80
GII.10    MKMASNDAAPSNDGAAGLVPESNNEVMALEPVAGASLAAPVTGQTNIIDPWIRMNFVQAPNGEFTVSPRNSPGEVLLNLE   80

GIV.2     LSPRLNPYLDHLSKMYNAYAGGMEVEIILAGNAFTAGKVLIAAVPPNFPIENISASQASQFPHVIVDVRTLEPIRLPLPD  160
GII.10    LGPELNPYLAHLSRMYNGYAGGMEVQIMLAGNAFTAGKLIFAAVPPHFPIENLSPPQITMFPHVIIDVRTLEPVLLPMPD  160

GIV.2     VRTNFFHYTTQEEPRMRIVAWLYTPLRTNGSGDDSFTVSGRILTRPSPDFEFSFLVPPTVETKTVSFSVPGLVVEDMSNS  240
GII.10    IRNSFFHFIQRDEPKMRLVAMLYTPLRSNGSGDDVFTVSCRVLTRPTPDFDFTYLVPPTVESKSKPFTLPILTLGELTNS  240

GIV.2     RWPAQINGLVVRGNEAQVVHFQNGRCTTEGTLLGTTTLSINSICGLRGLSVSQASVRGAPALTEEMPPLEDEVADGAAAT  320
GII.10    RFPLPIDVLYTNPNESAIVQCQNGRCTLDGELQGTTQLLPTGICAFRGKVTQQV---------------QDEHRG-----  300

GIV.2     YTLARAADTTLWLRVEEPDGRPYDIFGDQPAPLGTPDFTAVIVGTAIR--PRTASG------AYLHDAYVDTTPGDADFT  392
GII.10    --------THWNMTVTNLNGTPFDPTEDVPAPLGTPDFSGQIYGVISQRNTNTVPGEGNLPANRAHEAVIATYS--PKFT  370

GIV.2     PSTGNTKIVLRGGGSGHVGQQHYWQFRPIAVEGGGSRPQYQEYNLPDYAGPTASNHDLAPPVAPRMPGELLLLFESDMPV  472
GII.10    PKLGN--IQFSTWETQDVSSGQPTKFTPVGLASVDANSHFDQWTLPSYSGALTLNMNLAPSVAPVFPGECLLFFRSFIPL  448

GIV.2     WDNGAGAAPAQKIHCLLPNEFITHLFDLQAPALAEAALLRYVHPDSGRTLFECKLYREGYMVVAAP-AGRLNFPLDGYFR  551
GII.10    KG-GYGNP---AIDCLMPQEWVQHLYQESAPSLSDVALVRYVNPETGRTLFEAKLHRNGFLTVARNSAGPVVAPTNGYFR  524

GIV.2     FDSWVSAFYILSPVGSGQGRRGRSKAA   578
GII.10    FDSWVNQFYTLAPMGNGSGRR-RMQ--   548
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Fig. 1. The X-ray crystal structure of GIV.2 feline norovirus P domain and an amino acid sequence alignment. (A) The GIV.2 P domain dimer was colored according to monomers (chains A and B) and P1 and P2 subdomains. Chain A: P1 (yellow–orange), chain A: P2 (fire-brick), chain B: P1 (deep-blue), and chain B: P2 (lime-green). Chain A residues 297–327 and chain B residues 297–319 were not modeled into the structure due to poor electron density. Part of the P2 subdomain (B chain residues 320–327) contained an α-helix structure. (B) The capsid amino acid alignment sequences of feline GIV.2 and human GII.10 noroviruses were aligned using ClustalX. The feline GIV.2 P2 subdomain contained an insertion in the P2 subdomain between ~295 and 329. The P1 and P2 subdomains were colored deep-blue and lime-green, respectively. The S domain was not labeled. The GII.10 P domain residues involved directly or indirectly with HBGAs (Hansman et al., 2011) were highlighted, side-chain interactions (red), backbone interactions (blue), and hydrophobic interaction (purple). The asterisks show conserved residues.

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