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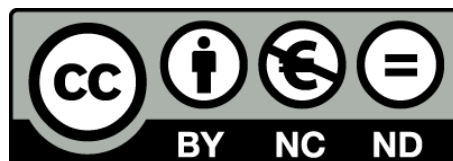
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1 **Review**

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4 **A review of fibropapillomatosis in Green turtles (*Chelonia mydas*)**

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19 **Highlights**

- 20 • Fibropapillomatosis (FP), an emerging disease in green turtles, is reviewed
- 21 • Chelonid herpesvirus 5 is the likely aetiological agent of FP
- 22 • The route of transmission and conditions facilitating lesion development are uncertain
- 23 • High prevalence of FP is observed in areas of reduced water quality
- 24 • A multi-factorial interplay between a range of factors is likely to be occurring

25

26 **Abstract**

27 Despite being identified in 1938, many aspects of the pathogenesis and epidemiology of
28 fibropapillomatosis (FP) in marine turtles are yet to be fully uncovered. Current knowledge
29 suggests that FP is an emerging infectious disease, with the prevalence varying both spatially and
30 temporally, even between localities in close proximity to each other. A high prevalence of FP in
31 marine turtles has been correlated with residency in areas of reduced water quality, indicating
32 that there is an environmental influence on disease presentation.

33

34 Chelonid herpesvirus 5 (ChHV5) has been identified as the likely aetiological agent of
35 FP. The current taxonomic position of ChHV5 is in the family *Herpesviridae*, subfamily
36 *Alphaherpesvirinae*, genus *Scutavirus*. Molecular differentiation of strains has revealed that a
37 viral variant is typically present at specific locations, even within sympatric species of marine
38 turtles, indicating that the disease FP originates regionally. There is uncertainty surrounding the
39 exact path of transmission and the conditions that facilitate lesion development, although recent
40 research has identified atypical genes within the genome of ChHV5 that may play a role in
41 pathogenesis. This review discusses emerging areas where researchers might focus and theories
42 behind the emergence of FP globally since the 1980s, which appear to be a multi-factorial
43 interplay between the virus, the host and environmental factors influencing disease expression.

44

45 **Keywords:** Fibropapillomatosis; Marine turtle; Herpesvirus; Chelonid herpesvirus 5; Green turtle

46 **Introduction**

47 The Green turtle (*Chelonia mydas*) is one of seven species of marine turtle and is
48 internationally recognised as endangered by the International Union for the Conservation of
49 Nature (Seminoff, 2004). Eleven discrete population segments of Green turtles have been
50 identified, each of which is considered biologically and ecologically significant (NMFS and
51 USFWS, 2014). Green turtles also hold great cultural significance for many indigenous peoples
52 and are of economic interest, playing a significant role in ecotourism (Dobbs, 2001; Gulko,
53 2004). The species has a global distribution and a complex life history, occupying a range of
54 habitats. Hatchling turtles have a pelagic existence and recruit into benthic inshore waters at the
55 age of 3-5 years (Reich et al., 2007). With the exception of migration for breeding, turtles
56 typically remain in these inshore environments, which are commonly associated with seagrass
57 meadows or coral reefs, for the remainder of their life (Musick and Limpus, 1997) (Fig. 1).

58
59 Green turtles are exposed to a number of threats including ingestion of marine debris,
60 degradation, urbanisation and pollution of nesting habitats and foraging areas, nest and hatchling
61 depredation by wild, feral and domestic animals, boat strike, traditional hunting and egg harvest,
62 the impacts of climate change on the marine and terrestrial environment, and entanglement in
63 fishing nets and lines (Bjorndal, 1995; Herbst and Klein, 1995a; Lutz, 2002; Van Houtan et al.,
64 2010). Conservation efforts which aim to abate many of these threats have assisted in the
65 recovery of some of the major Green turtle populations (Chaloupka et al., 2008a). However,
66 outbreaks of disease are also contributing to morbidity and mortality in this already vulnerable
67 species (Foley et al., 2005; Chaloupka et al., 2008; Flint et al., 2010c).

68
69 Fibropapillomatosis (FP) is a disease that has now been reported in every species of
70 marine turtle; Green (Smith and Coates, 1938), Loggerhead (*Caretta caretta*) (Harshbarger,

71 1991), Kemp's Ridley (*Lepidochelys kempii*) (Barragan and Sarti, 1994), Hawksbill
72 (*Eretmochelys imbricata*) (D'Amato and Moraes-Neto, 2000), Olive Ridley (*Lepidochelys*
73 *olivacea*) (Aguirre et al., 1999), Flatback (*Natator depressus*) (Limpus et al., 1993), and
74 Leatherback (*Dermochelys coriacea*) (Huerta et al., 2002) turtles. FP is of greatest concern in
75 Green turtles as it has only reached a panzootic status in this species (Williams et al., 1994).

76
77 FP is a neoplastic condition which may lead to the growth of lesions on the skin, oral
78 cavity, shell, eyes and internal organs of the affected turtle, which in severe cases reduces the
79 probability of survival (Flint et al., 2010a; Herbst, 1995; Work et al., 2004). The disease was first
80 identified in a Green turtle with multiple wart-like lesions on display at the New York Aquarium,
81 although originally from Key West, Florida (Smith and Coates, 1938). Despite being described
82 in 1938 (Lucke, 1938; Smith and Coates, 1938), FP did not reach epizootic proportions until the
83 1980s (Herbst et al., 1994, 2004) and has now been reported from every major ocean basin that
84 Green turtles inhabit (Herbst, 1994).

85
86 This review covers the epidemiology and proposed aetiology of FP in Green turtles, with
87 considerable emphasis on the primary candidate for the aetiological agent, chelonid herpesvirus
88 5 (ChHV5).

89

90 **Disease presentation**

91 FP can be identified in marine turtles by the presence of single or multiple benign
92 fibroepithelial lesions. The characteristic lesions are easily noticed and are pathognomonic for
93 FP, often limiting or obstructing the vision, feeding and locomotive ability of the affected turtle
94 (Herbst, 1994, 1995; Work et al., 2004; Flint et al., 2010a). Cutaneous lesions are typically
95 present on the external soft tissue of the turtle, but may grow on the carapace, plastron (Smith
96 and Coates, 1938; Jacobson et al., 1989; Balazs and Pooley, 1991; Brooks et al., 1994; Herbst,

1994) and cornea of affected turtles (Brooks et al., 1994; Flint et al., 2010a). The lesions can be observed on all visceral organs (Herbst 1994; Work et al., 2004; Foley et al. 2005) and are thought to develop during later stages of the disease (Herbst et al. 1999; Wyneken et al. 2006). However, as most visceral lesions are observed during post mortem investigations, the data available on the prevalence of this type of lesion are skewed. Individual lesions can range from 0.1 to 30 cm in diameter and can be sessile or pedunculated. The appearance of these lesions can vary from smooth to verrucous and the colour is dependent on the pigment at the site of origin (Herbst, 1994) (Fig. 2).

Myxofibromas, fibrosarcomas, papillomas, fibromas and fibropapillomas have all been found to be associated with FP (Norton et al., 1990; Work et al., 2004). Three of these lesions are thought to be linked with different stages of lesion development (Herbst, 1994; Kang et al., 2008). The early development phase is associated with papilloma lesions, proliferation of epidermal cells, with little or no involvement of the dermal layer. The chronic phase of lesion development is marked by the presence of fibromas, with proliferation of the dermal layer, while the epidermal layer remains normal. Fibropapillomas represent the intermediate phase of lesion development and consist of characteristics of both the papillomas and fibromas (Herbst, 1994; Kang et al., 2008).

Histological studies on FP lesions have observed orthokeratotic hyperkeratosis and varying degrees of epidermal hyperplasia. Key features observed in FP lesions include cytoplasmic vacuolation and ballooning degeneration of superficial epidermal cells (Jacobson et al., 1989, 1991; Herbst, 1994; Adnyana et al., 1997).

121 Haematological and biochemical signs of immunosuppression, chronic stress, and
122 chronic inflammation such as anaemia, lymphocytopenia, neutrophilia, monocytosis,
123 hypoproteinaemia and hyperglobulinaemia have been observed in turtles with clinical signs of
124 FP (Aguirre et al., 1995; Work et al., 2001; dos Santos et al., 2010; Page-Karjian et al. 2014).
125 Although it is still unclear whether the immunosuppression occurs as a result of or as a precursor
126 to FP development, it has been suggested that immunosuppression occurs as a result of FP
127 (Work et al., 2001). While further study is essential to confirm the relationship between
128 immunosuppression and FP infection, it is clear that immunosuppression leaves turtles with FP
129 lesions susceptible to secondary infections and opportunistic pathogens (Work et al., 2001, 2003;
130 Stacey et al., 2008; dos Santos et al., 2010). Impacts of such secondary infections, combined
131 with FP in marine turtles, are a major cause for concern in an already vulnerable species.

132

133 **Epidemiology of fibropapillomatosis in marine turtles**

134 FP typically occurs in marine turtles inhabiting neritic tropical and sub-tropical areas
135 (Herbst, 1994; Adnyana et al., 1997; Work et al., 2004; Ene et al., 2005). The disease is most
136 frequently observed in juvenile turtles; FP has also been reported in sub-adults and less
137 commonly in adults (Herbst, 1994; Herbst and Klein, 1995b; Adnyana et al., 1997; Work et al.,
138 2004; Ene et al., 2005; Patrício et al., 2012; Page-Karjian et al., 2014). This apparent age
139 differentiation in certain locations may indicate that affected juveniles perish from the population
140 altogether or recover with acquired immunity that protects them as adults (Van Houtan et al.,
141 2010). Alternatively, it is possible that these adults were never exposed to this disease.

142

143 There are no reports of FP in pelagic post hatchlings or new recruits that have recently
144 taken up residence in inshore foraging habitats (Herbst, 1994). Sex is not thought to be a

145 contributing factor, as no significant difference has been observed in prevalence between males
146 and females (Work et al., 2004).

147

148 **Disease prevalence and impact**

149 Smith and Coates (1938) reported a prevalence of 1.5% in the Florida Keys region. The
150 disease was not documented in the area again until the 1980s, where the prevalence was then
151 reported to range between 20-60% throughout the subsequent decade. The early to mid-1990s
152 saw FP emerge in the Eastern Pacific, Hawaiian Islands, Indonesia and Australia. As the disease
153 reached epizootic status in several locations globally, it is now considered a panzootic (Williams
154 et al., 1994). Due to the conspicuous presentation of FP, any prior presence would have been
155 noticed in a region where it currently occurs. The incidence of turtles with FP lesions as a
156 percentage of total turtles captured is reported in the Appendix (Supplementary Table 1).
157 Although age class is a risk factor, not all reports of FP prevalence have been corrected by
158 demographic proportions and future reports would benefit from making this distinction.

159

160 The prevalence of FP varies both spatially and temporally - see Appendix
161 (Supplementary Table 1). The sporadic reports of the disease over time, in combination with a
162 lack of oral history prior to the 1980s, indicate that FP is globally emerging (Greenblatt et al.,
163 2005b; Duarte et al., 2012). In several cases, a significantly different prevalence of the disease in
164 nearby regions has been observed. In Florida, a prevalence of approximately 50% was observed
165 in Green turtle aggregations in the Indian River region. However, less than 1 km away at the
166 Sabellariid worm reef, FP was not observed at all (Herbst, 1994). At Pala'au, Molokai, FP was
167 not observed at all until 1985, with the prevalence increasing from 1% in 1987 to 60.7% in 1995
168 - see Appendix (Supplementary Table 1).

169

170 A shift in FP prevalence at two closely monitored sites in Puerto Rico has been observed
171 in recent years; FP prevalence began decreasing Puerto Manglar and increasing at Tortuga Bay
172 in 2009 (Patrício et al., 2011). In Australia, FP has been reported in a number of locations since
173 it was first observed in Queensland in the early 1970s (C. Limpus, personal communication).

174
175 The contribution of this disease to morbidity and mortality in affected turtles has also
176 been widely discussed (Herbst, 1994; Ene et al., 2005; Foley et al., 2005; Chaloupka et al., 2008,
177 2009; Flint et al., 2010c). A study on Green turtles at Palaau, Hawaii found that this population
178 was already recovering from previous overharvesting at the time of the FP outbreak in this
179 region. The FP prevalence in this region has also been in decline since the mid-1990s
180 (Chaloupka et al., 2009).

181
182 Studies on regions in Australia (Flint et al., 2010c), Puerto Rico (Patrício et al., 2011) and
183 Florida (Hirama and Ehrhart, 2007) have all concluded that FP is not a significant factor in
184 mortality of turtles. Conversely, a study conducted on data accumulated over 21 years from
185 Hawaii implicated FP as the primary cause of strandings (Chaloupka et al., 2008).

186
187 Despite some conflicting conclusions, the overwhelming consensus is that FP does not
188 significantly impact the survival of turtle populations. However, Hamann et al. (2010) highlights
189 that understanding and managing this disease is a priority research area for sea turtle
190 conservation. Without a more complete understanding of the fundamental elements of this
191 disease, FP cannot be discounted as a threat to the survival of this species.

192

193 **Aetiology of fibropapillomatosis in marine turtles**

194 Research to date suggests that FP is associated with a herpesvirus infection (Herbst et al.,
195 1995; Quackenbush et al., 1998, 2001; Lackovich et al., 1999). Despite ongoing research, this
196 virus cannot be cultured in vitro and therefore Koch's postulates have not been fulfilled (Herbst,
197 1994, 1995; Moore et al., 1997; Lu et al., 1999; Work et al., 2009). Molecular techniques
198 (Quackenbush et al. 1998, 2001; Lackovich et al. 1999) have proven a strong association
199 between FP and a herpesvirus and, according to the criteria established by Hill (1965), the
200 relationship seems to be that of cause and effect. Chelonid herpesvirus 5 (ChHV5) is now the
201 primary focus of research in this area and belongs to the subfamily *Alphaherpesvirinae*, genus
202 *Scutavirus* (Davison and McGeoch, 2010). However, there are still some uncertainties
203 surrounding the transmission of the virus, the circumstances that lead to lesion development and
204 the role of environmental factors in the development of this disease.

205

206 **Infectious nature of fibropapillomatosis**

207 The epizootic nature of FP and the significant variation in the prevalence of FP between
208 different populations of marine turtles, even between nearby localities, led to speculation that FP
209 was primarily caused by an infectious agent.

210

211 Herbst et al. (1995) successfully transferred FP between animals by using cell-free lesion
212 extracts from turtles with lesions to inoculate young captive-reared turtles that were theoretically
213 naive to FP. All turtles in 3/4 experimental groups developed FP lesions. Control animals, which
214 were housed in the same facility and conditions as the experimental turtles, did not develop FP
215 during the same study period. The lesion extracts used in this experiment were filtered through a
216 0.45 μm syringe tip filter to prevent most pathogens, other than viruses, from being transferred.
217 These findings support the case for the role of a viral agent in FP transmission in marine turtles.

218

219 Although in their initial description of FP, Smith and Coates (1938) did not identify any
220 viral elements in histological examination of FP lesions, modern theories have focused on
221 viruses as the primary aetiological agent of FP. A range of viruses are capable of producing
222 neoplasms such as those seen in Green turtle FP. As a result, papillomavirus (Herbst, 1994),
223 papova-like virus (Lu et al., 2000a), retrovirus (Casey et al., 1997) and herpesviruses (Jacobson
224 et al., 1991; Quackenbush et al., 1998; Herbst et al., 1994, 2004) have all been proposed as
225 potential candidates for the aetiological agents of FP in marine turtles.

226
227 Current research suggests that FP is associated with ChHV5 infection. Early molecular
228 studies tested a range of tissues from turtles both with and without FP lesions and all concluded
229 that while ChHV5 could be detected in lesion biopsies from turtles with FP, the virus was rarely
230 detected in normal skin samples from the same turtles (Quackenbush et al., 1998; Lackovich et
231 al., 1999). Samples from turtles without FP lesions did not react in any of the PCR assays
232 conducted in these early studies (Quackenbush et al., 1998; Lackovich et al., 1999; Lu et al.,
233 2000b). These results support a strong association between the presence of ChHV5 and the
234 presence of FP lesions.

235
236 Quackenbush et al. (2001) first successfully amplified ChHV5 from skin samples
237 collected from turtles without FP lesions. Although only a subset of samples from turtles without
238 FP lesions reacted in the assay, the results showed that the virus may be present in turtles despite
239 a lack of clinical signs of disease. More recently, ChHV5 sequences have been amplified from
240 skin samples of turtles without FP lesions with greater success (Page-Karjian et al., 2012;
241 Alfaro-Núñez et al., 2014). These results indicate that early or latent infection with ChHV5 is
242 more common than previously thought. The prevalence of turtles with FP lesions may be small
243 relative to the number of turtles infected with ChHV5. Therefore, an absence of FP lesions does

244 not imply absence of ChHV5 infection. As latency is a typical feature of herpesviruses (Fields et
245 al., 2013), such results are to be expected. The improved sensitivity and specificity of the assays
246 used in these studies have revealed a feature of the disease that was undetectable using earlier
247 assays.

248
249 If disease presentation is not dependent on viral infection alone, other factors contributing
250 to lesion development must be considered. An interaction between host, pathogen and the
251 environment (García-Sastre and Sansonetti, 2010) which tips the balance in favour of lesion
252 development may be at play. Differences in host immunity may be preventing certain turtles
253 from mounting a response to the virus (Griffin et al., 2010). Studies on other viral infections
254 have shown that variants of a virus can have different levels of virulence and as such, disease
255 presentation and severity may differ with each variant (Laegreid et al., 1993; Kaashoek et al.,
256 1996; Berumen et al., 2001; Zhang et al., 2001; Yunis et al., 2004).

257
258 It is possible that the development of FP lesions is dependent on which viral variant a
259 turtle is infected with. It is also possible that turtles infected with the virus only develop lesions
260 when the viral load surpasses a certain threshold. While the relationship between viral titre and
261 lesion development has not been resolved for ChHV5, this relationship has been described in
262 other viral infections (Brodie et al., 1992; Liu et al., 2000; Zhang et al., 2000; Rosell et al., 2000;
263 Quintana et al., 2001; Ladekjær-Mikkelsen et al., 2002; Rovira et al., 2002; Olvera et al., 2004;
264 Islam et al., 2006; Ravazzolo et al., 2006; Nsubuga et al., 2008; Haralambus et al., 2010). The
265 consistent association of high viral load and lesion development provides support for the theory
266 that this may be the case for ChHV5.

267

268 **Chelonid herpesvirus 5**

269 *Nomenclature and taxonomy*

270 There are currently six herpesviruses documented in chelonids, named chelonid
271 herpesvirus 1 to 6 (ChHV1-6). Chelonid herpesvirus 1, 5 and 6 are described in marine turtles
272 whilst the others have been reported in freshwater turtles (Tidona and Darai, 2011). In the
273 absence of sequence data, ChHV1, ChHV2, ChHV3 and ChHV4 remain unrecognised by the
274 International Committee on Taxonomy of Viruses (ICTV) and their taxonomic place is unclear
275 (Davison and McGeoch, 2010). With respect to the marine turtle herpesviruses, ChHV1 is
276 described in association with grey patch disease (Haines et al., 1974; Rebell et al., 1975),
277 ChHV5 is associated with FP and ChHV6 is known to be associated with lung-eye-trachea
278 disease (Jacobson et al., 1986; Curry et al., 2000; Coberley et al., 2001a, 2002).

279

280 Chelonid fibropapilloma-associated herpesvirus (CFPHV) or ChHV5 (Davison and
281 McGeoch, 2010) is now the more commonly used name for this virus. However, it should be
282 noted that previous studies have used a range of names for this virus – see Appendix
283 (Supplementary Table 2). This review refers to the virus as ChHV5.

284

285 Histological investigations of FP lesions showed indications of herpesvirus infection and
286 subsequent studies using electron microscopy concluded that the virus-like particles that were
287 observed were likely to belong to the family Herpesviridae based on location, size and
288 morphology (Jacobson et al., 1989, 1991; Herbst et al., 1995).

289

290 More recent studies using a range of molecular techniques have confirmed herpesviral
291 elements are present in FP lesions (Quackenbush et al., 1998, 2001; Lackovich et al., 1999; Lu et
292 al., 2000a, b, 2003; Yu et al., 2000, 2001; Nigro et al., 2004a, b). Phylogenetic analysis of the
293 ChHV5 genes DNA polymerase and DNA binding protein sequences revealed that ChHV5

294 clusters closely with, but separate to, other members of the *Alphaherpesvirinae* subfamily
295 (Greenblatt et al., 2005b; McGeoch and Gatherer, 2005). Davison and McGeoch (2010) targeted
296 the single-stranded DNA-binding protein, glycoprotein B, the major capsid protein, DNA
297 polymerase and two subunits of the DNA packaging terminase (genes UL29, UL27, UL19,
298 UL30, UL15 and UL28, respectively). The resulting Bayesian phylogenetic tree shows that
299 ChHV5 exists as an out-group, clearly separate from the current genera. A Minimum Evolution
300 phylogenetic tree of *Alphaherpesvirinae* based on full length DNA polymerase sequence further
301 supports this result (Fig. 3). Consequently, it has been proposed that ChHV5 be placed in its own
302 genus. The proposed genus, *Scutavirus*, sits within the *Alphaherpesvirinae* subfamily of
303 *Herpesviridae*.

304

305 *Variants of chelonid herpesvirus 5*

306 Based on nucleotide sequence diversity, four viral variants of ChHV5 have been recorded
307 in waters around Florida. At present, they are known as A, B, C and D (Herbst et al., 2004; Ene
308 et al., 2005). Variant A is the most prevalent in the region, yet there is variation in relative
309 prevalence of variants at each site. Co-infection with variants A and B was also found in one
310 Green turtle (Ene et al., 2005). Perhaps even more significantly, different species of marine turtle
311 shared the same variant if they were present in the same locality (Herbst et al., 2004; Ene et al.,
312 2005). This indicates a strong geographic role in the transmission of the virus.

313

314 In a recent study, ChHV5 was examined using samples from a variety of locations in
315 order to create a global phylogeography of the virus. Four phylogeographical groups of ChHV5
316 were identified: eastern Pacific, western Atlantic/eastern Caribbean, mid-west Pacific and
317 Atlantic (Patrício et al., 2012). The results of the study showed that the viral variant is similar
318 between nearby foraging grounds while distant regions are considerably divergent. The study by

319 Patrício et al. (2012) also found that sympatric species of marine turtle were infected with the
320 same viral variant, further supporting the results of Herbst et al. (2004) and Ene et al. (2005).
321 These findings indicate that individual turtles are likely to be infected with the virus through
322 horizontal transmission in neritic bays (Patrício et al., 2012).

323

324 *Co-evolution of virus and host*

325 Herbst et al. (2004) suggested that the virus diverged prior to the separation of avian and
326 mammalian alphaherpesviruses. This would mean that ChHV5 became specific to marine turtles
327 approximately 300 million years ago (mya). In addition, it was estimated that the two most
328 divergent clades were separated approximately 1.6-4.0 mya. These results led to speculation that
329 the rise of the Isthmus of Panama (3.1-3.5 mya) was responsible for the divergence as it
330 prevented genetic exchange between these clades. Patrício et al. (2012) found that the most
331 recent common ancestor of the currently known variants of this virus existed 193-430 years ago.
332 This estimate is considerably more recent than the work of Herbst et al. (2004) but both studies
333 demonstrate that ChHV5 has evolved with marine turtles and, in either case, it is likely ChHV5
334 has undergone region specific co-evolution with its host.

335

336 While further research is needed to resolve the time of divergence, there is one clear
337 conclusion; it is not a new virus, or even recent mutations in an old virus, that is causing lesions
338 to develop. This evidence further supports the theory that the recent emergence of FP is linked to
339 modern day extrinsic environmental factors promoting lesion development.

340

341 *Genome organisation*

342 The herpesvirus genome is divided into two unique regions, one composed of a unique
343 long (UL) sequence and the other region is composed of a unique short (US) sequence. These

344 unique sequences are flanked by repeat sequences. The number, position and direction of these
345 sequences can vary and as a result, there are multiple types of herpesvirus genome structures.
346 Current literature lists between four and six known herpesvirus genome types. Fauquet et al.
347 (2005) recognised four herpesvirus genome types (denoted Type 1-4) while Pellet and Roizmann
348 (2007) described six different genome types (denoted Type A-F).

349
350 A recent study has described the entire genome of ChHV5 (Ackermann et al., 2012). The
351 extensive sequence data generated from this study showed a clear division of the genome into
352 UL and US regions. Inverted repeat sequences (IRS) were also found to flank the US sequence.
353 This configuration is consistent with ChHV5 having a type D genome (Ackermann et al., 2012).

354
355 Ackermann et al. (2012) also described four genes that are atypical for an
356 alphaherpesvirus genome. Two members of the C-type lectin-like domain superfamily (F-lec1,
357 F-lec2), an orthologue to the mouse cytomegalovirus M04 (F-M04) and a viral sialyltransferase
358 (F-sial) were all found to be present in the ChHV5 genome (Ackermann et al., 2012). While the
359 products of these genes may not be critical for viral replication, each one has a potential role in
360 pathogenesis or immune deviation (Ackermann et al., 2012). Orthologues to these genes have
361 been described in other viral families and host cells (Neilan et al., 1999; Wilcock et al., 1999;
362 Voigt et al., 2001; Markine-Goriaynoff et al., 2004). However, until now, none of these genes
363 has ever been reported in the genome of an alphaherpesvirus. Two of these atypical genes (F-sial
364 and F-M04) were found to be expressed in the FP lesions and it has been suggested that these
365 genes may play a role in FP pathogenesis (Ackermann et al., 2012).

366

367 **Transmission of chelonid herpesvirus 5**

368 As this disease has not been observed in pelagic juveniles, it is thought that turtles are
369 exposed to ChHV5 upon recruitment to neritic zones, indicating horizontal transmission (Herbst,
370 1994; Ene et al., 2005; Patrício et al., 2012). These new recruits may be exposed to several
371 stressors associated with migration, adaptation to a new environment, and changes in population
372 density, diet and pathogen exposure, which may all combine to reduce the efficacy of the
373 immune system and make these juveniles more susceptible to infection (Ritchie, 2006) with
374 ChHV5 and development of FP. It is also possible that these stressors combine to enhance
375 transmission or elicit herpesviral recrudescence in latently infected turtles (Ritchie, 2006)
376 leading to the development of FP lesions. Alternatively, direct transmission may be occurring
377 between co-habiting turtles via interactions such as mating and aggression.

378
379 Researchers have speculated on means of transmission of FP as an infectious disease and
380 possible vectors. Marine turtles host a range of parasites and correlations have been made
381 between parasite load and individual health. Spirochid trematodes (Jacobson et al., 1989, 1991;
382 Norton et al., 1990; Aguirre et al., 1994, 1998b; Williams et al., 1994), coral reef cleaner fish
383 (Booth and Peters, 1972; Losey et al., 1994; Lu et al., 2000c), saddleback wrasse (*Thalassoma*
384 *duperrey*) (Lu et al., 2000c) and marine leeches (*Ozobranchus* spp.) (Greenblatt et al., 2004)
385 have all been proposed as potential vectors of ChHV5. Significantly higher viral loads were
386 detected in marine leeches when compared with the other parasites examined (Greenblatt et al.,
387 2004) and they are currently the leading candidate for a mechanical vector. Although
388 *Ozobranchus* leeches are the most likely candidates for transmission vectors of ChHV5, their
389 exact role has not yet been confirmed. This is partly due to the possible latent state of the virus
390 and involvement of other co-factors in disease expression of FP (Greenblatt et al., 2004).
391

392 Other marine turtle epibiota, including bladder parasites (*Pyelosomum longicaecum*),
393 barnacles (*Platylepas* spp.), amphipods of the skin and oral cavity (order *Talitroidea*) and blood
394 flukes of the genera *Carretacola*, *Hapalotrema* and *Laeredius* have been ruled out as potential
395 vectors (Greenblatt et al., 2004).

396

397 **Environmental factors**

398 Marine turtles are particularly susceptible to changes in their environment as they are
399 long-lived animals with a complex life history (Aguirre and Lutz, 2004). A marine turtle will
400 access a range of habitat types during its lifetime, but exhibits a high degree of site fidelity once
401 recruited into a near shore foraging area. Mature female turtles are known to return to the natal
402 area from which they originated as hatchlings in order to lay their eggs (Limpus, 2008). Due to
403 this site fidelity, marine turtles are likely to persist in, or return to, their chosen localities despite
404 unfavourable changes to the environment. As a result, any damage to or destruction of these sites
405 could have extremely detrimental effects on populations that inhabit them (Hawkes et al., 2009;
406 Poloczanska et al., 2010; GBRMPA, 2014).

407

408 It has been suggested that environmental factors may play a role in the development of
409 FP (Herbst, 1994; Herbst and Klein, 1995a; Adnyana et al., 1997; Aguirre and Lutz, 2004;
410 Chaloupka et al., 2009; dos Santos et al., 2010; Van Houtan et al., 2014). Moreover, the presence
411 of chemical contaminants may be part of a multifactorial problem that leads to FP (Herbst,
412 1994). Early proponents of a possible relationship between degraded water quality and the
413 presence of FP proposed that chemical contaminants present in the water acted as immunotoxins
414 or were causing damage at the cellular or genetic level (Herbst, 1994).

415

416 Indirect disturbances to the immune system may occur if the chemical contaminants
417 create a disruption of neuroendocrine function (Zeeman and Brindley, 1981; Anderson et al.,
418 1984; Dean et al., 1990; Colborn et al., 1993; Arkoosh et al., 1994; Dunier, 1994). Herbst (1994)
419 demonstrated that a positive correlation exists between the prevalence of FP in Green turtle
420 populations adjacent to regions associated with agriculture, industry and urban development.
421 Subsequent studies have observed the same correlation (Adnyana et al., 1997; Foley et al., 2005;
422 dos Santos et al., 2010; Van Houtan et al., 2010). Although initial reports in Puerto Rico
423 observed the same relationship, this trend was reversed after several years; the prevalence of FP
424 at the more pristine site is now considerably higher than at the site which is subjected to high
425 levels of human activity (Patrício et al., 2011; Page-Karjian et al., 2012). Researchers attempted
426 to quantify this relationship in Hawaii by developing an information-rich index of eutrophication
427 from the analysis of 82 different watersheds. The results showed a strong association between FP
428 rates, nitrogen-footprints and macroalgae consumed by turtles (Van Houtan et al. 2010).
429 Different quantification studies were also undertaken in waters around Brazil and found that
430 Green turtles residing in areas with degraded water quality had a higher prevalence of FP.
431 However, this study based the assessment of water quality on the presence of benthic
432 macrophytes and nutrient levels; pollution and the presence of chemical contaminants were not
433 considered (dos Santos et al., 2010).

434
435 Only very low concentrations of persistent organic pollutants (Keller et al., 2014) and
436 selected trace metals and organic pollutants (Aguirre et al., 1994) have been detected in turtles
437 with FP lesions. Although these results suggest that the pollutants examined do not significantly
438 contribute to FP development, it is possible that further investigations will uncover a relationship
439 between this disease and other environmental contaminants (Keller et al., 2014).

440

441 Water temperature may also be a factor in lesion development and growth rate. It is
442 possible that warmer water temperatures during summer promote lesion growth, resulting in
443 lesions of a debilitating size by autumn (Herbst, 1994; Herbst et al., 1995). This seasonal trend
444 has been observed in Florida, where a higher rate of FP is observed in turtles that strand in winter
445 (Herbst, 1994). However, no seasonal trends have been observed in Hawaii (Murakawa et al.,
446 2000), which may be because there is less seasonal fluctuation in water temperature in this
447 region (Foley et al., 2005).

448
449 Natural biotoxins have also been implicated as a co-factor involved in FP development.
450 Landsberg et al. (1999) identified a correlation between high-risk FP areas in the Hawaiian
451 Islands and prevalence of *Prorocentrum*, a species that produces okadaic acid, a known tumour
452 promoter (Suganuma et al., 1988; Haystead et al., 1989; Cohen et al., 1990; Huynh et al., 1997).
453 Similarly, tissue concentrations of lyngbyatoxin A, produced by *Lyngbya majuscula*, have been
454 correlated with the presence of FP lesions in dead Green turtles (Arthur et al., 2006, 2008).
455 However, this species constituted less than 2% of total dietary intake and subsequently, any
456 biotoxins would be at a low concentration in the turtles (Arthur et al., 2008). If the dietary items
457 containing these biotoxins form a natural component of the diet of Green turtles and the amount
458 being consumed was not altered, these toxins should have no influence on the development of
459 FP.

460
461 An increased concentration of arginine in the diet of Green turtles as a result of invasive
462 macroalgae blooms has also been linked to an increasing prevalence of FP (van Houtan et al.,
463 2010). Arginine is a regulator of immune activity (Peranzoni et al., 2008) and is known to
464 promote herpesviruses and contribute to tumour formation (Mannick et al., 1994). This amino

465 acid is also a major component of glycoproteins on the viral envelope of herpesviruses (van
466 Houtan et al. 2010; van Houtan et al. 2014).

467
468 The results of a subsequent study found an association between eutrophication and
469 arginine content of macroalgae, with the intake of arginine in turtles at eutrophied sites being up
470 to 14 times the background level. This increased arginine content may metabolically promote
471 ChHV5, leading to FP lesion development (Van Houtan et al., 2014). Although the conclusions
472 from this study were subsequently challenged (Work et al., 2014), the epidemiological link
473 between the prevalence of disease and feeding ecology found in Van Houtan et al. (2014)
474 provides strong support that environmental factors play a role in the development of this disease.
475 However, the environmental factors leading to the bloom of macroalgae may be causing the
476 development of FP lesions directly, and the algal blooms may not be involved in lesion
477 development at all. If this is the case, it is difficult to link cause and effect.

478
479 Despite there being a strong positive correlation between the prevalence of FP in Green
480 turtle populations and areas with degraded water quality, it is difficult to identify one specific
481 causal contaminant or a combination of such working synergistically to the detriment of the
482 turtles. Studies on toxicity usually focus on chemicals that are persistent in the environment or
483 can bio-accumulate. Genetic damage as a result of a toxin may occur as a consequence of
484 transient exposure and as such, future studies would need to be expanded to include transient
485 chemicals that could have this effect on Green turtles. The practicality of such investigations is
486 daunting considering the vast marine environment and the known and unknown possible causes
487 of FP (Herbst, 1994; Herbst and Klein, 1995a).

488

489 One way that potential links between FP and anthropogenic contaminants might be
490 identified is to develop a monitoring program that records and compares contaminant residue
491 levels, genetic changes and viral load in blood and/or tissue samples collected from turtles with
492 and without FP lesions over a wide geographic area and across several seasons. Such a program
493 could be integrated into existing turtle monitoring activities. Controlled laboratory studies in a
494 closed experimental system may be needed to conclusively evaluate the roles of various
495 environmental factors in FP development (Herbst and Klein 1995a). Alternatively, results from
496 both field and laboratory based studies may work synergistically to fully resolve this
497 relationship.

498

499 **Direction of future research**

500 The longevity of marine turtles, coupled with their close association with inshore habitats
501 and seagrass meadows and coral reefs in these habitats, has led to the proposal that they may act
502 as sentinel indicators of marine ecosystem health (Aguirre and Lutz, 2004). Gaining a better
503 understanding of the health and prevalence of diseases in marine turtle populations provides a
504 critical link between ecosystem health and turtle health. Effective management of both the
505 habitat and the species that rely on it is critical for effective species conservation. As FP has been
506 found to be associated with turtles resident in areas exposed to poor water quality (Herbst, 1994;
507 dos Santos et al., 2010; Van Houtan et al., 2010, 2014), FP prevalence may be a vital tool in
508 monitoring inshore marine habitats. Many of these marine environments are also utilised by
509 humans and consequently, research into the epidemiology of this disease could be mutually
510 beneficial for Green turtles, other species in these ecosystems and humans alike (Aguirre and
511 Lutz, 2004; Flint et al., 2010c). Long term monitoring of populations will allow researchers to
512 more accurately establish disease prevalence, corrected by demographic proportions.

513

514 Whether the development of FP lesions is a result of a single agent or the interaction
515 between multiple factors is yet to be determined. It is clear that it is an infectious disease with a
516 strong link to ChHV5. In addition, the strong influence of different geographic regions on the
517 prevalence of FP and each of the viral variants indicate that FP is geographically specific (Herbst
518 et al., 2004; Ene et al., 2005; Patrício et al., 2012). The results from molecular studies targeting
519 ChHV5 in samples from turtles show that the virus is present in turtles with and without FP
520 lesions (Quackenbush et al., 2001; Page-Karjian et al., 2012; Alfaro-Núñez et al., 2014). Future
521 molecular studies targeting ChHV5 should consider these results and screen all samples for
522 ChHV5, not only those from turtles with FP lesions. Biosecurity and potential zoonosis should
523 always be considered by those handling marine turtles in both field and captive situations.
524 However, future research should prioritise understanding the triggers for lesion development.

525

526 **Conclusions**

527 There are many aspects of FP in marine turtles that are yet to be resolved and future
528 research needs to target those gaps which will ultimately aid in managing the disease.
529 Understanding how ChHV5 is transmitted between turtles and between regions is a key priority.
530 Molecular epidemiology is a useful tool for revealing genetic differences in this virus between
531 regions; possible relationships between host lineage and viral strain and the genes responsible for
532 pathogenesis and viral replication. Molecular investigations on ChHV5 from different regions
533 are essential to improve our understanding of the epidemiology and pathogenesis of this virus
534 which will in turn inform the management and conservation of a vulnerable species, the Green
535 turtle.

536

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541

542 **Appendix: Supplementary material**

543 Supplementary data associated with this article can be found in the online version
544 at.....**setters please insert doi number**

545

546 **Conflict of interest statement**

547 None of the authors of this paper has a financial or personal relationship with other
548 people or organisations that could inappropriately influence or bias the content of the paper.

549

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1349 **Figure legends**
1350
1351 Fig. 1. The complex life history of Green turtles. Adapted from Lanyon et al. (1989).
1352
1353 Fig. 2. The plastron and hind flippers of a Green turtle severely affected by fibropapillomatosis
1354 highlighting the diverse range of lesion appearance.
1355
1356 Fig. 3. A Minimum Evolution phylogenetic tree of *Alphaherpesvirinae* based on full length DNA
1357 polymerase sequence retrieved from GenBank (Accession numbers provided in tree). Bootstrap
1358 values for each node are provided (1000 replicates). The analysis involved 27 nucleotide
1359 sequences resulting in a total of 2593 positions in the final dataset. Evolutionary analyses were
1360 conducted in MEGA6 (Tamura et al., 2013)
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