Identification of a duplicated V3 domain in NS5A associated with cirrhosis and hepatocellular carcinoma in HCV-1b patients

Titre	Identification of a duplicated V3 domain in NS5A associated with cirrhosis and hepatocellular carcinoma in HCV-1b patients
Type de publication	Article de revue
Auteur	Le Guillou-Guillemette, Hélène [1], Ducancelle, Alexandra [2], Bertrais, Sandrine [3], Lemarié, Carole [4], Pivert, Adeline [5], Veillon, Pascal [6], Bouthry, E. [7], Alain, Sophie [8], Thibault, Vincent [9], Abravanel, Florence [10], Rosenberg, Arielle R [11], Henquell, Cécile [12], André-Garnier, E. [13], Petsaris, O. [14], Vallet, Sophie [15], Bour, J.B. [16], Baazia, Yazid [17], Trimoulet, Pascale [18], André, P. [19], Gaudy-Graffin, Catherine [20], Bettinger, Dominique [21], Larrat, Sylvie [22], Signori-Schmuck, Anne [23], Saoudin, Hénia [24], Pozzetto, Bruno [25], Lagathu, Giséle [26], Minjolle-Cha, S. [27], Stoll-Keller, Françoise [28], Pawlotsky, Jean-Michel [29], Izopet, Jacques [30], Payan, Christopher [31], Lunel-Fabiani, Françoise [32]
Pays	Pays-Bas
Editeur	Elsevier
Ville	Amsterdam
Type	Article scientifique dans une revue à comité de lecture
Année	2015
Langue	Anglais
Date	août 2015
Pagination	203-209
Volume	69
Titre de la revue	Journal of Clinical Virology
ISSN	13866532
Mots-clés	cirrhosis [33], Hepatitis C virus [34], Hepatocellular carcinoma [35], NS5A [36], V3 domain [37]

Résumé en anglais	BACKGROUND: The NS5A protein of the hepatitis C virus has been shown to be involved in the development of hepatocellular carcinoma. OBJECTIVES: In a French multicenter study, we investigated the clinical and epidemiological features of a new HCV genotype 1b strain bearing a wide insertion into the V3 domain. STUDY DESIGN: We studied NS5A gene sequences in 821 French patients infected with genotype 1b HCV. RESULTS: We identified an uncharacterized V3 insertion without ORF disruption in 3.05% of the HCV sequences. The insertion comprised 31 amino-acids for the majority of patients; 3 patients had 27 amino-acids insertions and 1 had a 12 amino-acids insertion. Sequence identity between the 31 amino-acids insertions and the V3 domain ranged from 48 to 96% with E-values above 4e(-5), thus illustrating sequence homology and a partial gene duplication event that to our knowledge has never been reported in HCV. Moreover we showed the presence of the duplication at the time of infection and its persistence at least during 12 years in the entire quasispecies. No association was found with extrahepatic diseases. Conversely, patients with cirrhosis were two times more likely to have HCV with this genetic characteristic (p=0.04). Moreover, its prevalence increased with liver disease severity (from 3.0% in patients without cirrhosis to 9.4% in patients with both cirrhosis and HCC, p for trend=0.045). CONCLUSIONS: We identified a duplicated V3 domain in the HCV-1b NS5A protein for the first time. The duplication may be associated with unfavorable evolution of liver disease including a possible involvement in liver carcinogenesis.
URL de la notice	http://okina.univ-angers.fr/publications/ua14253 [38]
DOI	10.1016/j.jcv.2015.06.096 [39]
Lien vers le document	http://www.journalofclinicalvirology.com/article/S1386-6532%2815%2900281... [40]
Titre abrégé	J. clin. virol.

Liens

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