

a series of fact sheets written
by experts in the field of liver
disease

HCV: Genotype & Quasispecies

Alan Franciscus, Editor-in-Chief

The term genotype refers to different genetic variations or strains of hepatitis C. The variance in genetic differences is approximately 1/3 between the different genotypes. There are six major groups or genotypes numbered 1 to 6 although some experts believe that there may be as many as 11. Within each genotype are further divisions called subtypes (for example 1a and 1b) and quasispecies.

HCV constantly changes and mutates as it replicates—more than 1 trillion hepatitis C virions replicate each day. During the replication process, the hepatitis C virus will make ‘bad’ copies or errors in the genetic make-up of the newly replicated viruses. The process of constant mutation helps the virus evade the body’s immune response---when the dominant quasi-species is eradicated, another quasi-species emerges. This requires the immune system to constantly identify and kill the newly emerged variants. This is one of the reasons why so many people develop chronic disease. Scientists believe there are literally millions of different HCV quasispecies in everyone infected with hepatitis C, which are unique to everyone because of

the individual’s immune response to HCV and quasispecies constantly change over time. In addition, it has been suggested that quasispecies play a role in disease progression and treatment response, but this is still controversial and more studies are needed to fully appreciate the role of quasi-species.

This variability (genotype, subtypes and quasi-species) of hepatitis C has made it difficult to treat and to develop a vaccine that will protect against all HCV strains although recent advances in vaccine development have been encouraging.

Testing for Genotype, Subtype & Quasispecies

A blood test is required for the genotype test. Generally, a quasispecies test is only performed for research purposes. HCV genotype testing is only done once since the genotype does not change.

Genotype Distribution

HCV genotypes and subtypes are distributed differently in different parts of the world, and certain genotypes predominate in certain areas. Genotypes 1-3 are widely distributed throughout the world. Subtype 1a is prevalent in North and South America, Europe, and Australia. Subtype 1b is common in North America and Europe, and is also found in parts of Asia. Genotype 2 is present in most developed countries, but is less common than genotype 1. Some studies suggest that different types of HCV may be associated with different transmission routes. Subtype 3a appears to be prevalent among injection drug users and it is believed that they were introduced into North American and the United Kingdom with the widespread use of heroin in the 1960s.

Worldwide

HCV Genotype	Distribution
1, 2, 3	Worldwide
4	Middle East, Africa
5	South Africa
6	Southeast Asia

United States

HCV Genotype	Percent of Population	U.S. Population
1	~70%	2,800,000
2	~15%	600,000
3	~12%	480,000
4	~2%	80,000
6	~1.5%	60,000

Importance of Genotype Information

HCV Genotype information is important because of the role it plays in predicting HCV medical treatment response, treatment duration and the dose of ribavirin. However, it should never be used as a reason to deny treatment.

Prediction of Treatment Response

Genotype information is important because it can be used as a predictor of a positive treatment outcome or response. The sustained virological response rates for pegylated interferon plus ribavirin are much higher in genotype 2 and 3 compared with genotype 1.

Other predictors of treatment response include:

- Age of Patient – younger patients respond more favorably especially people under 30 years old.
- Sex of Patient – women are more likely to respond to therapy than men
- Histological (health of the liver) – people with minimal damage respond better to treatment
- Viral Load – the lower the viral load (less than 800,000 IU/mL) the more likely one is to respond to current medications
- Obesity or high Body Mass Index is associated with lower treatment response rates
- Steatosis or fatty liver reduces the chance of responding to treatment.
- Race—Caucasians and Asians respond better to current HCV medications.

Genotype and Treatment Response

Genotype 1 is considered the most difficult to treat with current HCV medications. However,

treatment response rates with the newer forms of pegylated interferon plus ribavirin have been remarkably high—up to a 51 % sustained virological response rate (SVR – undetectable viral load six months post treatment). Genotype 2 and 3 respond even better to current medications—up to 80%. There is some evidence that genotype 2 responds better to current HCV therapies than genotype 3, but this needs to be confirmed in prospective studies. The reason that a particular genotype responds to treatment differently is unknown, but it is speculated that specific genotypes of the hepatitis C virus live longer or shorter than others. For example, it has been theorized that genotype 2 and 3 of the hepatitis C virus do not live as long (viral lifecycle) as genotype 1 thus making eradication of genotype 2 and 3 easier.

Genotype and Treatment Duration

Genotype is also a factor in the period of time required to treat with current HCV medications. Generally, genotype 1 is treated for 48 weeks and genotype 2 and 3 are treated for 24 weeks. However, there are studies underway to determine the most optimal treatment duration based on certain factors. For instance, some experts believe that people with genotype 1, high viral load should be treated for 72 weeks instead of 48 weeks to maximize treatment response rates. There are also studies evaluating treating people with genotype 2 for 12 weeks and genotype 3 for 48 weeks.

Genotype and HCV Medication Dosage

Genotype information is also important for establishing the appropriate dose of ribavirin. For instance, people with genotype 2 and 3 are given 800 mg a day of ribavirin (flat dose), whereas the ribavirin dose for people with genotype 1 is dosed by body weight.

Mixed Genotypes

A person can become infected with more than one genotype. Data is almost non-existent on being infected with more than one genotype, but some experts believe it may effect treatment response and HCV disease progression.

Steatosis and Genotype

Steatosis (fatty infiltrates of the liver) is a well recognized feature of hepatitis C infection. Steatosis can contribute to HCV disease progression and lower treatment response although the exact mechanism is not completely understood. People with HCV genotype 3 are more likely to develop steatosis and it is believed that HCV genotype 3 is an independent risk factor and may actually play a direct role in the development of steatosis. It has been reported that when genotype 3 individuals are successfully treated that steatosis will generally improve and for some steatosis will disappear.

Genotype and HCV Disease Progression

In regards to genotype and HCV disease progression, early limited data suggested that genotype 1b was associated with a more severe disease progression than in genotype 1a or 2, but further studies have not been able to confirm this observation.

Genotype and Liver Transplantation

Genotype 1 (especially 1b) has been associated with a more rapid fibrosis progression in people who have received a liver transplant.

For more information about hepatitis C, hepatitis B and HCV coinfections, please visit www.hcvadvocate.org.

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Executive Director

Editor-in-Chief, HCSP Publications

Alan Franciscus

Design

Paula Fener

Production

C.D. Mazoff, PhD

Contact information:

Hepatitis C Support Project

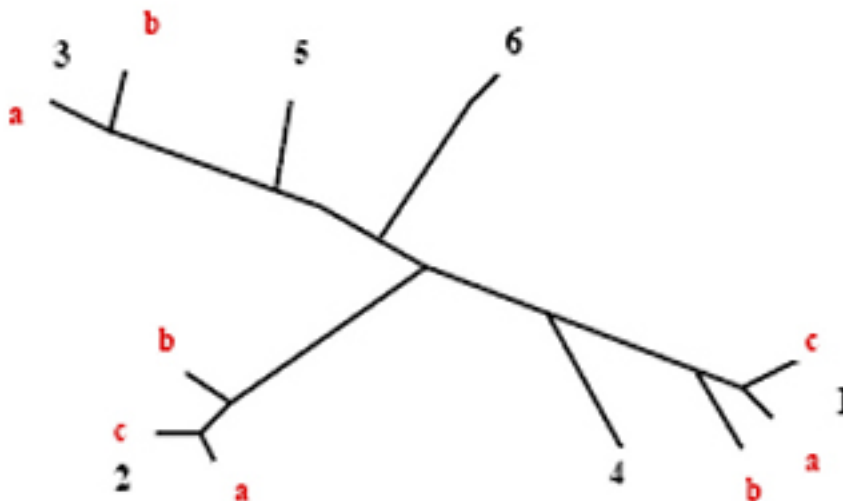
PO Box 427037

San Francisco, CA 94142-7037

alanfranciscus@hcvadvocate.org

The information in this fact sheet is designed to help you understand and manage HCV and is not intended as medical advice. All persons with HCV should consult a medical practitioner for diagnosis and treatment of HCV.

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Genetic Diversity of Hepatitis C - Genotypes