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My46 Trait Profile

Warfarin sensitivity

Other Names: U.S. brand names of warfarin: Coumadin, Jantoven

Warfarin sensitivity is a condition in which individuals break down more slowly the blood thinner medication called warfarin. Therefore, individuals with this condition react more strongly to warfarin and may have a higher chance of experiencing serious side effects from an average dose of warfarin.

Characteristics of Warfarin sensitivity

Warfarin is an anticoagulant medication (i.e., a blood-thinning drug used to prevent blood clots from forming). It is one of the most widely used anticoagulant medications worldwide. Healthcare providers often prescribe warfarin for individuals at high risk of developing blood clots in the veins or lungs, individuals with heart valve disease or who have had their heart valve replaced, individuals with an irregular heart beat called atrial fibrillation, and individuals who are recovering from a heart attack or stroke. The amount of warfarin (i.e., the dose) a person needs to prevent clotting varies between individuals: too little medication can lead to a blood clot, but too much medication can lead to severe bleeding. An individual who is on warfarin must have their ability to form clots checked regularly so that the dose of warfarin given prevents blood clots, but avoids excessive bleeding. An individual who is sensitive to warfarin requires a lower does than the average warfarin dose. Warfarin sensitivity is common among European Americans, and less common among African Americans and East Asians. Approximately 30-40% of variation in warfarin dosing among European Americans can be explained by variants in the CYP2C9 and VKORC1 genes. However, variation in warfarin response is influenced by many other factors as well including diet, age, weight, gender, and other medications.

Diagnosis/Testing

Many factors influence an individuals ideal dose of warfarin, but changes or variants in the CYP2C9 and VKORC1 genes play an important role. The CYP2C9 gene makes one of the main enzymes involved in the metabolism of warfarin. Variants in the CYP2C9 gene (e.g., CYP2C9*2 and CYP2C9*3) cause this enzyme to not work as well. Thus, for an individual who is taking warfarin and has a CYP2C9 variant, warfarin is metabolized at a much slower rate (i.e. slow metabolizer), and in turn, the medication stays in the body longer.

The VKORC1 gene makes an enzyme called vitamin K epoxide reductase which is a protein that warfarin affects to thin the blood. Individuals with variants (e.g., -1639G>A) in the VKORC1 gene are also more sensitive to warfarin. These individuals also require a lower dose of warfarin than individuals without such a variant in VKORC1.

The combination of CYP2C9 and VKORC1 gene copies that an individual has can determine the overall effect of warfarin and how rapidly it is metabolized and cleared from the body. Accordingly, knowing an individuals CYP2C9 and/or VKORC1 variant status can be used to help guide what is the best dose of warfarin to give an individual.

Management/Surveillance

Individuals with variants in the CYP2C9 and/or VKORC1 genes may require a reduced warfarin dose. The level of dose reduction depends on how many of each variant an individual carries. Individuals with variants in both genes may require a large reduction in warfarin dose. It is important to know that regardless of genetic test results, response to warfarin therapy still requires monitoring with regular blood tests (e.g., PT/INR tests) or other appropriate clinical monitoring.

Mode of inheritance

Response to warfarin is a complex condition, which means that it is caused by a combination of many different factors. These factors can be genetic or non-genetic (such as environmental factors and lifestyle choices such as smoking). Complex conditions are inherited in a multifactorial pattern. This means that the chance for an individual to develop warfarin sensitivity is influenced by the number and type of genetic and non-genetic factors occur together to which an individual is exposed. In other words, no single gene, and no single environmental factor causes warfarin sensitivity. Not all of these genetic factors and environmental factors are known.

Risk to family members

Complex conditions, like response to warfarin, tend to recur in families, because they are partly influenced by genetic variants.

Special considerations

Warfarin is not the only medication that CYP2C9 metabolizes. The family of cytochrome P450 genes, which the CYP2C9 gene belongs to, is responsible for the metabolism of approximately 15-20% of the medications used in clinical practice. CYP2C9 is the main metabolizer of most non-steroid anti-inflammatory drugs (e.g., aspirin, ibuprofen, and naproxen), certain seizure medications (e.g., phenytoin and valproic acid), some diabetic medications (e.g., sulfonylureas), and many others.

Resources

WarfarinDosing
http://warfarindosing.org
PharmGKB: The Pharmacogenomics Knowledgebase
http://www.pharmgkb.org
Genetic Home Reference: CYP2C9
http://ghr.nlm.nih.gov/gene/CYP2C9
Genetic Home Reference: VKORC1
http://ghr.nlm.nih.gov/gene/VKORC1

References

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