

Risk factor: molecular genetics essays examples

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Introduction

The term “ risk factor” is very common in epidemiology. In general sense, it refers to a particular variable that is associated with an elevated risk of infection or disease. Since the number of diseases in the world is very large, the number of risk factors is also every large. The risk factors however vary from one disease or infection to another. However, there are a number of risk factors that are very common and play a significant role in many infections. One of these factors is molecular genetics. As the name suggest, molecular genetics is a genre that mainly deals with the functions and structures of genes at a molecular level. This discipline employs various molecular biology and genetics methods to expound on the molecular interactions and functions among genes. The question of risk factor in molecular genetics comes into play in instances where the diseases in an individual are purely dependent on their genetic makeup. This paper seeks to conduct a literature review of two articles that exemplify molecular genetics as a risk factor of certain disease. The paper will conclusively analyze the two articles and supplement their content with two extra articles that also touch on the similar subject of molecular genetics as a risk factor. The two main articles were chosen found after a comprehensive search at the UMUC on-line Library.

Article 1

Kluijtmans, L. A., Heuvel, L. P., Boers, G. H., Frosst, P., Stevens, E. M., Oost, B. A., . . . Blom, H. J. (1996). Molecular genetic analysis in mild hyperhomocysteinemia : a common mutation in the

methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease. American Journal of Human Genetics, 58(1), 35-41.

Summary

This article explores the genetic risk factors for cardiovascular disease. Mild hyperhomocysteinemia has been established to be one of the cardiovascular disease risk factors. In particular, the presence of genetic aberrations in the MTHFR (methylenetetrahydrofolate reductase) as well as the CBS (cystathionine B-synthase) genes has been established to account for reduced enzyme activity as well as raised plasma homocysteine levels (Kluijtmans Et al 1996). In a search conducted on a sample of Dutch subjects who exhibited homozygous CBS deficiency, an 833T→C (I278T) mutation was established in about 50% of the alleles. In a more recent research, a common mutation of (677C→T; A→V) was observed in the MTHFR gene. This gene in its homozygous state, is actually responsible for the thermolabile phenotype. It is also associated with lessened specific MTHFR activity as well as raised homocysteine levels. In light of these factors, the authors of these articles conducted a research on sixty cardiovascular patients for the mutations mentioned above to establish or determine whether the two genetic mutations are actually risk factors for the premature cardiovascular disease (Kluijtmans Et al 1996). The results showed that there was a high prevalence for the 833T→C (I278T) mutation in the homozygotes for the CBS deficiency and there was the absence of it in the sixty cardiovascular patients. This led them to conclude that the heterozygosity for the CBS deficiency is not really involved in premature cardiovascular disease. It is therefore not a risk factor. However, the frequent homozygous mutation

shown in the MTHFR gene is involved or associated with an increased risk of premature cardiovascular disease.

Thesis/Purpose of the article

As observed above, the main purpose of this research and indeed the article was to show that a genetic mutation of the Methylenetetrahydrofolate Reductase MTHFR gene is actually a genetic risk factor for premature cardiovascular disease. The article sought to show that if this mutation takes place, then this individual is at a higher risk of experiencing or contracting the cardiovascular disease.

Methods, Evidence and Evaluation of the Article

Both the cardiovascular patients and the control group were exposed to an oral methionine-loading test. Their total homocysteine concentrations were then measured in EDTA plasma by using fluorescence detection and HPLC Chromatography.

Their CBS activity was also measured in terms of the nanomoles of cystathionine formed per milligram protein per hour. In addition, the residual and specific MTHFR activities in the participant's isolated lymphocytes were also measured and determined radiochemically. These were measured in terms of nanomoles of formaldehyde formed per milligram protein per hour (Kluijtmans Et al 1996).

The participants were then subjected to mutational analysis where DNA was extracted from their peripheral lymphocytes and utilized for PCR amplification. The detection of both types of mutations, that is the 833T→C transition (for the CBS gene) and the 677C→T mixture (for the MTHFR gene

were performed using specific parameters. For instance, in the case of the 677C→T transition in the MTHFR gene, the PCR was performed by using 100ng forward and a reverse primer among other parameters. The results established were expressed in the form of mean \pm sd. Some of the calculations done included the mean differences (MD) and the 95% confidence intervals for the specific MTHFR activity, homocysteine concentrations and specific MTHFR activity. These were measured as statistical significance estimates between the different groups. To establish the relative risks associated with homozygous mutation and those of homocysteine concentration, a 95% confidence interval and as odd ratios were calculated. A logistic regression model was used to adjust the odd ratios gender and age. The spearman's' rank correlation test was used to perform correlation analysis (Kluijtmans Et al 1996). The results showed that the mean homocysteine concentrations in the vascular patients were actually higher than those of the control group. the 833T→C was not detected in the patient cardiovascular patient group. However, 1 heterozygote for this kind of mutation was observed among the control subjects. Both the specific and residual MTHFR activities were measured in the cardiovascular patient isolated lymphocytes. The specific MTHFR activity was observed to be lower in the cardiovascular patients was lower than in the control group.

Finding

The most significant result that was found however was that the homozygous mutation, 677C→T, which is the cause of thermolabile mutation acts a risk factor for cardiovascular disease related to arteriosclerosis,

including cerebral and peripheral arterial occlusive disease. There is also lack of evidence that the heterozygosity for CBS deficiency is a risk factor for premature cardiovascular disease. Common mutation (677C→T) in the Methylenetetrahydrofolate Reductase (MTHFR) gene causes raised homocysteine levels and this is a risk factor for premature cardiovascular disease (Kluijtmans Et al 1996).

Supporting Article

Willems, F. F., Kluijtmans, L. E., Kastelein, J. P., Lindemans, J., Boers, G. H., Bruschke, A. V., . . . Blom, H. J. (1998). Thermolabile methylenetetrahydrofolate reductase in coronary artery disease. *Journal of The American College of Cardiology*, 48(3), 536-545.

Summary

This article explores the role of the Methylenetetrahydrofolate Reductase in cardiovascular disease, specifically the coronary heart disease as molecular genetic risk factor. According to the article, the Methylenetetrahydrofolate Reductase (MTHFR) acts as catalyst in the methylenetetrahydrofolate-methyltetrahydrofolate conversion process. The latter acts as a methyl donor when homocysteine is remethylated to methionine. In addition, a mutation referred to as 677C→T which occurs in the MTHFR gene often leads to raised homocysteine concentrations in individuals with the homozygous (+/+) characteristic (Willems et al 1998). The authors of this article conducted a research on a large number of participants who had CAD. The researchers wanted to establish the frequency of the mentioned mutation as well as the relationship between it and the concentration of homocysteine serum. The final result and conclusion was that the homozygous (+/+) genotype was a

significantly modest risk factor for coronary artery disease which is a cardiovascular disease (Willems et al 1998).

Relationship

The facts established and discussed in this article reinforce those established in the first article. In the first article, it was found that the 677C→T mutation which occurs in the Methylenetetrahydrofolate Reductase (MTHFR) gene increases the concentration of homocysteine or raises its levels. This fact was also established in the second article. The implication of this is increased susceptibility to cardiovascular diseases. The second article particularly traced the role of this mutation in the emergence of one cardiovascular disease, the coronary artery disease. As observed, the two articles are complementary of each other. They show how molecular genetics act as risk factors to cardiovascular disease. In this case, the particular aspect of molecular genetics that acts as a risk factor is the 677C→T mutation of the Methylenetetrahydrofolate Reductase (MTHFR) gene increases the concentration of homocysteine or raises its levels and consequently increases an individual's susceptibility to cardiovascular disease.

Article 2

Đorđević, V., Pruner, I., & Radojković, D. (2014). Molecular Basis of Thrombophilia. *Journal Of Medical Biochemistry*, 33(1), 22-27.

Summary

This article explores the genetic risk factors that are associated with thrombophilia. The article reports on a secondary research conducted to

investigate the risk factors related to molecular genetics that increase the emergence of this disorder. Thrombophilia is a disorder that involves both acquired and genetic risk factors that affect the natural balance between anticoagulant and procoagulant factors and ultimately leading to increased thrombotic tendency (Đorđević et al 2014). According to the article, advancements in DNA technology have played an enormous role in the identification of the deficiencies that lead to thrombophilia. Two of the major discoveries made have been made due to this advancement in DNA technology is discovery of the F-Leiden gene mutation and the activated protein resistance. In addition, a variant, in the Factor II 3' untranslated region that is associated with increased Factor II in plasma concentration. According to the article, it these two genes variants that represent the most common risk factors for thrombophilia (Đorđević et al 2014). However, they are not the only ones as new thrombotic risk factors continue to be established every day in light of in light of advanced DNA technology (Đorđević et al 2014).

Thesis

Thrombophilia is a disorder that is associated with several genetic risk factors with the two major ones being the F-Leiden gene mutation and the activated protein resistance. The purpose of the article is to show the role of these genetic risk factors in causing thrombophilia.

Evaluation

According to the article, the term thrombophilia was coined in the year 1956 by Jordan and Nangorff. It was at this time used to label the familial tendency

shown in the thromboembolic disease. However, in recent years, thrombophilia has been used to describe an individual's increased tendency for the development of clots in his/her blood vessels. Genetic risk factors for thrombophilia have been identified over time and can be divided into three major groups:

- Those affecting the coagulation inhibitor' genes and therefore leading to a reduced coagulation inhibition
- Those affecting the procoagulant factor genes and therefore resulting in the genes impaired in-inhibition or even gain of function
- Those affecting the fibrinolytic system genes and therefore resulting in impaired fibrinolysis.

Since protein C, protein S (PS) and the antithrombin (AT) are natural inhibitors of coagulation factors, a process which is crucial for homeostatic balance, defects in them increase the probability of thrombophilia occurrence. A deficiency particularly results from a mutation of the SERPINC1 gene (Đorđević et al 2014). The mutant protein becomes unable to perform its primary functions. The SERPINC1 which actually codes the antithrombin is prone to private mutations and this leads to a deficiency of the AT.

Deficiency in Protein C, (PC), is mainly caused by mutation of the PROC1 gene. According to research, this deficiency occurs in one person out of every 200-4000.

However, one of the major genetic risk factor of thrombophilia is brought about by the FV Leiden gene variant. In fact, the major breakthrough in thrombophilia genetic research happened when the activated protein resistance and the mutation of FV Leiden was discovered. A researcher by

the name Dahlback found out in 1993 that the plasma of patients who had the familiar thrombosis had a reduced response to the APC addition. A discovery was later made that a point mutation (G1691A) that happened in the FV gene and that results in the substitution of the arginine at position 506 by a glutamine molecule was actually responsible for the AOC resistance phenotype observed (Đorđević et al 2014). The overall implication of this is that it results in increased susceptibility to thrombophilia.

The other genetic variant that acts as a risk factor of thrombosis is the FII G20210A gene variant. This variant is associated with elevated or increased concentrations of the F II gene in the blood plasma. This inadvertently leads to raised thrombin generation as well as hypercoagulability. The FII G20210A was found in 16 to 18% of all thrombophilia patients and the presence of its allele is associated with a n increased risk for thrombophilia.

Conclusion

Thrombophilia is a disorder that had a wide range of genetic risk factors with the main ones being the the activated protein resistance and the mutation of FV Leiden and the FII G20210A gene variant. It has however been shown that thrombotic disorders may not solely be caused buy a single genetic risk factors. Alternatively, the thrombotic disorders may be caused by a combination of different gene variants. This combinations increase an individual's susceptibility to the thrombotic tendency.

Supporting Article

Zöller, B., Frutos, P. G., Hillarp, A., & Dahlbäck, B. (1999). Thrombophilia as a multigenic disease. *Haematologica*, 84(1), 59-70.

This article focuses on the role of genetic factors in inherited thrombophilia pathogenesis. It particularly emphasizes on those defects that affect the PC (Protein C System). The article integrates information and research from a variety of sources covering the thrombophilia disorder. According to this article, the risk of contracting thrombosis increases particularly when the anticoagulant and procoagulant forces in the body system are shifted to favor coagulation. When this arises because of genetic inheritance, the hypercoagulable state becomes a lifelong risk factor for the disorder that is thrombosis (Zöller et al 1999). According to this article, the most common genetically inherited hypercoagulable state is the APC resistance (active protein C resistance). In fact, this is the state mostly associate with venous thrombosis. The article goes on to state that this resistance is caused by a Factor V Leiden single point mutation where the Arg506 is substituted with a glucagon (Zöller et al 1999). Apart from the APC resistance, the second most important genetically inherited factor for the occurrence of thrombosis is a variant (or point mutation involving G20210A), in the Factor II 3' untranslated region. In addition to these two major genetic risk factors, other minor factors include deficiencies in anticoagulant proteins that include antithrombin, protein S and protein C. the article goes on to state that different genetic defects are very common in the general population due to the prevalence of the G20210A mutation in the prothrombin gene and the APC resistance transmitted through genetic inheritance (Zöller et al 1999). Because a single genetic is usually an independent thrombosis risk factor, those individuals with various different genetic defects have an elevated risk of the disorder.

Relationship between the two articles

The two articles talk about similar fact. The second article complements the facts brought out by the first article. For instance, both articles contend that thrombophilia is a disease that has multiple genetic risk factors. Out of these multiple genetic risk factors, the major ones are activated protein resistance caused by F-Leiden gene mutation and the FII G20210A variant (or point mutation) in the Factor II 3' untranslated region. The articles are in agreement that these two risk factors increase an individual's susceptibility to thrombotic disorder. The second article particularly looks at how these two factors are inherited genetically from one generation to another and how they eventually lead to thrombotic disorders. Apart from these two, there is a statement in the two articles that the deficiency anticoagulant proteins like antithrombin caused by gene mutations are also another genetic risk factor. The final point of agreement of the two articles is that thrombosis may not be caused by single genetic risk factor. The disorder may be caused by a combination of various genetic risk factors. As a result, individuals exhibiting a host of genetic defects are at a higher risk of contracting thrombotic disorders than their counterparts who may be exposed to only a single genetic disorder.

In conclusion, it is safe to state that molecular genetics is one of the most common risk factors for a variety of disease. As seen in the literature review of these articles, different genetic aspects play a significant role in the emergence and development of diseases in humans. In this particular paper, the molecular genetics risk factor was explored for two diseases, cardiovascular diseases and thrombophilia. In spite of various genetic risk

factors being established for some of the existing world disease, there is still a lot of research that needs to be conducted in this area. The great advancement of DNA technology will go a long way in aiding this research.

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