Secretors and non secretors in human population antigens biology essay

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Human population can be categorized into secretors and non-secretors based on A, B and H antigen on basis of presence or absence of these blood group antigens in the body fluids and secretions, such as saliva, sweat, tears, semen, serum, mucus present in the digestive tract or respiratory cavities etc. Secretors are individuals that secrete blood group antigens in their body fluids while non-secretors are the individuals that do not secrete them in their body fluids and secretions.

It is a known fact that ABO blood type is controlled by blood type coding genes present on the chromosome 9q34 but the secretor status of an individual is decided by interaction of a separate gene (called secreting gene) with these blood type genes. The presence of the secreting gene in a person’s genome makes him a secretor and absence makes him a non secretor. The gene is designated as (Se) for Secretors and (se) for Non-secretors and it is entirely independent of the blood type A, B, AB or O. The individuals secreting antigens in the body fluid are designated as ‘ ABH secretors’ in blood banks. Individuals having O blood group secrete antigen H, A blood group secrete A and H antigens, B blood group secrete B and H antigens in the fluids.

A secretor gene helps a person to gain a degree of protection against different environmental conditions especially the micro flora of a particular environment and also the lectins present in them. It helps them in promoting the growth of friendly, stable blood type intestinal bacterial ecosystem which depends on the blood type antigens present in the mucus of an individual. Secretor status does modify carbohydrates in the fluids present in the body and their secretions and it also affects and influences the attachment and

persistence of the micro flora present in the body. Secretors are at a higher advantage than non-secretors. Non-secretors have a potential health disadvantage. They possess many metabolic traits such as carbohydrate intolerance, immune susceptibilities. Different tests are available for determining an individual’s secretor status. Most common test uses saliva or other body fluids of an individual for testing the secretor status. These tests are based on the principle of Agglutination Inhibition where the antigens are neutralized by the corresponding antibodies so that these antibodies will not be further be available to neutralize or agglutinate the same antigens residing on the red blood cells. ELISA could also be used for determining the presence of the secreted Lewis antigens in the saliva or other body fluids.

Statistics 1

Place

Population

Tested

% Secretor

Frequency

% Non-Secretor

Frequency

New York

Negroes

178

61. 2

0. 38

38. 8

0. 62

Copenhagen

Danes

263

74. 0

0. 49

26. 0

0. 51

Japan

Japanese

424

75. 7

0. 51

24. 3

0. 49

Berlin

Germans

363

78. 0

0. 53

22. 0

0. 47

Poland

Poles

88

79. 4

0. 54

21. 6

0. 46

New York

Whites

74

82. 4

0. 58

17. 6

0. 42

Helsinki

Finns

196

86. 3

0. 63

13. 7

0. 37

New Mexico

American Indians

69

98. 5

0. 88

1. 5

0. 12

Utah

American Indians

79

100. 0

1. 00

0

0

The alleles Se and se differ in the frequency and have an anthropological value. They occur in different frequency in different populations. They have a high frequency in the American Indiana and a low frequency in the southern Indians. In US 20% of the population is secretors whereas 80% of the population consist of non-secretors. The fusion allele of the FUT2 (secretor type alpha(1, 2)-fucosyltransferase) gene at a high frequency and a new se385 allele in a Korean population

SECRETOR AND NON-SECRETOR

A person secreting blood group antigens into the body fluids and other secretions like saliva, semen, tear, mucous in the digestive tract and respiratory cavities are named as secretors. In similar terms they put their blood type antigens in the body fluids. They secrete antigens according to their blood type, A secrete antigen A and H, B secret antigen B and H, O secrete antigen O and AB secrete A, B and H antigen. Secretors expresses Lewis b (Leb) antigens on the RBC where as non-secretor expresses Lewis a (Le a) on their RBC. These antigens in the body fluids give additional protection to the individual against the various microorganisms and the lectins present all around us.

15- 20% of the population consists of non-secretor. These individual fail to secrete the blood group antigens in their body fluids hence they become susceptible to bacterial and superficial yeast infections. A large no of them sometimes also suffer from the autoimmune disorder. This could also be correlated with the secretor and non-secretor phenotype. The body secretions of secretors and non-secretors differ quantitatively and also qualitatively. The type and quantity of the antigens present in it differ among different individuals. In some cases the non-secretors may contain the A and B antigens in the saliva but the quantity is less and even quality is very low hence they have similar functional problem.

There are certain properties which are specific for secretors and differ in non-secretors. Some are listed below:

Intestinal alkaline phosphatase activity

ABH secretor correlates the activity of alkaline phosphatase and serum alkaline phosphatase present in the intestine. Non-secretors have low activity of alkaline phosphatase and serum alkaline phosphatase which is responsible for the breakdown of fat and assimilate calcium. 2-5 Low molecular weight alkaline is present in both secretors and non-secretors and high molecular weight alkaline phosphatase is present only is secretors. 6

Bacterial flora

The ABH blood types influence the population of bacteria residing in the local vicinity of the gut mucin glycoproteins. Bacteria produce enzymes that have the capability to degrade the end sugar of A, B, and H blood antigens and which are consumed as food by them. The B antigen degrading bacteria produce enzyme to remove the end alpha-D-galactose and A antigen degrading bacteria produce enzyme to detach N-acetylgalactosamine which are used as a source of food by them. 7, 8

Blood clotting

The secretor and the ABO genetics influence each other and effect upto 60% of the vWf concentration variation in plasma. Raised levels of factor VIII and vWf may cause thrombotic and heart disease in future. Secretors have the slowest clotting time, thinnest blood, least tendency of platelet aggregation, low amount of factor VIII and von Willebrand factor (vWf). 9, 10 The non-secretors have highest clotting time, thick blood, high amount of factor VIII and von Willebrand factor (vWf) and low bleeding time. The blood viscosity is also influenced by the secretor status of that individual.

Phenotype – Lewis

Characteristics of Clotting

Le (a- b-) maximum action of factor VIII and vWf

Very Low bleeding times (seen in A, B and AB)

Le (a+ b-) intermediary action

Low bleeding times (seen in O)

Le (a- b+) minimum action of factor VIII and vWf

Very Long bleeding times (seen in O)

Blood Type – Lewis and Factors effect Blood Clotting

Immunoglobulin Variations

ABH non-secretors express low concentration of IgG immunoglobulin. 11, 12 The secretion of varying concentration of diverse constituents of the blood group is controlled by the secretor gene and it also affects the phagocytic activity of the leucocytes which provides an added advantage to the non-secretors. The leucocytes of the non-secretors possess a greater ingestion power when compared to the secretors. The O and B blood group non-secretors have the highest phagocytic activity. 13

The presence of different concentration of anti-I in the an individuals serum is affected by the ABO group, secretor status and sex of the individual. The secretors females have a high level of anti-I in the serum as compared to the

males. 14 The non-secretor have low levels of IgA and IgG antibodies and hence have frequent problems with the heart valve.

Genetics and Biochemical pathways

The secretion of the blood group antigens in the body fluids and other secretions are genetically influenced by certain allelomorphic genes. Secretor gene contains two alleles (Se) and (se). The dominant gene (Se) is present in the homozygous or heterozygous condition in the secretors which lead to the secretion of antigens into the body fluids. (se) is recessive allele and is present in non-secretors in the homozygous condition. SeSe and seSe produces a dominant secretor phenotype and sese produces a recessive non-secretor phenotype.

Basically three genes are responsible for the formation of the A and B antigens. They are namely ABO, Hh, and Sese genes encoding glycosyltransferases which produces the A and B antigens. H antigen present in the individual with O blood group is the precursor for the formation of A and B antigens. H antigen acts as a backbone for A and B antigens. The O gene is considered as amorphic. The allele Hh and Sese reside on each locus and are closely linked together. It is also suggested that one of the allele has arisen by the gene duplication of the other. The second allele on the same locus is really rare. The product related to this allele hasn’t been discovered yet and hence it is considered as amorph.

The oligosaccharide responsible for the formation of the A and B antigen can exist in a simple linear fashion or a complex branched fashion. Infants A, B and H antigens contain high amount of linear chained oligosaccharide

whereas oligosaccharides present in an adult contain high amount of branched chained oligosaccharides. 15

The A and B antigen is synthesized from a common intermediate known as substance H. The conversion is carried out by the addition of a sugar molecule to the non reducing end of the H oligosaccharide chains. This addition affects the reactivity of H antigen. 16, 17

The ABH substances are secreted in the Urinary respiratory tract, gastrointestinal tract by mucous glands residing there. The secretor gene regulates the synthesis of blood group antigens in the glands of small intestinal mucosa. The secretors and non-secretors produce A and B substances which are basically glycoproteins in pylorus and Brunner’s glands and produce A and B substances those are soluble in alcohol and glycosphingolipids in nature. 18, 19, 20

The secretors also produce ABH substances in the prostate and lactating mammary glands. 20 The secretion of breast is rich in H substance but poor in substance A and virtually absent in substance B. The synthesis of these constituents in the pancreas and secretory cells of sweat gland is not controlled by the secretor gene. 21 The blood groups substances were also found in the calyxes and collecting tubules of the secretors (Se) but it could not be concluded that whether they are produced by the kidneys or are generally excreted. These secretions were noticed in the eight to nine weeks old salivary glands and stomach and later it appears throughout the gastrointestinal tract. 19, 22

Glycosphingolipids carrying the A or B oligosaccharides are present on the membranes of RBC’s, epithelial and endothelial cells and are also present in the plasma in the soluble form. The glycoproteins carrying the similar A and B oligosaccharides are responsible for their activity in the body fluids. In the body fluids they are present in the secreted form. The A and B oligosaccharides which do not contain the carrier proteins are present in the milk and urine.

The chromosome 19 contains FUT 1 and FUT 2 genes which code for fucosyltransferase. 23 FUT genes numbered from 1-7 and form clusters which are responsible for the production of enzymes called as fucosyltranferases. The cluster is located on chromosome 19q13. 3. Fucosyltranferase helps in the formation of fucose moiety which is added to the H antigen and further gylcosylate the A or/and B antigens. 24, 25

H antigen is a basic blood group antigen present in each and every human being but the content varies in different individuals of the same ABO group. A general pattern indicates that its strength varies as O> A2> A2B> B> A1> A1B. Water soluble H antigen has been demonstrated in the saliva and the body fluids of the individuals. H antigens are fucose containing glycan units which are present on the glycolipids or glycoproteins residing on the erythrocyte’s membrane or in the secretions. The fucosylatedglycans are the substrate for the enzyme glycosytransferases that are responsible for the formation of the Lewis and A, B blood group antigen epitopes.

Secretors contain both the alleles whereas non secretor contains the “ null allele” for FUT2 gene. The FUT 2 gene codes for fucosyltranferaseenzyme in

the exocrine tissues which lead to formation of antigens in the body secretions and body fluids.

The A and B genes produce glycosyltranferase that add sugar to oligosaccharide chains that is converted to H antigen. The H antigen are constructed on the oligosaccharide chain. The oligosaccharide chains could be of two type: Type 1 and type 2. 15 The glycosphingolipids present in the plasma and on the membranes of glandular and parenchymal cells and glycoproteins present on the cell surfaces or body fluids carry either the type 1 or type 2 chains. The glycolipids antigens present on the RBC contain type 2 chains.

A gene encodes N-acetyl-galactosaminyl-transferase and B gene-encodes galactosaminyl-transferase and add GalNAc and Gal in alpha (1-3) linkages which is acts on the H gene transferase. The H gene produces fucosyltransferase that add fucose to the terminal Galactose molecule of type 2 chain. It forms an alpha (1-2) linkage. A and B antigens are constructed when the A and B transferases attach respective sugars to the type 1 or type 2 chain substituted with Fucose. 26

The secretor gene FUT2 located at 19q13. 3 and codes for the activity of the glycosyltransferasesin concert with the FUT1 gene coding for H antigen, needed to assemble both the ABO and Lewis blood group and are active in mucous gland and goblet cells which interact with each other and lead to secretions of antigens in the fluids.

The expression patterns of both the genes are different. The FUT1 (H) gene is dominantly expressed in the erythroid tissues which lead to the formation of the H enzyme whereas the FUT2 (secretor) gene is expressed in the secretory tissues and lead to the formation of secretor enzyme. The product of the H enzyme or H gene resides on the erythrocytes and product of secretor gene resides on mucins in secretions.

If an individual lack these alleles, he/she will not be able to express the above active enzymes therefore they would be deficient of the substrates which are required by the A or B glycosyltransferases. Therefore they would not express the A and B epitopes.

Correlation between Lewis Phenotype and ABH Secretor status

The Lewis typing also helps in finding the ABH secretor status. The production of Lewis antigens is genetically controlled. Individuals possessing the Lewis (Le) gene would produce the Lewis antigens which are carried in the plasma by different substances and are absorbed onto the Red blood Cells present in one’s blood.

The ABO determinants and H/h blood groups factors seem to show structurally corelation to Lewis blood determinants. FUT1 provide the glycans for glycosyltransferases which convert Lewis antigen to ABH antigens. FUT2 allele is expressed in the secretor and is responsible for the expression of type1 H determinant.

The secretors convert their Lewis a antigen to Lewis b therefore they are (a-b+) and the non-secretor are (a+b-) as they lack the FUT2 responsible for glycosyltransferase which could convert Lewis a antigen to Lewis b antigen.

Lewis (Le) gene and Secreting (Se) gene interact with each other. Initially Lewisais formed and if Se gene is absent in an individual the Lewisa substance is absorbed on the RBC and the individual is typed as Lewisa but in secretors the Se gene controls the activation of the H gene which causes addition of an additional sugar to Lewisa which convert it to Lewisb. Secretors contain both Lewisa and Lewisb in their plasma but absorb Lewisb preferentially on the red blood cells and the individual is typed as Lewisb.

Hence we could interpret that presence of Lewis gene would type an individual as Lewisa positive or Lewisb negative or vice versa. An individual could not be positive for both. A person containing both Lewis gene and Secreting gene are typed as Lewisa negative and Lewisb positive whereas a person having the Lewis gene but not the secretor gene is typed as Lewisa positive and Lewisb negative. Individual who does not have Lewis gene regardless of secretor gene is typed as Lewisa negative and Lewisb negative. 27, 28

Note: Lewis Double Negative (LDN) is a sub type of non secretors but Lewis typing cannot be used for them to determine the ABH secretor status.

Detection methods29-31

The presence and absence of the antigens in the body fluids could be detected by Agglutination Inhibition and Lewis typing.

Agglutination Inhibition test could be divided into two parts:-

Part I – Antibody Neutralization:

To determining one's secretor status, the saliva of the individual is mixed by the antiserum (Anti-A, Anti-B or Anti-H) available commercially. In secretors the soluble substances i. e. blood group antigens will react with the antibodies present in the antiserum and will get neutralized.

Part II – Agglutination Inhibition:

The bed blood cells obtained commercially are added to the test mixture. In secretors agglutination of the RBC do not take place as no free antibodies are available to agglutinate them. All the antibodies have reacted with the soluble antigens present in the saliva whereas in non-secretors agglutination would occur upon addition of the RBC as no blood group antigens are present in the saliva so antibodies present in the antiserum are not neutralized and hence would be free to react with the test RBC cells which are added to the test mixture. Hence agglutination is a negative test for secretor status and positive test for the non-secretor status.

Note: Anti-H lectin containing phytohaemagglutinin virtually specific for human RBC. Thirteen Cucurbitaceaespecies have been investigated for the anti-H activity present in their seed lectins. Lectins has been extracted and purified from Ulexeuropaeus seeds. It could be used to demonstrate the H secretor status of blood group O individual and also for subgrouping the blood group A individuals.

Lewis typing:

Individuals carrying the Lewis gene produce Lewis antigens that are carried by the plasma and are also adsorbed on the red blood cells. Lewis antigens do not reside only on the red blood cells. Initially the gene gives rise to Lewisa. If Se gene is present it activates H gene which interact with the Lewisa and add a sugar to Lewisa and hence get converted it to Lewisb. Both Lewisa and Lewisb in present in the plasma of the secretors. If the Se gene is not present then the Lewisa substance is adsorbed on the red cells and individuals are typed as Lewisa.

The secretor status of an individual could be determined with help of Lewisa and Lewisb antibodies mixed with an individual’s saliva and observing the agglutination macroscopically.

Disease Susceptibility among Secretors and Non-secretors

Digestive system

Non-secretors are more prone to the diseases caused by the oral bacteria in the digestive system of an individual. It includes ulcers, celiac diseases gastric carcinoma pernicious anemia etc. It could lead to dysplasia or increase in the number of cavities present in the digestive tract. Non-

secretors are less resistant to the infection caused by Helicobacter pylori which could lead to the formation of peptic and duodenal ulcers. 32, 33 It could easily colonize and cause inflammation in the non-secretors. 34 The non-secretors lack the blood group antigens in the mucus secretions therefore H. pylori attach to the walls of the digestive tract and cause infection. The secretors have a tendency to secrete free ABH antigens in their intestinal secretions which effect the bacterial and lectins adherence to the microvilli present in the gut. The secretors produce these antigens and prevent H. pylori attachment. These antigens act as a decoy in the secretors which prevent them from attaching with the host tissues. The non-secretors also show a lower IgG immune response to the H. pylori. They have extreme rate of bleeding and stomach ulcers but correlation between these complications and the secretor status have not been documented yet. The non-secretors are not able to turn off the digestive enzymes and hence they produce large amount of enzyme pepsin and hence are more prone to duodenal ulcers. 50% of the duodenal ulcers are present in non-secretors. 30-40% of group O individuals are affected by the duodenal ulcers and 15-20 % are affected by the gastric ulcers. They show a high risk factor along with the gene coding for hyperpepsinogenemia I which impact in the risk of duodenal ulcers. 35, 36 Group A individuals have a higher tendency of having gastric cancer and pernicious anemia. Statistics shows that 20% of the group A individuals are affected by gastric cancers and 25% are affected by the pernicious anemia.

Oral pathology

The non-secretors are more prone to oral diseases like mouth and esophagus cancer, epithelial dysplasia etc. They have more cavities than secretors. 37

Diabetes

The ABH non-secretors and Lewis negative (Le a-b-) individuals have a high risk of developing insulin dependent diabetes or complications arising from diabetes. 38, 39 Secretors with juvenile diabetes have a low chance of developing retinopathy. 40 The ABH non secretors which are affected by insulin dependent diabetes mellitus, they show mean levels of C3c and C4 is lower as compared to ABH secretors.

Metabolic Syndrome X

The Lewis negative men are predisposing to syndrome X and prothrombic metabolism. They have high levels of BMI, SBP, triglycerides and low levels of insulin in serum and plasma glucose while fasting. This relationship is not true for women and is only applicable for the men. 41-43

Respiratory System

Secretors have an added protection against the harmful environmental assaults directed towards our lungs and as usual non-secretors have a health disadvantage. They are over represented among the people suffering from influenza viruses A and B, rhinoviruses, respiratory synsytial virus and echinoviruses. 44 Secretors who are miners or smokers do receive a protection against the disastrous effects of the cigarette smoking. Asthma is very common among the individuals working in the coal mines. Upon research it was concluded that asthma among them is also related to the

non-secretor phenotype present in them. The non-secretor has a tendency to snore and are more prone to COPD (Chronic Obstructive Pulmonary Disease). 45

Heart disease

The ABH non-secretor phenotype have a high risk of developing myocardial infarction and Lewis negative individuals have a high risk of developing chronic heart disease (CHD) and also ischemic heart disease (IHD). 46 They contain high levels of triglycerides. 47 Alcoholism has a positive interaction with the Lewis negative individuals. Alcohol consumption is protective in these individuals. 48, 49

Autoimmune Disease

Autoimmune disorders such as Sjogren's syndrome, spondylitis, sclerosis, arthropathy, arthritis, and Grave's disease are more prone in non-secretors. 50-52 The ABH non-secretors affected with grave's disease produces high levels of antitubulin antibodies as compared to secretors and are unable to produce the water soluble glycoproteins in the saliva. 53

Fetal Loss and Infertility

ABO antigens are also found on the sperm of the secretors. 54 These are obtained from the seminal secretions present in them. ABO incompatibility could exist between the wife and husband if could affect the fertility of an individual. 55, 56 This issue has not been properly studied and is therefore under research.

Rheumatic Fever

The secretors and group O individuals are resistant to Rheumatic fever and more number of cases have been recorded in the non-secretors. 57, 58 Secretor status could also determine whether the rheumatic fever would be followed by streptococcal pharyngitis or not. 59-61

Neisseria species

The non-secretors who do not produce water soluble antigens in the saliva are at the risk of getting infected by Neisseria meningcococcal disease. 62 The immune capabilities of the secretor provide a relative protection in the secretors. The ABH non-secretors produce low level of anti-meningococcal salivary IgM antibodies which provide protection to the secretors against the microorganism. 63

Candida species

Non-secretors are barriers of candida species and therefore are frequently affected by the candida infections. The glycocompounds secreted by secretors in the body fluids inhibit adhesins present on the yeast which are responsible for their adhesion with the body tissues. 64-66 This leads to the development of the chronic hyperplastic Candidiasis. Statistics shows that 68% on the non-secretors are affected by chronic hyperplastic candidiasis. 67 Non-secretor women are affected by recurrent idiopathic vulvovaginal Candidiasis. An individual with a combination of non-secretors and absence of Lewis gene are at relative risk of developing recurrent idiopathic vulvovaginal Candidiasis. 68

Tumor Markers

The individuals with homozygous active Le alleles (Le/Le) and inactive (se/se) alleles shows a highest mean value of CA19-9 tumor marker. 69 The Lewis negative individuals irrespective of Se genotype have negative values for CA19-9. The Lewis negative individuals have higher mean value for DU PAN-2 as compared to Le-positive individuals. 70 We can conclude that CA 19-9 marker is not an appropriate tumor marker for Le-negative individuals but DU-PAN-9 is an appropriate tumor marker. 71

UTI

Non-secretors show a higher risk of getting recurrent urinary tract infection (UTI) and renal scars as compared to secretors. This susceptibility is higher among negative Lewis subset. Statistics of a study done on women affected with recurrent urinary tract infection stated that 29% of the non-secretor women were affected by UTI and 26% of Lewis (a-b-) women were affected by the UTI. 72-74 The non-secretor phenotype and blood group B and AB phenotype work together to increase the risk of UTI among women. Women and children suffering from renal scarring with and without the antibiotic treatment for UTI are prone to UTI and pyelonephritis. 75-77 55-60% of non-secretors develop renal scars and 16% on secretors develop renal scars. 78 C-reactive protein levels, erythrocyte sedimentation rate and body temperature are higher in the non-secretors that in secretors with recurrent UTI. 79

Conclusion

It concludes that there exist a statistical association between the individual’s blood-group secretor phenotype and the diseases they are susceptible to. So knowing your secretor status is advantageous as we can use the nutritional supplements more intelligently and effectively. It also makes us aware of the diseases, illness and metabolic dysfunction we are prone to, difference in the levels of intestinal alkaline phosphatase activity, propensities towards blood clotting, tumor markers and different ingredients of breast milk so that we can manage them before hand and would be prepared for them in the near future.