Single Gene Disorder

(Name)

(University)

Single Gene Disorders

Mutations

Even though there are currently over 6,000 identified single-gene or monogenic disorders, they undergo several dissimilar mutations, which can result in a similar disorder but with varying relentless levels and phenotype (Badano & Katsanis, 2002). The disorders are caused by the mutation of protein products of just one gene. In that regard, mutation is an enduring alteration or deletion inside the DNA sequence of a gene, such that the amino acid series of that protein that are programmed by the gene become distorted (Kelsell, Blaydon, & Mein, 2007). The mutations vary in dimension from single DNA building block to outsized sections of a chromosome. Germ-line mutations take place in gametes and the alterations may take place on one or both chromosomes, even as one chromosome is inherited from each parent (Kelsell, Blaydon, & Mein, 2007). Conversely, acquired or somatic mutation takes place inside the DNA of single cells in non-gamete body cells, such that the mutations may passed via mitosis to every successive somatic germ-cell alteration of that cell line, but at some point during the person lifetime. Somatic mutation are mostly due to environmental factors or errors made when a DNA duplicates itself through cell-division and cannot be inherited, since the mutated gene is either altered or deleted (Risch, 2000).

Moreover, mutations can be impulsive when errors are made in DNA through in-coding or non-coding areas of the gene (Badano & Katsanis, 2002). The mutations can result in attainment of functions or failure of functions and in dominant-negative function the non-functional protein hinders the role of typical protein product in the other allele, since the mutated allele controls other allele (Risch, 2000). However, mutation outcomes can be some loci having

smaller or numerous others alleles. While length mutations results in insertions, erasures, or modifications in the repeat, point mutations produce transformations in solitary base pair and may be silent, drivel, missense or frame-shift (Kelsell, Blaydon, & Mein, 2007). The silent mutations are those that do not modify the amino-acid sequence, and are thus polymorphisms. While missense mutations are those that lead to a transformation in amino-acid code, the nonsense mutations result in discontinued codon, point-insertions or deletions, since they affect every amino acid (Badano & Katsanis, 2002). Mutations that take place within an egg, sperm cell, or following fertilization are referred to as de novo mutations, and result in genetic disorders whereby affected person has mutation in all cells even without a family history of that particular disorder (Kelsell, Blaydon, & Mein, 2007).

In that regard, single gene disorder mutations arise from alterations that either form an atypical protein or result in a decrease in the productivity of the single gene product (Kelsell, Blaydon, & Mein, 2007). While the defects arising from the mutations can be in enzyme, membrane receptors or the transport systems, the alterations take place in protein structures, thus affecting the role and amount of non-enzyme proteins. Single-gene disorders can be dominant or recessive, autosomal or sex-linked (Badano & Katsanis, 2002). While in dominant disorders the mutated gene is on one of the two inherited chromosomes, recessive disorders are those in which the gene is on both inherited chromosomes. In particular, the mutations take place during cell partitions when the DNA becomes duplicated. In autosomal mutation, there is the creation of prejudiced expression within the heterozygote, and a complete expression inside the homozygote (Kelsell, Blaydon, & Mein, 2007).

Cystic Fibrosis

Incidence

Cystic fibrosis is caused by the mutations in the cystic fibrosis trans-membrane conductance regulator gene or CFTR and which can take place in either six classes (Rohlfs & ettal, 2002). CFTR is an ATP-binding sealed unit transporter, whose role is to offer instructions used in creating conduits that convey negatively charged elements referred to as chloride ions across cell membranes. The most widespread mutation is the deletion of the three-bases encoding of phenylalanine residue that impairs the capacity of CFTR to fold inside the endoplasmic reticulum. Over 1,000 mutations have been identified to occur in CFTR gene with majority of such mutations altering the single amino acids inside the CFTR protein and even deleting a small amount of CFTR gene DNA (Bobadilla & ettal, 2002). This widespread mutation is referred to as delta F508 since it deletes a single amino acid in location 508 of the CFTR. Since the resulting anomalous channel is broken shortly after being formed, it never arrives to cell membranes in order to carry chloride ions (Rohlfs & ettal, 2002).

Secondly, there may be a mutation, which is based on introduction of a stop codon or else nonsense within the mRNA, thus resulting in severe splicing such that the truncated CFTR protein is unstable and swiftly degraded (Bobadilla & ettal, 2002). Thirdly, there can be a mutation which alters the conduit/channel regulation, such that the altered protein cannot be activated and operate as chloride channel. Another mutation arises from missenses positioned in membrane-spanning area such that they impinge on chloride conductance (Rohlfs & ettal, 2002). These mutations are severe since they produce characteristic CF phenotype leading to pancreatic insufficiency and lung disease. Other mutations include partially anomalous splicing arising from an incompetent trafficking missenses, and alterations, which reduce CFTR stability and regulation of numerous channels. These two mutations can retain several key CFTR activities but present milder phenotype (Bobadilla & ettal, 2002).

While most affected people have placid mutations in no less than one copy of the CFTR gene in every cell, those with ruthless cystic fibrosis undergo mutation in the other replica of CFTR gene (Rohlfs & ettal, 2002). Individuals having a single standard CFTR gene and another defective CFTR gene are considered cystic fibrosis carriers, and they do not have symptoms but can pass the defective CFTR genes to their offspring's (Bobadilla & ettal, 2002). Overall, mutations inside the CFTR gene interrupt the operations of the chloride channels, hence stopping them from regulating streaming of not just chloride ions but also water in and out of cells. Consequently, the cells that line the passageways of important organs like lungs and pancreas generate abnormal mucus that is thick and tacky, such that it blocks the airways and numerous ducts. People with cystic fibrosis inherit the ailment from parents, and it is a common genetic disorder in the Caucasian Northern and northern European community compared to other ethnic groups. (Rohlfs & ettal, 2002).

Presentation

The manifestation of the disease and severity varies from one affected person to another. However, it is frequently characterized by an accumulation of solid but sticky mucus, which is irregularly produced and can harm several body organs (Macek & ettal, 2008). The mucus then clogs airways resulting in severe breathing problems coupled with bacterial infections within the lungs. The symptoms include chronic coughing, wheezing, and lung inflammation. Eventually, the abnormal mucus accumulation and subsequent infections leads to lasting lung damage, and creation of scar tissues or fibrosis and cysts inside the lungs (Moskowitz & ettal, 2008). The main signs of cystic fibrosis comprise damages to the respiratory system, and the chronic digestive system. The digestive problems arise due to the mucus build-up in the pancreas ducts, such that they reduce manufacture of insulin. This then halts the digestive enzymes from getting

into the intestines to assist in digestion. Consequently, the person develops diarrhoea, undernourishment, poor growth, and unintended weight loss (Moskowitz & ettal, 2008).

During adulthood, such people experience a deficiency of insulin, which leads to cystic fibrosis diabetes that is associated with diabetes mellitus. For adult men, they acquire congenital bilateral deficiency of the vas deferens or CBAVD, as they become infertile since the mucus blocks sperm-carrying tubes (Claustres, 2005). CFTR gene mutation also results in rhinosinusitis or the chronic swelling of tissues that line sinuses, resulting in sinus pain, headache, agitation, and nasal congestion. Bronchiectasis is also another sign of cystic fibrosis and it destroys passages from windpipe to lungs, especially allergic bronchopulmonary aspergillosis which arises from hypersensitivity reactions to fungal infection (Moskowitz & ettal, 2008).

Diagnosis

Since some individuals do not show any symptoms or complications, phenotype blood examinations will normally reveal whether the pancreas is operating properly (Macek & ettal, 2008). The other precise test is the gene test especially when one family member is found to have the deficiency. The genetic test will reveal whether the person has faulty CFTR genes, in particular prenatal genetic analysis will reveal whether the foetus has the gene and level of cystic fibrosis (Macek & ettal, 2008). Confirmation is done using sweat test since the test measures the level of salt in that person sweat, as elevated salt levels reveal presence of cystic fibrosis. Chest x ray will reveal whether the affected person lungs are swollen or scarred such that they trap air. However, a sinus x-ray will reveal whether there is sinusitis, which is a common cystic fibrosis complication. Furthermore, Lung function tests will gauge how much air the person can breathe and how fast, while a sputum culture will reveal if mucoid Pseudomonas bacteria are growing, so

that drastic treatment options could be undertaken since the presence of the bacteria reveals an advanced cystic fibrosis (Moskowitz & ettal, 2008).

Treatment

The ailment has no substantial cure and current treatment options are based on easing its symptoms and minimization of long-term infectious damages (Moskowitz & ettal, 2008). However, due to enhanced treatment options coupled with enhanced management options, many individuals with cystic fibrosis are now able to live normal lifespan. Medication is used to clear and manage lung and digestive system infections (Moskowitz & ettal, 2008). For instance, antibiotics are used to protect affected person from certain bacteria while steroids help to minimize swelling of airways and in tackling nasal polyps. Others take Pulmozyme enzyme in order to thin out the adhesive mucus in the lungs. Insulin helps to manage diet to even out blood sugar levels coupled with a high calorie diet in order to digest food they eat. Severe cases calls for lung transplant or the use of bronchodilators (Macek & ettal, 2008).

References

Badano, J. L., & Katsanis, N. (2002). Beyond Mendel: An evolving view of human genetic disease transmission. *Nature Reviews Genetics , 3*, 779–789.

Bobadilla, J. L., & ettal. (2002). Cystic Fibrosis: A Worldwide Analysis of CFTR Mutations:Correlation With Incidence Data and Application to Screening. *HUMAN MUTATION , 19*, 575-606.

Claustres, M. (2005). Molecular pathology of the CFTR locus in male infertility. *Reprod Biomed Online , 10* (1), 14-41.

Kelsell, D. P., Blaydon, D., & Mein, C. A. (2007). *Identifying Mutations in Single Gene Disorders. Bioinformatics for Geneticists* (Vol. 147). NewYork: John Wiley & Sons.

Macek, M. J., & ettal. (2008). Castellani C, Cuppens H, Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. *J Cyst Fibros , 7*, 179–196.

Moskowitz, S. M., & ettal. (2008). *CFTR-Related Disorders.* Retrieved November 23, 2013, from http://www.ncbi.nlm.nih.gov: http://www.ncbi.nlm.nih.gov/books/NBK1250/#_ncbi_dlg_citbx_NBK1250

Risch, N. J. (2000). Searching for genetic determinants in the new millennium. *Nature , 405* (6788), 847-856.

Rohlfs, E. M., & ettal. (2002). The I148T CFTR allele occurs on multiple haplotypes: a complex allele is associated with cystic fibrosis. *Genet Med , 4* (5), 319-23.