Single Gene Inheritance Disorders

Research Project

Submitted to the department of (**Biology)** in partial fulfillment of the

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ ﴿١﴾ خَلَقَ الْإِنسَانَ مِنْ عَلَقٍ ﴿٢﴾اقْرَأْ وَرَبُّكَ الْأَكْرَمُ ﴿٣﴾ الَّذِي عَلَّمَ بِالْقَلَمِ ﴿٤﴾ عَلَّمَ الْإِنسَانَ مَا لَمْ يَعْلَمْ ﴿٥﴾ كَلَّا إِنَّ الْإِنسَانَ لَيَطْغَىٰ ﴿٦﴾

صدق اللَّهُ العظيم

سورة العلق

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Supervisor's Confirmation

I certify that the preparation of this graduation research project titled "**Single Gene Inheritance Disorders** " was under my supervision at the Department of Biology \ Salahaddin University-Erbil in partial fulfilment of the requirements for the degree of (B.Sc.) In Biology.

Signature:

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Committee Confirmation

We certify that this graduation research project titled " **Single Gene Inheritance Disorders** " was read and examined the students:

Shilan Sardar Mohsin

In it's content and in what is related to; in our opinion it meets the standard of a graduation research project for the degree of (B.Sc.) in **Biology** .

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Abstract

This study explored the Single-gene disorders have a straightforward inheritance pattern . and the genetic causes can be traced to changes in specific individual genes. The main objective of the paper is first A particular disorder could be rare; however, as a group, single-gene disorders are responsible for a significant percentage of pediatric diseases. Autosomes refer to the numbered chromosomes (chromosome 1–22), as opposed to the sex chromosomes, X and Y. Every individual carries two copies of each autosome and, therefore, also has two copies of every gene carried on those chromosomes, one inherited from each parent. Based on the location of the relevant genes, single-gene traits can be divided into autosomal inheritance and sex-linked. Autosomal inheritance, depending on whether one or two mutant alleles are required to cause a phenotype, can be divided into autosomal dominant or autosomal recessive. Based on Mendel's laws, the two alleles segregate and pass to different offspring,

Keyword: Single-gene disorders, autosomal, Test, chromosome, inheritance

Contents

Section One :

Introduction

1.1 General Background

Single-gene disorders have a straightforward inheritance pattern, and the genetic causes can be traced to changes in specific individual genes. A specific disorder may be rare; however, as a group, single gene disorders are responsible for a large percentage of childhood diseases. The autosome refers to the numbered chromosomes (chromosome 1-22), in contrast to the sex chromosomes, X and Y. Each individual carries two copies of each autosome, and therefore, as well as two copies of all the genes that carry on those chromosomes, one is inherited from each parent. Based on the location of the related genes, single gene traits can be divided into autotropy and sex. (Huang and Keiles 2012)

Since only seven years have passed since the first human genes were cloned and sequenced, significant progress has been made in the detection of molecular diseases of individual genetic disorders. Perhaps we already have a good idea of the repertoire of molecular defects that lie behind most of them, and have been making a start in trying to link these lesions to the associated clinical phenotypes. These developments have important practical implications for carrier detection and prenatal diagnosis of genetic diseases and in the long term may enable us to begin to understand the molecular basis of common multidisciplinary diseases such as heart disease, diabetes and major psychosis. The new technologies that have led to these developments are therefore likely to have a wide-ranging application in diagnostic pathology in the future. (Weatherall 1987)

Single gene complaints are amid the most well-understood genetic disorders given their straightforward inheritance patterns (recessive or dominant) and relatively simple genetic etiologyAlthough most of these diseases are rare, they affect millions of Americans in total. Some of the more common single gene disorders include cystic fibrosis, hemochromatosis, Tay-Sachs, and sickle cell anemia. Although these diseases are primarily caused by a single gene, many different mutations can lead to the same disease but of varying degrees of severity and phenotype. But even the same mutation can lead to slightly different phenotypes. This may be due to differences in the patient's environment and / or other genetic differences that may affect the disease phenotype or outcomes. (Alliance 2010)

In 1960, Dr. Robert Guthrie, who suffered from his niece phenylketonuria and his son also had mental disability, a more sensitive method to detect high levels of phenylalanine in the blood, allowed for diagnosis Phenylketonuria within three days after delivery. Using Guthrie's bacterial test, unable to make their own phenylalanine crystals report high phenylalanine in baby blood samples through ankle tingling. With Guthrie's method, the phenylalanine-deficient bacteria were grown in media together with a paper disk spotted with a drop of the infant's blood. If the phenylalanine levels in the blood were high, the bacteria would grow robustly, and a diagnosis of Phenylketonuria could be made. Through the ability to discover that their child had Phenylketonuria at such an early age, parents became able to respond immediately by feeding their child a modified diet low in proteins and phenylalanine, thereby allowing more normal cognitive development. Guthrie's test continues to be used today, and the practice of obtaining an infant's blood sample via heel prick is now used in numerous additional diagnostic tests.(Chial 2008)

In this short review, we will summarize some known knowledge about the structure of normal human genes, describe the different types of defects that lead to

defects in genes, and how they are produced, and describe some examples of how the structure and function of abnormal genes are linked with related clinical pictures. There are many accounts. About recombinant DNA technology for the unprofessional reader (Emery 1984)(Weatherall 1985).

1.2 Aims of the Project

The aim of this study is to classify the Single gene disorders are among the most well-understood genetic disorders given their straightforward inheritance patterns (recessive or dominant) and relatively simple genetic etiology. Although the majority of these diseases are rare, in total, they affect millions of Americans. Some of the more common single-gene disorders include cystic fibrosis, hemochromatosis, Tay-Sachs, and sickle cell anemia. Even though these diseases are primarily caused by a single gene, several different mutations can result in the same disease but with varying degrees of severity and phenotype. But even the same mutation can result in slightly different phenotypes. This may be caused by differences in the patient's environment and/or other genetic variations that may influence the disease phenotype or outcome. For example, other genes have been shown to modify the cystic fibrosis phenotype in children who carry the same CFTR mutation. In addition, for some disorders such as galactosemia, mutations in different genes can result in similar phenotypes. (Andrew E. Czeizel (2004)

Definitions:

Single-gene disorder is a disease caused by a known alteration or mutation in one of more than 20.000 genes in nearly every cell in the body. Single-gene disorder may be inherited from both members of a couple carry the same condition. It can also be inherited through one or more generations in the family.

single gene disorders are only viable in their mosaic form and appear to have embryonic lethality and therefore are never seen in their nonmosaic form. These include such disorders as proteus syndrome secondary to mosaicism in AKT1 and hemimegalencephaly secondary to mutations in PIK3CA (Biesecker and Spinner, 2013)

Outline of the Project

In the first section, the research display of Single gene disorders, the general background, the objective of the project, and the importance of the project. We review the analysis of literature in second section and in this section we discuss more about years that researchers have attempted in front of us. We will provide details, results and discussion in the next methodological section of this section. The last section is the final proposal for a section of suggestions and summaries. Finally, the study ends with the list of references used in the current study.

Section two:

Literature Review

2.1 Autosomal Recessive Single-Gene Diseases

Autosomal recessive single-gene diseases occur only in individuals with two mutant alleles of the disease-associated gene. Remember, for any given gene, a person inherits one allele from his or her mother and one allele from his or her father. Therefore, individuals with an autosomal recessive single-gene disease inherit one mutant allele of the disease-associated gene from each of their parents. In pedigrees of families with multiple affected generations, autosomal recessive single-gene diseases often show a clear pattern in which the disease "skips" one or more generations.Phenylketonuria (PKU) is a prominent example of a single-gene disease with an autosomal recessive inheritance pattern. PKU is associated with mutations in the gene that encodes the enzyme phenylalanine hydroxylase (PAH); when a person has these mutations, he or she cannot properly manufacture PAH, so he or she is subsequently unable to break down the amino acid phenylalanine, which is an essential building block of dietary proteins. As a result, individuals with PKU accumulate high levels of phenylalanine in their urine and blood, and this buildup eventually causes mental retardation and behavioral abnormalities. The PKU-associated enzyme deficiency was determined biochemically in the 1950s—long before the PAH-encoding gene was mapped to human chromosome 12 and cloned in 1983. Specifically, Dr. Willard Centerwall, whose child was mentally handicapped, developed the first diagnostic test for PKU in 1957. Called the "wet diaper" test, Centerwall's test involved adding a drop of ferric chloride to a wet diaper; if the diaper turned green, the infant was diagnosed with PKU. The wet diaper test was used to reliably test infants at eight weeks after birth; by this time,

however, infants who were affected by PKU had already often suffered irreversible brain damage. (Antonarakis, 2006)

Approach to Single-Gene Disorders Single-gene disorders have a straightforward inheritance pattern, and the genetic causes can be traced to changes in specific individual genes. A particular disorder could berate; however, as a group, single-gene disorders are responsible for a significant percentage of pediatric diseases. Autosomes refer to the numbered chromosomes(chromosome 1–22), as opposed to the sex chromosomes and Y. Every individual carries two copies of each autosome and, therefore, also has two copies of every gene carried on those chromosomes, one inherited from each parent. Based on the location of the relevant genes, single-gene traits can be divided into autosomal inheritance and sex-linked. Autosomal inheritance, depending on whether one or two mutant alleles are required to cause phenotype, can be divided into autosomal dominant or autosomal recessive. Based on Mendel's laws, the two alleles segregate and pass to different offspring, (Alliance G. 2010)

2.2 Autosomal Dominant Single-Gene Diseases

Autosomal dominant single-gene diseases occur in individuals who have a single mutant copy of the disease-associated gene. In this case, the presence of a single nonmutant or "wild-type" copy of the gene is not enough to prevent the disease. Individuals can inherit the mutant copy of the disease-associated gene from either an affected mother or an affected father. Huntington's disease, a progressive neurodegenerative disorder, is a well-known example of an autosomal dominant single-gene disease; most individuals with a single copy of the mutant huntingtin gene (HTT) will have Huntington's disease later in life. Typically, autosomal dominant diseases affect individuals in their early years and prevent them from

living past infancy or childhood, which in turn precludes these individuals from reproducing and potentially passing on the mutation to their offspring. In the case of Huntington's disease, however, the late onset of the disorder means that many affected individuals have already had children before they are even aware that they carry the mutation. Disease-associated changes in the huntingtin gene consist of a special type of mutation called triplet repeats; these mutations are simply extra repetitions of the three-base DNA sequence CAG. The number of CAG repeats in a mutated huntingtin gene determines the age at which a person will develop Huntington's disease, as well as how severe the condition will be. Genetic tests can be used to determine how many CAG repeats are in an individual's huntingtin gene, thereby providing a highly accurate assessment of the individual's disease risk. Because affected parents have a 50% chance of passing a mutant copy of the huntingtin gene on to each of their offspring, children of people with Huntington's disease are often faced with the dilemma of whether to undergo such testing. Genetic testing can either provide immediate relief in knowing that one is free from the disease, or the confirmation that one will certainly suffer from the condition at some point in the future. (Weatherall DJ 1985)

2.3 X Chromosome–Linked Recessive Single-Gene Diseases

Single-gene diseases that involve genes found on the sex chromosomes have somewhat different inheritance patterns than those that involve genes found on person’s autosomes. The reason for these differences lies in the genetic distinction between males and females. Recall that females have two copies of the X-chromosome, and they receive one copy from each parent. Therefore, females with an X chromosome-linked recessive disease inherit one copy of the mutant gene from an affected father and the second copy of the mutant gene from their mother, who is most often a carrier (heterozygous) but who might be affected (homozygous). Males,

on the other hand, have only one copy of the X chromosome, which they always receive from their mother. Therefore, males with an X chromosome-linked disease always receive the mutant copy of the gene from their mother. Moreover, because men don't have a second copy of the X chromosome to potentially "cancel out" the negative effects of X-linked mutations, they are far more likely than women to be affected by X chromosome-linked recessive diseases. The blood-clotting disorder hemophilia A is one of several single-gene diseases that exhibit an X chromosome-linked recessive pattern of inheritance. Males who have a mutant copy of the factor VIII gene (F8) will always have hemophilia. In contrast, women are rarely affected by this disease, although they are most often carries of the mutated gene. Duchenne muscular dystrophy is another example of a single-gene disease that exhibits an X chromosome-linked recessive inheritance pattern. This condition is associated with mutations in the dystrophin gene (DMD). (Portela A, Esteller M (2010).

2.4 X Chromosome–Linked Dominant Single-Gene Diseases

Few dominantly inherited forms of human disease are X chromosome linked. Females with an X chromosome-linked dominant disease can inherit the mutant gene from either an affected mother or an affected father, whereas males always inherit such diseases from an affected mother. Examples of X chromosome-linked dominant diseases are rare, but several do exist. For instance, dominant mutations in the phosphate-regulating endopeptidase gene (PHEX), which resides on the X chromosome, are associated with X-linked dominant hypophosphatemic rickets. Similarly, Rett syndrome, a neurodevelopmental disease, is associated with dominant mutations in the methyl-CpG-binding protein 2 gene (MECP2). Rett syndrome almost exclusively affects females, because male embryos with a

dominant mutation in the MECP2 gene rarely survive. (Portela A, Esteller M (2010).

2.5 Y Chromosome–Linked Single-Gene Disease

Like X-linked dominant diseases, Y chromosome-linked diseases are also extremely rare. Because only males have a Y chromosome and they always receive heir Y chromosome from their father, Y-linked single-gene diseases are always passed on from affected fathers to their sons. It makes no difference whether the Y chromosome-linked mutation is dominant or recessive, because only one copy of the mutated gene is ever present; thus, the disease-associated phenotype always shows. One example of a Y-linked disorder is nonobstructive spermatogenic failure, a condition that leads to infertility problems in males. This disorder is associated with mutations in the ubiquitin-specific protease 9Y gene (USP9Y) on the Y chromosome.

Section Three :

3.1 Genetic Epidemiology

Genetics epidemiology is quickly expanding research field concerned with considerate the heritable aspect of disease risk, individual propensity to disease and eventually with contributing to a complete molecular understanding of pathogenesis (Smith et al., 2005). It is a discipline that focuses on the familial and in particular genetic determinants of disease and the joint effects of genes and non-genetic determinants (Burton et al., 2005). A major issue for genetic epidemiology is being able to identify both, environmental and genetic factors that alter risk in individuals who have, or are strongly suspected of having inherited disease-predisposing mutations. Obtaining this information requires large numbers of known carriers and their relatives, but suitable statistical inferences about modifiers of risk are difficult if ascertainment of the families was not systematic and well designed. Population-based case-control family studies are likely to give clearer answers than analysis of members of mutation-carrying families ascertained through opportunistic sampling from genetics clinics (Hopper et al., 2005).

3.2 X-Linked Dominant Traits

For X-linked dominant conditions, the phenotypes in females are generally milder than in males. Therefore, daughters and sons of affected females are at 50% risk of being affected. All daughters but no sons of affected males will be affected. An example of an X-linked dominant condition is Rett syndrome . In a female, classical Rett syndrome is a progressive neurodevelopmental disorder. Clinical features include normal psychomotor development during the first 6–18 months of life

followed by a period of developmental stagnation, then rapid regression in language and motor skills. During the progressive period, the typical clinical signs are repetitive stereotypic hand movements. Other clinical features include screaming, inconsolable crying, and autistic tendencies. Head growth may begin decelerating as early as 3 months of age. Brain size may be smaller than normal, but microcephaly is not an invariant feature of Rett syndrome. Seizures occur in 90% of affected females. Generalized tonic-clonic seizures and partial complex seizures are common. Failure to thrive is also often seen in affected females. It is possible that this may be associated with oropharyngeal and gastroesophageal incoordination, which cause poor feeding. In classical Rett syndrome, the female can survive into adulthood. Most males with Rett syndrome do not survive pregnancy, but some affected males present with severe neonatal encephalopathy, which usually results in death before age two. . (Mendelian genetics (2008).

3.3 Genomic Imprinting

For a majority of autosomal genes, the paternal and maternal alleles are both expressed. However, a small portion of genes are expressed in a parent-of-origin-specific manner. For example, gene H19 on Chromosome 11 is only expressed from the maternal allele. In contrast, IGF2 on the same chromosome is only expressed fromthe paternal allele. This phenomenon is referred to as genomic imprinting. Prader–Willi syndrome is a typical example of a disorder of genomic imprinting. Prader–Willi syndrome is characterized by hypotonia, short stature, sity, and small hands and feet. Hypogonadism retardation also occur. The disorder resul expression of a gene on chromosome expressed from the paternal copy. A mutation can lead to Prader–Willi syndrome. common is deletion of the region on 15q mechanism is uniparental disomy, in which 15 are derived from the mother. Deletion of the

maternal uniparental disomy results in a different Angelman syndrome, characterized by delay, and poorly coordinated In summary, Mendelian disorders important component of pediatric The most critical diagnostic tool is the Being able to accurately analyze the tance can help making a diagnosis and at-risk family members. (Louis, Mosby , (2009).

Section Four :

4. 1 Conclusion

The incidences of genetic disorders are increasing year from year due to high rate of consanguinity and chronic exposure to various environmental pollutants. If such conditions persist, the percentage of genetic disorders will abruptly increase. In such communities awareness should be created against the negative effects of consanguinity and about the hazardous effects of various pollutants on incoming progeny. Families at risk are advised newborn screening as early detection, diagnosis, and intervention can prevent death or disability and enable children to reach their full potential . This review provides an evaluation of the most common autosomal single-genes disorders involved in human infertility. An increasing number of autosomic genes were reported to be expressed throughout the hypothalamic-pituitary–gonadal-out flow tract axis and to have critical roles in pubertal and reproductive deficiencies in humans. Mutations in these genes may be transmitted to the offspring by a dominant or a recessive inheritance. Although a large number of these genetic disorders can be treated by administering hormones such as pulsatile GnRH or exogenous gonadotrophins or by following different artificial procedures like ICSI, several other genetic defects may cause an untreatable infertility. In addition these artificial procedures do not avoid the transmission of these genetic abnormalities to the offspring who manifest with higher risk of infertility and congenital abnormalities. Consequently.(Bamshad MJ 2009) .

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