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Short Communication

Jewish Genetic Diseases

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Genes

What makes you, you? Your genes. Every human has a unique genetic code made of genes. Genes are the basic physical and functional unit of heredity and are made of DNA. Each gene ranges from a few hundred DNA bases to more than 2 million. A human being has between 20,000 to 25,000 genes. Each person inherits two copies of each gene, one copy from the mother and the other from the father. Most of our genes are the same; less than one percent of genes differ between people. These differing components are known as alleles. Alleles are forms of the same gene but with small differences in their DNA bases, and alleles are what make each one of us unique. One's genotype is the internal, inherited genetic code inside all living organisms. A phenotype is the outside, physical manifestation of those genes. Phenotype examples include skin, eye, and hair color. They are related to all that is physical, functional, or behavioral [1,2].

What is a Genetic Disease?

Genetic diseases are caused by an abnormality in a person's genetic makeup. This abnormality can be due to a tiny aberration in a single base in the DNA, or due to a chromosomal addition or subtraction of either a single or set of chromosomes. These diseases can be inherited from parents, acquired mutations in a pre-existing gene, a random occurrence, or environmentally caused. Inherited genetic disorders include single gene disorders or those that are multifactorial. They may arise from the chromosomes or mitochondria [3].

There are thousands of disorders related to single gene inheritance. Also known as Mendelian or monogenetic inheritance, single gene inheritance occurs when a mutation or change happens in the DNA sequence of a single gene. Single gene inheritance disorders can be autosomal dominant, autosomal recessive, or x-linked. Autosomal dominant disorders occur when one copy of a defective gene is passed from either parent to the child. Individuals with autosomal recessive disorders inherit two copies of a defective gene, one from each parent. X-linked disorders are those where defective genes are passed on from the mother to her child. Examples of single-gene diseases include Cystic Fibrosis, Fragile X Syndrome, and Alpha and Beta-thalassemias [3].

Multifactorial genetic disorders, also known as complex or polygenic inheritance, have several causes. Most disorders or diseases are due to mutations in multiple genes and environmental factors. Examples of multifactorial diseases include heart disease, breast cancer, diabetes, and Alzheimer's Disease [3].

Chromosomal Abnormalities [3]

Small Info Box: Chromosomes are located in the nucleus of the cell and made up of DNA (genetic material) and protein.

A chromosomal abnormality occurs when the structure or the number of chromosomes is atypical, or where parts of the chromosomes are exchanged (translocated). Examples of chromosomal abnormalities include Down syndrome (three copies of chromosome 21; also known as trisomy 21), Turner syndrome (45 chromosomes and missing one X), and Klinefelter syndrome (47 chromosomes and affected males have an extra X chromosome).

Mitochondrial Inheritance [3]

Small Info Box: Mitochondria are the rod or round organelles involved in cellular respiration. Each has between 5-10 pieces of DNA. Egg cells keep their mitochondria during fertilization. This type of DNA is always inherited from the mother.

Mitochondrial disorders occur when the non-nuclear DNA of the mitochondria develops mutations. Examples of mitochon-

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drial disorders include myoclonic epilepsy and Leber's hereditary optic atrophy.

Medical Genetic History of Jews

Jews are a religious and ethnic group that originated in the Middle East more than 4,000 years ago. Although Jews originated in the Middle East, the historical exiles of Jews from their homeland meant that almost all Jewish populations were widely dispersed. The study of population genetics investigated the origins of these disparate populations to determine if there was a common genetic heritage. Multiple studies of autosomal DNA show that the genetics of Ashkenazi, Sephardi, and Mizrachi Jews share ancestry despite the thousands of years of separation [4,5].

How did the Jews keep it, so to speak, "in the family" if they lived in various non-Jewish communities? Interfaith marriage in Judaism (intermarriage) was highly discouraged. In the Bible in Deuteronomy 7:3 it states: "You shall not intermarry with them; you shall not give your daughter to his son, and you shall not take his daughter for your son" [6]. As a result, Jewish law and custom prohibited marriage between a Jew and a non-Jew. It appears most Jews were careful to only marry other Jews in the subsequent millennia.

The Jewish Talmud discusses hereditary diseases including hemophilia, epilepsy, and leprosy [7]. While there were some in Jewish communities who were fearful of genetic testing due to concerns about medical racism and the threat of eugenics, the overall goal of identifying people at risk of either being born with or developing a genetic disease in the future propelled modern genetic testing programs [8].

There are approximately 10 million Ashkenazi Jews in the world today with close to 3 million living in Israel. Ashkenazi Jews descend from a small number of founders with a strong tradition of marriage within their own community (endogamy). This custom of faith created a much more homogenous genetic background as compared to other groups. There is a high incidence of rare genetic diseases within the Ashkenazi Jewish population as opposed to the larger population. The origin of currently investigated mutations can be traced back to the time period between the 9th and 14th centuries. The high frequency of specific genetic disorders occurring in the Ashkenazi Jewish population leads us to assume that a "founder" chromosome, carrying the disease allele, was in a very small group (estimated to be approximately 100 people) [9-11].

When a small group of individuals isolates themselves from a larger group, this new isolated group will resemble only the individuals in this distinct population. A founder mutation (or effect or variant) occurs when there is a genetic alteration caused by an ancestor carrier of an altered gene in an isolated group. This is known as the founder effect [12].

Each person has paired genes: one from the father and the other from the mother. Inheriting a genetic disease or condition depends on the type of chromosome affected (sex or non-sex chromosome). An autosomal disorder is when there is an abnormal gene on one of the first 22 (non-sex) chromosomes. The trait may be dominant or recessive [13].

A **carrier** is a person who has a change in only one gene. Carriers are healthy people who are at risk of passing this mutation on to their children. Carrier frequency tells us how often a mutated gene is present in a specific group. If both parents are carriers of a defective or mutated gene, there is a 25% chance they will give birth to an affected child, a 50% chance they will give birth to a carrier (like themselves), and a 25% chance of giving birth to a child who is neither affected nor a carrier [14].

Genetic Diseases in the Ashkenazi Jewish Community

Many genetic disorders affecting the Ashkenazi Jewish community are lysosomal or non-lysosomal storage disorders. Lysosomes are cell organelles and contain enzymes that metabolize lipids, glycoproteins, or mucopolysaccharides. They function as a recycling center. If any of the enzymes are missing or defective due to a genetic mutation, these molecules continue to accumulate inside the cell, eventually destroying it. These disorders can be caused by recessive or dominant genes. Lysosomal storage diseases that affect the Ashkenazi Jewish population include Tay Sachs (recessive), Gaucher's (recessive), Niemann-Pick (recessive), and Mucolipidosis (recessive). Non-lysosomal storage diseases affecting the Ashkenazi Jewish populations include Bloom Syndrome (recessive), Fanconi Anemia Type C (recessive), Canavan (recessive), and Familial Dysautonomia (recessive. [14,15].

Autosomal Recessive Diseases

An individual must inherit two mutations of the same disease for a genetic recessive disease to occur. The following diseases are especially common in Ashkenazi Jews due to high carrier frequency*.

Gaucher Disease (1 in 15)

Gaucher (pronounced go-shay) Disease can be classified into three different types due to a deficiency of the glucocerebrosidase (GCase) enzyme. Ashkenazi Jews most commonly present with Type 1 Gaucher Disease. Features include an enlarged, overactive, and painful spleen, low white blood cell count, and anemia. Bone deterioration causing disability and pain may also be present. Symptoms can appear anytime from childhood to adulthood and progression of the disease is variable. Enzyme replacement therapy can help prevent or lessen the severity of this disease. Partial or full splenectomy, blood transfusions, joint replacement, and FDA-approved *eliglustat tartrate* are among the treatments for Gaucher Disease. Individuals who present with Gaucher Disease Type 2 and 3 may suffer from profound brain damage, for which there is currently no treatment [16].

Cystic Fibrosis (1 in 24)

Cystic Fibrosis (CF) affects multiple body systems as an accumulation of thick, sticky mucus that damages the lungs and other internal organs. This results in chronic lung infections, wheezing, year-round allergies, and a progressive decrease in lung function. Gastrointestinal symptoms include recurrent pancreatitis, foul, greasy bowel movements, chronic constipation, and diabetic-like symptoms such as constant thirst and urination. Patients may sweat excessively, and their sweat may "taste" very salty. Due to impaired absorption, patients with CF have poor growth. Chronic infections, declining lung function, and poor nutritional absorption lead to a shortened lifespan. The carrier test has a 97% detection rate for Ashkenazi Jews [17].

Tay-Sachs Disease (1 in 30)

Tay-Sachs is a severe neurodegenerative disease with deterioration of neurons in the brain and spinal cord due to a lack of the hexosaminidase (Hex A) enzyme. An infant with Tay-Sachs

develops normally until four to six months of age, and then the Central Nervous System (CNS) begins to degenerate. The most common first symptom, prior to CNS deterioration, is a cherry-red spot on the back of the eye. Early symptoms seen in these infants include mild muscle weakness, twitching or myoclonic jerks, and an exaggerated startle response. The baby then develops seizures, spasticity, loss of all motor skills, deafness, blindness, and non-responsiveness with death at about age four or five. There is currently no cure for Tay-Sachs [18].

Familial Dysautonomia (1 in 35)

Familial Dysautonomia (FD) causes malfunctions in the nerves responsible for most involuntary body functions of the autonomic nervous system. This affects the body's stress response, blood pressure, regulation of body temperature, and swallowing. Symptoms include poor weight gain, indifference to pain, gastrointestinal issues, and the inability to produce tears when crying. Prior to 1960, 50% of affected individuals died before age five. People with this disease have a shortened lifespan [19].

Spinal Muscular Atrophy (1 in 76 Ashkenazi; 1 in 34 Sephardi)

Spinal Muscular Atrophy (SMA) is characterized by loss of control of muscle movement with reduction of motor neurons in the brain and spinal cord. Physical and speech therapy, assistive devices to aid in functional independence, and proper nutrition are some of the treatments used for patients with SMA. In December 2016, the Food and Drug Administration (FDA) approved nusinersen (Spinraza), a drug injected into the fluid surrounding the spinal cord as a treatment for children and adults with SMA. Infants and children respond best to this treatment as compared to adults. In May 2019, the FDA approved a gene therapy called Zolgensma (onasemnogene abeparovec-xioi) for children under age two with infantile SMA. This gene therapy delivers a virus to specific motor neurons to improve muscle movement, muscle function, and patient survival. The cost for Zolgensma is $2 million, and this drug received tremendous media attention when a young Jewish baby girl with SMA crowdfunded $2.2 million from 23,000 donors in under five days. The baby received the treatment merely days before turning two years old. Besides this new genetic therapy, there currently is no cure for SMA. [20,21]

Canavan Disease (1 in 50)

Similar to Tay Sachs, Canavan Disease is a progressive, noncurable, neurological disorder. Oligodendrocytes, the cells responsible for making myelin sheaths to cover the axon, cannot complete their task due to a mutation in the enzyme aspartoacylase. The brain degenerates into spongy tissue. Symptoms usually begin the first three to six months of the infant's life, and signs and symptoms include an abnormally large and poorly controlled head, lack of motor development, weak or stiff muscle tone, feeding difficulties, blindness, deafness, and paralysis. Death usually occurs at age four to five years. There is no cure [22].

Fanconi Anemia – Type C (1 in 82)

Fanconi anemia affects the bone marrow, decreasing the production of white cells, red blood cells, and platelets. This condition is diagnosed in childhood rather than during the infancy stage. Symptoms include abnormal heart, lungs, and gastrointestinal tract, characteristic café au lait spots, vitiligo, deafness, short stature, improperly formed kidneys, and intellectual and learning disabilities. Scoliosis, missing, extra, or misshapen bones in the arms and hands are present in this disease. Fanconi Anemia is associated with a predisposition to leukemia and other cancers. There is no cure; treatment is limited to symptomatic care [23].

Mucolipidosis IV (1 in 92)

Mucolipidosis is characterized by an accumulation of abnormal amounts of lipids and carbohydrates in cells, damaging the cells. There are four types of Mucolipidosis, and in type IV, manifestations of the disease can begin in early infancy. Symptoms include a cloudy cornea and profound motor and developmental delays as disease progression causes a crippling of the CNS. Most children with this disease never walk, and some are severely developmentally delayed by age three. Treatments include supportive care and addressing specific symptoms. There currently is no cure [24].

Niemann-Pick Disease – Type A (1 in 98)

Niemann-Pick is a progressive neurodegenerative disease. It is caused by a buildup of lipids in the brain, spleen, liver, lungs, and bone marrow and a deficiency in the enzyme sphingomyelinase. This enzyme deficiency allows for the continual toxic build-up of sphingomyelin, a fatty substance contained in every cell of the body. There are several variations of Niemann-Pick Disease; Type A is the one most frequently found among Ashkenazi Jews. Death occurs between 18 months and three years of age. At age six months, infants will have recurrent vomiting, lack of muscle control, enlarged spleens and livers, swollen lymph nodes, and profound brain damage. Type B and Type C are less common in Jewish populations. Both occur past infancy. There is no cure or treatment for Type A. For Type B, there have been some treatment attempts such as bone marrow transplants, enzyme, and gene therapy [25].

Bloom Syndrome (1 in 117)

Blood Syndrome is characterized by short stature, and those affected record height and weight in the third percentile starting from birth. These individuals rarely reach a height of five feet tall during adulthood. Other signs and symptoms include reddened patches on the nose, cheeks, and skin, telangiectasias (clusters of enlarged blood vessels) in the eyes or on the skin, as well as hypo or hyperpigmentation. This disorder is rare in the general population. Bloom Syndrome greatly increases the risk of any cancer, with cancer developing earlier than the general population, and developing more than one type of cancer. There is no cure: treatment is limited to symptomatic care [26].

Autosomal Dominant Diseases

An autosomal dominant disease occurs when only one abnormal gene from one parent can cause disease even though the matching gene from the other parent is normal. In this situation, the abnormal gene dominates over the healthy gene. A parent with an autosomal dominant disease has a 50% chance of giving birth to a child who will have this disease. This is true for each pregnancy. A baby who does not inherit the abnormal gene will not develop or be able to pass on the disease. This disease can also happen in a child when neither parent has the abnormal gene. If the child is diagnosed with an autosomal dominant disease, the parents should be tested [27].

There are autosomal dominant diseases that are more prevalent in the Ashkenazi Jewish population. Some of the more common ones are:

Breast Cancer (BRCA1/2 incidence 1 in 40)

The BRCA genetic mutation increases the risk for melanoma, breast (female and male), ovarian, prostate, and pancreatic cancers in Ashkenazi Jews at more than 10 times the rate than the general population. There are three specific mutations (two in the BRCA1 gene and one in the BRCA2 gene) seen in the Ashkenazi Jewish population. Jewish men can also inherit BRCA2, and to a lesser extent, BRCA1, which increases their risk for breast and prostate cancer. Both men and women are at increased risk for pancreatic cancer [28].

Gastro-Intestinal Cancers

There are two genetic mutations in Ashkenazi Jews linked to gastrointestinal cancers. One is known as APC (Adenomatous Polyposis Coli), which is found in about 6% of Ashkenazi Jews, increases the risk of colon cancer, and is double the risk of the general population. The second genetic mutation is HNPCC (Hereditary Nonpolyposis Colorectal Cancer or Lynch Syndrome), and this raises the risk of colon cancer at a much younger age (below 40 years old). The HNPCC mutation is also associated with other gastrointestinal cancers, including stomach, small intestine, bile duct, and pancreatic cancers. In addition, this mutation raises the risk of reproductive cancers and brain cancer [29].

Sephardi Genetic Diseases

Sephardi Jews have their own set of distinct genetic diseases based on their country of origin.

Beta-Thalassemia (1 in 30 carries/ 1 in 3,600 develops the disease)

Beta-thalassemia reduces the amount of hemoglobin found in the blood. The earlier the disease manifests, the more severe the condition. Symptoms of early-onset Thalassemia include anemia, weakness, jaundice, and failure to thrive. Patients may require multiple blood transfusions. Later onset of this disease has a milder manifestation with moderate anemia and bone abnormalities [30].

Familial Mediterranean fever (1 in 14 Sephardic, 1 in 15 Armenian and Turkish descent)

This disease affects North African (Moroccan, Tunisian, Libyan, Egyptian, Algerian) and Iraqi Jews, as well as those of Armenian and Turkish heritage. The disease is characterized by recurring 12 to 72-hour bouts of fever with painful inflammation in the chest, joints, or abdomen. This usually begins between ages five and 15. Prior to the attack, some patients have a prodrome, which is an uncomfortable feeling in the areas that will become inflamed in the attack. The attacks can vary in length of time and in severity, and the timing between attacks can vary as well. Without treatment to prevent attacks, protein deposits can build up in the body, especially in the kidneys, leading to kidney failure. Standard treatment is with Colchicine, and other treatments include medications that block interleukin-1 including canakinumab (Ilaris), rilonacept (Arcalyst), and anakinra (Kineret) [31,32].

Genetic Testing In Jewish Populations

Chromosomes were identified in the late 1800s and were linked to genetic diseases in the early 1900s. In the 1950s, scientists developed genetic testing for Down Syndrome, Duchenne muscular dystrophy, and cystic fibrosis. In the 1960s, genetic testing for diseases such as Phenylketonuria (PKU) was used to determine if a condition was a genetic disorder. Testing was done on newborn infants. Currently, there are more than 500 laboratories that perform genetic testing for more than 2,000 genetic conditions [33].

Genetic testing is divided into the following categories:

- **Diagnostic:** identifies the condition
- **Predictive (pre-symptomatic):** identifies genetic variations that increase the risk of developing a genetic disease
- **Carrier:** identifies genetics that can be passed on to the individual's children; either as a carrier or develop the disease
- **Prenatal:** done during pregnancy to identify disease in the fetus
- **Preimplantation:** determines if an embryo carries genetic disease, done prior to in vitro fertilization
- **Newborn:** tests infants for specific diseases within the first few days of birth

Some of these tests can be purchased or done directly by the consumer. Most require a medical professional to order and interpret. [33]

The American College of Obstetricians and Gynecologists (ACOG) recommends Ashkenazi pregnant individuals be offered screening as routine obstetrical care for diseases such as Tay-Sachs disease, Canavan Disease, Cystic Fibrosis, and Familial dysautonomia. Some advocate for additional testing for Bloom syndrome, Fanconi anemia, Gaucher, Mucolipidosis, Niemann-Pick, Maple syrup urine disease, Usher syndrome, Joubert syndrome, Glycogen storage disease, and Familial hyperinsulinism [34].

One of the first genetic tests, used in 1970, was used to identify carriers for Tay-Sachs disease. This had a tremendous impact on the incidence of this disease with a decrease in the amount of cases seen in the Ashkenazi Jewish community [35,36].

Dor Yeshorim (Upright Generation) was started by Rabbi Joseph Ekstein from Brooklyn, New York, in 1983. This program does anonymous genetic screening of individuals prior to marriage to determine their genetic status. Testing is usually done in large groups, such as high schools or *yeshiva*. The results are entered into a database and identified only with a unique PIN number that is given to the person who took the test. Most couples check their compatibility early during a dating relationship. If they are considering marriage, they call Dor Yeshorim and give their PIN numbers, and the organization checks if they are genetically compatible. If both individuals are carriers for a specific disease, the individuals are told the match is incompatible. If neither are carriers, or only one is a carrier, the match can proceed. Callers are not told which member is the carrier to prevent stigmatization of the individual or their family. By avoiding marriage between two carriers, the incidence of autonomous recessive disorders decreased dramatically [37].

This organization only screens for recessive genetic disorders. They currently test for Tay-Sachs, Familial dysautonomia, Cystic Fibrosis, Canavan disease, Glycogen storage disease type 1, Fanconi anemia type C, Bloom Syndrome, Niemann-Pick disease, Mucolipidosis type IV, and Gaucher (upon request). Dor Yeshorim does not screen for dominant gene mutations, even though these do occur in the Ashkenazi Jewish community [37].

JScreen, a new non-profit organization, tests for more than 200 genetic conditions. While most genetic testing is done in a large community setting (Dor Yeshorim) or in a doctor's office, JScreen is done in the privacy of an individual's own home. They screen for over 200 recessive genetic diseases that are common in Ashkenazi, Sephardi, and Mizrachi populations. Similar to Dor Yeshorim, JScreen offers tests for future reproductive recessive genetic disorders. JScreen also screens for common genetic markers for cancer in Ashkenazi Jewish individuals [38].

Ideally, carrier screening, and if necessary, counseling, should be done prior to getting pregnant. Dor Yeshorim, JScreen, and ACOG recommend this to allow individuals and couples to learn about their reproductive risks. If an individual is found to be a carrier for a specific genetic condition (whether recessive or dominant), they should inform their family at risk of carrying the same mutation to assess their own risk and do carrier screening. Screening is not mandatory, and an individual has the ability to decline any genetic test. If a couple is both found to be carriers, they should be offered genetic counseling. If one of the partners is a carrier, the other partner should be offered genetic testing to determine potential reproductive outcomes [34,37,38].

Web Resources for Jewish Genetic Diseases:

Jewish Genetic Diseases

https://www.jewishgeneticdiseases.org/jewish-genetic-diseases/

Dor Yeshurim

https://doryeshorim.org/

JScreen

www.jscreen.org

Gaucher

www.Gaucherdisease.org

*All carrier frequency information was retrieved from Mt. Sinai, NY [39].

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