

Biblical and Talmudic Human Genetics

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Neither the *Ta'nach* nor the Talmud is a scientific genetics textbook, yet each contains information relevant to human genetic health issues, and each makes note of various pathologies linked to defective genes. For example, from a hereditary viewpoint of the transmission of traits, recommendations are presented concerning which couples are suitable marriage partners and which are not. The first recorded case history of a genetically transmitted disease (i.e., hemophilia) is cited in the Talmud. The interactions between the environment and genetics (i.e., nature and nurture) in molding phenotype are noted, as well as hints for the newly discovered science of epigenetics. Rather a new science, epigenetics is the study of mechanisms that alter gene expression that can be transmitted from one generation to the next, but do not involve a change in the DNA sequence (i.e., are not mutagenic). Traits controlled by autosomes and by the X and Y sex chromosomes are discussed, as are sex-limited and sex-influenced traits. This manuscript reviews some of the human genetics noted in the *Ta'nach* and in the Talmud.

Multifactorial, Polygenic Traits

Gregor Mendel is credited with uncovering the principles of genetics, or the transmission of traits from one generation to the next. One of the several reasons presented to account for his success was that he selected a test organism, *Pisum sativum* (the garden pea plant), that exhibits contrasting characteristics - i.e., traits that were clearly “yes” or “no” situations, without blending and without producing intermediate traits. For example, for the trait of height, the plants were either tall or short; for the trait of pea coloration, the peas were either yellow or green, etc. In his studies, intermediate traits were not noted. In contrast, most human traits, such as height and skin color, vary continuously, as they are governed by a series of polygenes [1, 2].

Knowledge of the transmission of polygenic traits from parents to offspring was noted in Talmud Bechoros (45b), in which the following suggestions regarding marriage partners were presented: Reish Lakish said that a very tall man should not marry a very tall woman, lest a child as tall as a ship's mast emerge from them. Similarly, a dwarf should not marry a dwarf, lest a finger-sized child emerge from them. A very light skinned man should not marry a very light-skinned woman, lest an extremely white-skinned child will emerge from them. A very dark-skinned man should not marry a very dark-skinned woman, lest a very dark-skinned child emerge from them. The physical appearances of the offspring were presented as exaggerations to stress that individuals of marriageable age should try to produce offspring within the accepted norms of physical appearance. These enumerated human traits (i.e., height and skin color) are multifactorial, polygenic characteristics, influenced both by many genes and by environmental parameters

(e.g., nutrition, sunlight). Polygenic traits are controlled by two or more nonlinked, independently assorting genes, with each dominant allele exerting a small but equal contribution to the phenotype. The resultant phenotype is a summation of the contributions of all the genes, and the environment acts equally on all genes. The number of phenotypic classes within a polygenic trait assumes a bell-shaped distribution [1, 2].

Another suggestion regarding the selection of a marriage partner was proposed by Rava (Yevamos 64b). A person should not marry into a family in which three brothers or sisters of the prospective bride were afflicted with leprosy or with a “falling sickness,” usually identified as epilepsy. It was presumed that the prospective bride would transmit these pathologies to her progeny. Epilepsy is a genetic disease; several variants of this disease are known, with defective genes on chromosomes 1, 2, 3, 6, 8, 10, 11, and 21 [3]. Leprosy, however, is not a genetic disease. In principal, there are two distinct types of leprosy: One is a spiritual leprosy induced by a person speaking *lashan hara* (e.g., as with Doeg (Sanhedrin 106b)), and the other is a microbial-based leprosy. The statement by Rava apparently referred to the type of leprosy caused by the bacterium, *Mycobacterium leprae*, with the genetic parameter accounting for susceptibility to infection by *M. leprae*, possibly due to the inheritance of defective gene(s) of the immune system.

Nature versus Nurture

During the Yom Kippur service, the *kohen gadol* scooped the incense (*ketores*) with his cupped hands and placed it into a ladle. The amount transferred to the ladle was dependent upon the physical size of the hands of the *kohen gadol*. Apparently, Rabbi Yismael ben Kimichis, a *kohen gadol*, had enormous hands, as he scooped four *kabin* of incense. He attributed the large size of his hands to his mother, “All women received *zarid*, but my mother's *zarid* rose up to the roof.” There are two explanations of *zarid*. One explanation is that *zarid* is a nourishing cereal that was customarily served to pregnant women. Rabbi Yismael attributed his physical stature to the high quality of foods that his mother consumed while pregnant with him. Another explanation is that *zarid* is “that which is winnowed,” referring to the quality of the specific sperm cell that fertilized the egg from which he was conceived. An ejaculate of male semen contains millions of sperm cells, of which only one fertilizes the egg. According to this explanation, Rabbi Yismael attributed his unusual physique to the superior quality of the sperm cell that fertilized his mother's egg from which he developed (Yoma, 47a; see Artscroll edition, 47a², see note 19). Both explanations are correct, as an individual is the product both of genetics and of the environment.

In the Talmud (Eduyos 4a), mention was made of polygenic traits transmitted from parents to children. Rabbi Akiva noted that a

father transmits beauty, physical strength, material wealth, wisdom, and long life to his son. Aside from wealth, the other four traits - overall appearance, physical stature, intelligence, and longevity - all have strong polygenic components coupled with environmental aspects [1, 2].

Many, but not all, behavioral traits are learned rather than are inherited. The Talmud in Bava Basra (100a) alluded to such behavioral traits with genetic components. It presented the suggestion that a man seeking to marry a specific woman should examine the character traits of her brothers. Furthermore, a *Baraisa* added that most sons resemble the brothers of the mother. A woman's brothers had the same upbringing that she herself received from her parents and that she, most likely, would transmit to her own children. If so, the values and character traits of the mother's brothers are an appropriate barometer of the behavioral character traits of her sons (Bava Basra 100a', Artscroll edition, see note 9). Although not specifically identified in the *gemora*, there are other behavioral traits with a strong genetic component, such as unipolar disorder, bipolar disorder, autism spectrum disorder, and schizophrenia [1, 2].

The interaction between genotype and phenotype, as mediated through the environment, is noted in *gemora* Shabbos (31a). A story is presented about an individual who asked Hillel many questions, with the intent to provoke Hillel to lose his temper. One question concerned why the eyes of Tarmodians were especially round and unattractive. These people dwelled in Tarmod, an oasis in the Syrian desert. Hillel explained that their rounded eyes also had smaller eye sockets, thereby affording them some protection from blowing sands during desert windstorms. Another question concerned why Africans have very wide feet. Hillel replied that these Africans lived in marshland and their wide feet protected them from sinking into the wet land. An alternative explanation was that their custom of not wearing shoes caused their feet to widen (Rashi). Although the relationship between these particular phenotypes and specific genes is not known, interactions between genes and environmental factors are well known, with natural selection favoring those genotypes most suited for a particular environment.

Another instance in which the Talmud discussed a trait with both genetic and environmental components involved the X-linked recessive gene for glucose-6-phosphate dehydrogenase (G6PD). Natural selection for the X-linked recessive gene for glucose-6-phosphate dehydrogenase (abbreviated G6PD) deficiency is seen in regions around the Mediterranean Sea where malaria is a major health risk. G6PD is a metabolic enzyme involved in red blood cell metabolism. The clinical severity of G6PD deficiency varies, with most individuals with G6PD deficiency being asymptomatic; severe symptoms, however, include hemolytic anemia. It has been suggested that the G6PD deficiency offers protection against malaria infection transmitted by mosquitoes carrying the protozoan, *Plasmodium falciparum*. Hemizygous G6PD-deficient males and homozygous G6PD-deficient females infected with *P. falciparum* are less prone to malaria than are non-G6PD-deficient individuals. Protozoan infection is usually not lethal in G6PD-deficient individuals. Jewish populations in Mediterranean areas that are endemic with malaria resemble their host populations, in which the mutant gene for G6PD deficiency is at an unusually high level, as it increases fitness in malarial environments [4].

Recessive Autosomal Traits

There are many causes of deafness, including a form that is related to a defective gene. In the general population, including the Jewish population, roughly 1 in 1,000 children are born deaf, with half resulting from hereditary deafness. In the late 1990s, a report emerged that identified a particular genetic mutation more common among deaf Jewish people than among deaf people from other backgrounds [5]. Familial deafness was cited in the Yerushalmi Talmud regarding the obligation of an individual to give *terumah*, with a distinction made between a person deaf from birth and a person born with normal hearing but who acquired deafness later in life (Terumos 1b). In addition, the sons of Rabbi Yochanan of Godgada were deaf, apparently indicating familial deafness (Tosefta, Terumos, chapter 1).

Dominant Autosomal Traits

In Dovid's later years, the Philistines again arose to make troubles for Israel. Dovid sent his troops into several battles, each against a specific giant from the family of Goliath. One of the gigantic warriors was described as "a man of huge dimensions, whose fingers and toes were six each, twenty four in number" (II Samuel 21: 20-21; I Chronicles 20:4-8). This trait, termed polydactyly, is manifested by extra fingers and toes and is controlled by the dominant mutant gene, *P*. Interestingly, the dominant allele (*P*) does not always express itself in the phenotype of the individual. Thus, a heterozygote (*Pp*) may or may not exhibit additional fingers and toes; this is termed reduced penetrance [6]. Thus, genotypically, both Goliath and his brother may have been heterozygotes (*Pp*), but only the brother exhibited the trait.

Y-Linked Traits

There are relatively few genes on the Y chromosome. The most studied gene is SRY, sex-determining region of the Y chromosome. This gene, located at the upper 0.5% of the Y chromosome, encodes the protein TDF, or testis determining factor, which programs the fetus's undifferentiated bipotential gonads to develop into testes, resulting in a male child. SRY, activated on about day 40 of fetal development, may explain the *gemora* in Berachos (60a), which stated that 3 days after intimacy, the husband should pray that his sperm remains viable and from day 3 to day 40, he should pray that the fetus is a healthy male. What is so special about day 40?

The developing fetus, in theory, closely resembles the first human who was created. Regarding the creation of the first human, it is stated: "He created them male and female" (Bereishis 5:2), indicating some sort of fusion of a male and a female (Berachos 61a). Similarly, until day 40, the human fetus is a potential fusion of two sexes - it contains bipotential gonads, which will develop either into the testes or the ovaries. It also contains two sets of tubes: the Wolffian ducts, which are the forerunners of the male reproductive system, and the Mullerian ducts, which are the forerunners of the female reproductive system. If the fetal somatic cells have a Y chromosome, then on day 40 of fetal development, the SRY gene is activated, and TDF is produced. TDF programs the bipotential gonads to form the testes, producing testosterone and Mullerian-inhibiting substance, which stimulates the Wolffian ducts to develop

into the male reproductive structures and induces the degeneration of the Mullerian ducts, respectively. If there is no Y chromosome, then, by default, the fetus develops into a female. The biochemical events leading to gender determination are ignited on day 40 of fetal development. Thus, after day 40, to pray for a child of a specific gender is useless, as the biochemical pathways for maleness or femaleness have been triggered and are irreversible.

X-linked Recessive Traits

The somatic (or body) cells of human females contain two X chromosomes, and those of a human male contain an X and a Y chromosome. Genes on the X chromosome are said to be X-linked. For a defective, recessive X-linked gene, a male will exhibit the pathology, as he has only one X chromosome. An example of a sex-linked recessive trait is red-green colorblindness, which is more common in males than in females. A human female with a defective recessive gene on only one of her X chromosomes will not manifest the pathology, as the woman has another X chromosome with the normal functioning gene. However, for this “carrier” female, if she marries a normal male, there is 50% chance that a son will be normal and a 50% chance that a son will show the pathology. Another sex-linked recessive trait is hemophilia, a bleeding disorder. For a woman who is a carrier for the hemophilic gene, of her sons, there is a 50% chance of the child being normal and a 50% of the child exhibiting hemophilia. Female hemophiliacs are rare, as both X chromosomes must carry the defective gene. A case history is presented in the Talmud (Yevamos 64b) that is credited as the first recorded report for the transmission of a genetic disease. The disease, thought to be hemophilia, involved the death of the eight-day-old infant following the *bris*. The case is related as follows: For it was taught in a *Baraisa*: If a woman had the first of her sons circumcised, and the child died as a result of the circumcision, and she then had the second of her sons circumcised, and this child, too, died as a result of the circumcision, then she should not have the third son circumcised. These are the words of Rebbe. But Rabban Shimon ben Gamliel said she should have the third son circumcised. If this son also dies, she should not have the fourth son circumcised. This familial disease, described as that of thin blood (*i.e.*, blood that did not coagulate), is thought to be hemophilia, with the mother being the carrier of the defective gene.

A little later in the *gemora*, the following case was noted: There was an incident with four sisters in Tzipori in which the first sister had her son circumcised, and he died; the second sister had her son circumcised, and he died; and the third sister had her son circumcised, and he died. When the fourth sister came before Rabban Shimon ben Gamliel and asked whether she should have her newborn son circumcised, he said to her, “Do not circumcise him.” This later case confirmed the familial transmission of this bleeding disease, with each sister being a carrier of a defective X-linked gene for hemophilia.

Shared Genes: *Arayos*

Ramban in *parashas Acharei Mos* (*Vayikra* 18:6-23) discussed the prohibition of *arayos*, or illicit sexual conduct between close

relatives, such as between a mother-in-law and a son-in-law, a father-in-law and a daughter-in-law, a parent and a child, or a brother and a sister. After noting the necessity of sexual relations for the preservation of the species, Ramban noted that the specific sexual relations specified in this *parasha* were forbidden as they produced children that will neither have a healthy existence nor succeed. Rabbeinu Bachya concurred and noted there is no preservation of the species from illicit sexual conduct between close relatives. Rabbi M.J. Broyde [7] suggested that Ramban maintained that one aspect for the inhibition of incest was because it eliminated genetic diversity.

Others, however, suggested that Ramban’s statement was directed to explain that incest led to the propagation of unhealthy progeny. Regarding these cases, the incest being referred to is that between blood relatives (e.g., between a brother and a sister, not between mother-in-law and son-in-law). Rabbi Y. Nachshoni [8] noted that it is apparent that what Ramban meant is that marriages between forbidden (blood) relatives do not succeed and do not produce a family, “as doctors have shown that such marriages harm the existence of the family.” On this topic, Rav Avigdor Miller [9] stated that among the benefits of avoiding *arayos* “is the prevention against a concentration of genetic defects. In the early days of Mankind’s history, men possessed extremely robust bodies; and down to Moshe they lived even more than 120 years. The sons of Jacob were therefore able to wed their sisters without apprehension, because their genes were much more perfect. When *HaShem* shortened men’s lives by adding various flaws to the human constitution, from then on interbreeding became highly undesirable because of the concentration of identical flaws of the siblings. In addition, the family of the Fathers were far superior in purity of character, and therefore they required less strictures to maintain their virtue.” According to Rav Miller, the accumulation of deleterious mutations increased the farther removed one is from the generations of the founding Patriarchs and Matriarchs, thus, negating the genetic health of consanguineous marriages.

Apparently, according to Rabbis Nachshoni and Miller [8, 9], the focus was on the subset of *arayos* in which the individuals share a high percentage of genes (*i.e.*, are blood relatives). Everyone carries recessive genes that are potentially harmful. However, the expression of a deleterious gene on one homologous chromosome would be masked by the normal dominant gene present on the homolog. A brother and sister share 50% of their genes, and a parent and child share 50% of their genes. For incest between such close relatives, there is a high probability of common deleterious recessive genes on similar pairs of homologous chromosomes coming together in the zygote, thereby producing a child with a genetic defect.

Although not related to *arayos*, a similar issue arises for *halachically* permitted marriages between close blood relatives, such as an uncle and his niece or between first cousins. An uncle and his blood-related niece and blood-related first cousins share one-eighth of their genes. Recognizing that such *halachically* permitted marriages often lead to offspring with genetic pathologies, Rav Waldenberg recommended against these marriages (Tzitz Eliezer 15: *simon* 44). Consanguinity at the level of first cousin unions increases the risk of congenital heart disease, a common birth defect [10]; fetal

and infant death [11]; and preterm birth at less than 33 weeks of gestation [12]. A study noted that the prevalence of childhood deafness in the Jewish population in Jerusalem declined as the rate of consanguinity of their parents decreased [13]. In the 1970s, an elevated risk for acute lymphoblastic leukemia was noted in the Jewish Syrian community in Brooklyn, NY. Over a 15-year period, six young females were diagnosed with leukemia, which was a frequency 30 times higher than the expected rate. The increased incidence of this blood cancer was correlated with the high frequency of first cousin marriages [14].

Sex-Influenced Traits

An incident regarding Elisha as he departed from Jericho is noted in II Kings 2:19-24. Outside of the city, youths accosted and derided him, saying, "Go away, bald one, go away, bald one." Elisha was bald. There are many causes of baldness, e.g., poor nutrition, illness, and medications, and the cause of Elisha's baldness is unknown. However, one type of baldness, termed male pattern baldness, is under genetic autosomal control. In sex-limited inheritance, an allele is dominant in one sex but recessive in the other sex. Thus, sex-influenced traits are phenotypically different in heterozygotes. Assume gene *B* codes for male pattern baldness and its allele *B'* for non-pattern baldness. *B* is dominant in males and recessive in females; *B'* is recessive both in males and females. A male *B'B* would be pattern bald and a female *B'B* would be non-pattern bald. Pattern baldness is governed by testosterone. The gene for male pattern baldness encodes the overproduction of the enzyme, 5-alpha-reductase, which converts testosterone to 5-alpha-dihydroxytestosterone, affecting cells of the scalp. Because males synthesize more testosterone than females, this condition is most evident in males [6].

Sex-Limited Traits

Sex-limited traits occur only in one gender and are controlled by autosomal genes. Examples of sex-limited traits include secondary sexual characteristics, such as breasts in the human female and facial and body hair and muscle mass in the human male. The sex hormones, testosterone produced in the testes and estrogen in ovaries, regulate the expression of sex-limited genes. In addition to their production in the gonads, humans produce lower levels of both sex hormones in the adrenal glands, which lie on top of the kidneys [6].

At times, an imbalance in these hormones may occur. If the level of estrogen is too high or is out of balance with the level of testosterone, the male may exhibit gynecomastia, or female-type breasts. Various health conditions and medications may evoke gynecomastia. An interesting trigger for gynecomastia is smoking marijuana, as one of the breakdown products in the combustion of marijuana is a xenoestrogen. Associated with gynecomastia is galactorrhea, or male lactation. The *gemora* in Shabbos (53b) related an unusual case history of a poor man, whose wife died and left an infant son who needed to be nursed. Unable to afford a wet nurse, the father grew female-type lactating breasts, which allowed him to nurse the infant. There is also a thought that Mordechai nursed Esther (Bereshis Rabbah 30:8)

Female facial hair may be due to an imbalance of sex hormones, in particular to elevated levels of testosterone, perhaps because of a tumor of the adrenal gland. Female facial hair is associated with polycystic ovarian disorder. As discussed in the *gemora* (Kiddushin 35b), a woman, but not a man, is permitted to destroy facial hair.

Genomic Imprinting

Rav Yochanan, an exceedingly handsome individual (Bava Metzia 84a), would sit by the women's *mikveh*. The women finished their immersions, exited the *mikveh*, and viewed Rav Yochanan. Because of their viewing this handsome sage, they subsequently produced exceedingly beautiful progeny (Berachos 20a). Apparently, viewing this sage was a determining factor in the physical appearance of their offspring. A related incident is noted in Yalkut Shmoni (*parashas Nasso* 606) regarding a black Arab king and black queen. The queen gave birth to a white baby, and the concerned king, who initially wanted his wife executed, asked Rabbi Akiva what the possibility was of this occurrence. Rabbi Akiva questioned the color scheme of the bedroom - was it painted black or white? The king replied it was white, to which Rabbi Akiva replied that, apparently, the thoughts of the queen when she was intimate with the king were focused on the white walls, thereby influencing the pigmentation of the child who was conceived. The Yalkut Shmoni concluded that if the reader is surprised with this occurrence, he should examine the story of Yakov and the cut sticks presented before the breeding sheep. Two recent articles have explained the incident of Yakov and the sheep as a case of genomic imprinting [15, 16]. Genomic imprinting, a rather new concept in genetics, refers to the situation in which a segment of DNA is marked (i.e., a gene is down-regulated or up-regulated), and that imprint is retained and recognized through the life of the organism that inherited the marked DNA. Transgenerational transmission of imprinted genes from grandparents to parents to grandchildren has been shown [17]. Thus, by regulating the activity of a gene, the phenotype of an organism may be altered without changing its genotype through mutation (i.e., by altering the sequence of nitrogenous bases in the gene) [6]. For the two cases presented above, i.e., the women who viewed Rav Yochanan and the black queen who viewed the white walls, their feelings were so intense that biochemical events were ignited to mediate gene activities, which were transmitted to their progeny. For example, the period preceding the Six Day war was nerve-racking, as the fate of the State of Israel seemed to hang in the balance. Israeli women in the second month of pregnancy, when exposed to the psychological stress and anxiety of being in the war zone, gave birth to children who eventually developed schizophrenia. Female offspring were 4.3 times more likely to develop schizophrenia, whereas male offspring were 1.2 times more likely. Apparently, the excessive stress hormones produced in the pregnant mothers were responsible for gene imprinting in the fetuses [18].

Chromosomal Aberrations

The *gemora* (Shabbos 66b) discusses the permissibility of a woman carrying a "preserving stone" on *shabbos*. Such stones were believed to prevent miscarriage, and the importance of wearing it may be more psychological than physiological. A woman wore this stone

even on the possibility of pregnancy, so if actually pregnant, she would not miscarry. This case applied to a woman genetically predisposed to miscarriages, i.e., she was from a family whose females often miscarried (Artscroll edition, 66b⁴, see note #25). The incidence of aneuploidy, a significant cause of miscarriages, increases in maturing oocytes as a function of female age. Furthermore, females designated as inversion heterozygotes and translocation heterozygotes have an increased tendency to produce oocytes with unusual chromosomal numbers. Although the *gemora* noted only females, increasing age of the male and inversion heterozygotes and translocation heterozygotes in the male also may cause miscarriage of the fetus [6].

Concluding Remarks

The subject matter discussed above is interesting in itself; however, a basic knowledge of science adds to the understanding of these topics. Neither the Torah nor the Talmud are scientific sources and medical issues are discussed only in brief. Background knowledge in the sciences can add depth to such medical topics, as the Torah and science are not opposing entities. The *Torah U'Mada* approach has merit in that it deepens the analyses of such themes cited in the *Ta'nach* and in the Talmud.

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