

Letter to My Children

Genetic Considerations in Reproduction

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Dear Children (and other young adults of reproductive age):

You may soon attempt to start a family of your own. Congratulations! I think that bearing and raising children is one of the most wonderful experiences in life.

Virtually all parents want to have healthy and strong children. To me, this desire is normal and good. Unfortunately, a small fraction of children (approximately 5% -- one in twenty) are born with serious health problems or disabilities. While we all hope for the best in reproduction, it would be a big mistake to think that this couldn't happen to you. The parents of sick and disabled babies are often themselves healthy and unsuspecting. I'm sure that you would do your best to care for any children born to you, but it is smart and wise for all prospective parents to take actions to maximize their chances of having healthy children.

Some of these actions involve the health of the mother during pregnancy. A pregnant woman needs to visit her doctor for regular checkups. She also needs to be especially careful about what she eats and drinks, and to get appropriate exercise. This prenatal health care is very important. However, since I am a geneticist, the remainder of this letter deals specifically with the genetic aspects of reproduction.

Three Essential Facts

Before going into details, it is important to consider three essential facts about genetics and reproduction.

First, there is no such thing as a genetically perfect child. Every person carries thousands of DNA sequence variants which detract, at least somewhat, from an unattainable perfect state of health and ability. This is true for the most powerful politicians, the most talented athletes, the richest business people and the smartest scientists. There are no exceptions. Therefore, while we should make efforts to avoid severe health problems, it makes no sense to worry and fret about having a "perfect" child -- no such creature exists.

Second, we don't yet (if we ever will) have the knowledge and technology to guarantee parents a healthy child. We can improve a couple's chances, but we can't eliminate all risk. Risk -- real risk -- is inherent in reproduction. This is a gamble that all parents take.

Third, no person has any control over their own DNA. Parents have some control over their children's DNA, but not the children themselves. Each child is born with a set of DNA sequences which will be with them their entire lives. They will need to do their best to cope with these DNA sequences. No child can be justly blamed for their own DNA sequences.

On now to a little basic genetics. Remember from your biology lessons in school that we have two copies of each of our ~25,000 genes, and that each person inherits half of their DNA from their mother and half from their father. Gregor Mendel, a Catholic Priest, was the first to discover these basic genetic rules. He did this through breeding experiments in his Abbey garden with pea plants. Remember also that the genetic information is encoded as the *sequence* of chemical units along the linear DNA molecule.

Many of the most severe genetic birth defects have one of three relatively simple patterns of inheritance: recessive, dominant or X-linked. Several thousand disorders with these three patterns of inheritance are known. Individually, each of the disorders is rare to very rare, but together they affect a significant fraction of newborns.

Recessive Inheritance

In recessive (or more formally autosomal recessive) inheritance both copies of the gene that is involved must be dysfunctional. People who carry one dysfunctional gene and one functional gene usually show few, if any, signs of the disease. Children affected with recessive disorders nearly always inherit one dysfunctional gene from each of their healthy, carrier parents.

The chance that a prospective father and mother who are both carriers of the same dysfunctional gene will have an affected child is 1 in 4 (25%). This 1 in 4 chance applies independently to each pregnancy, regardless of the outcome of previous pregnancies. For example, if such a couple's first three children are unaffected, the fourth child is not "due" to be affected. The fourth child has the same 25% chance of being affected as all children born to such a couple.

The average person is thought to carry at least several dysfunctional genes which can lead to children with severe recessive disease or disability. Usually, the father and mother carry different dysfunctional genes and are therefore at very low risk for having a child with a recessive disorder. But occasionally (in roughly 1 out of 30 couples or 3%), both father and mother carry the same dysfunctional gene. This number is so high because some dysfunctional genes, like for example those responsible for cystic fibrosis, deafness and sickle cell anemia, are present at relatively high frequencies in American populations.

Due to the requirement that both father and mother carry the same dysfunctional gene, and because even with such a couple, only 1 in 4 children will on the average be affected, individual carrier rates are *much* higher than birth rates for recessive diseases. For example, about 1/30 Americans of North European ancestry carry a dysfunctional gene for cystic fibrosis, whereas the birth rate is only about 1/3500.

Couples that are related to each other, like for example first cousins, are at a considerably higher risk than average couples for having children with recessive disease. This is because they are more likely to carry the same dysfunctional gene inherited from a common ancestor. Also, couples that are both from the same small town or island, or the same isolated religious or ethnic group are in general at modestly increased risk for having children with recessive disease.

Dominant Inheritance

In dominant inheritance, only one of the two copies of the gene needs to be dysfunctional in order for the person to be affected. A parent affected with a dominant disorder has a 50% chance of passing the dysfunctional gene on to each child. The number of affected individuals within a family with a dominantly inherited disorder is usually much higher than a family with a recessively inherited disorder.

At a very low but finite rate, a gene passed on from a parent to a child will change. Geneticists call these normal and natural changes mutations. Rarely, a new (also called *de novo*) mutation will result in a healthier, stronger person. But in the great majority of cases, new mutations result in either no appreciable change in health or in reduced health. This is unpleasant, but it is the way nature works. Sometimes with dominant disorders, a sick child may be born to parents who are healthy. This is because the child receives a *de novo* mutation.

Quite often, the severity of the disorder will have a wide variability even among those who carry exactly the same mutation(s). For example, one child in a family with a dominant disorder may require hospitalization, while a sibling, who inherited the same dysfunctional gene, may require only minor treatment. This is because other DNA sequences and non-genetic, sometimes called environmental, factors modify the impact of the dysfunctional gene. Sometimes a mostly health parent who carries a dysfunctional gene for a dominant disorder will have a child who is more severely affected.

X-linked Inheritance

An exception to the rule that people have two copies of each gene is for the genes located on the sex chromosomes in males. Humans have 23 pairs of chromosomes: 22 pairs of autosomes and two sex chromosomes, the X and Y chromosomes. Each healthy person, regardless of gender, has two copies of each of the autosomes, but females have two copies of the X chromosome and no Y chromosome, and males have one X and one Y chromosome. Boys inherit their X chromosomes only from their mothers. The X chromosome contains many genes, but the Y chromosome contains just a few.

A disease which is caused by a dysfunctional gene located on the X chromosome usually shows X-linked recessive inheritance. In this type of inheritance, males are affected much more often than females. This is because females usually carry at most one copy of the dysfunctional gene and one normal gene. But males with the dysfunctional gene have no normal copy of the gene to compensate. Male children of carrier mothers are at a 50% risk of being affected. Female children can be at most carriers, unless their fathers are also affected. X-linked dominant inheritance is also known, but is quite rare compared to X-linked recessive.

Many forms of mental retardation exhibit X-linked recessive inheritance. This is why the incidence of retardation in boys is higher than in girls. Interestingly, some of the genes that are important in color vision are also located on the X chromosome. This is why boys are more often color blind than girls, and why females generally have a more acute sense of color than males.

Complex Inheritance

Many of our most common health problems such as asthma, diabetes, and heart disease (to mention just a few) have more complex patterns of inheritance than simple recessive, dominant and X-linked. Multiple genes are involved, and non-genetic factors are generally stronger. Researchers are making good progress in unraveling the genetics of complex disorders, but our knowledge is still puny. At this point there is little that can be done to improve the chances of bearing children who will be free from these complex disorders.

Last, and perhaps most importantly, I'll cover the actions that prospective parents can take to improve their genetic chances of having a health baby. A good starting point is to spend a few minutes to consider the health problems that may run in your families. Health care professionals call this a person's family history.

Family History

To construct your family history, begin by drawing your family tree. Forms and programs for doing this, along with lots of other useful information are freely available from <http://www.hhs.gov/familyhistory/>. You will then need to jot down the major health problems experienced by each family member. You will probably want to talk with your parents and/or other family members when collecting the family history. It seems that in nearly every family, there is at least one person who has lots of information that they are willing to share. The more information you accumulate, the better.

Genetic Counseling

Next, I suggest that you set up an appointment with a professional geneticist such as a medical geneticist (a physician who specializes in genetics) or a genetic counselor. The visit will cost some money, but having a child with a severe health problem is far, far more costly. Bring your family histories with you to the counseling session. You may also want to bring your medical records. The Geneticist will give you information and advice about reproductive planning. The Geneticist may also recommend that you receive one or more genetic (DNA) tests.

I think it is important for a prospective reproductive couple to freely share their genetic information with each other. If for example, one person knows of strong family history of a dominant disorder, then the other person should know this before, not after, a baby is conceived. Sharing such sensitive information requires a great deal of trust. There will be some loss of privacy through the sharing, but for two people who really love each other this should not be an overwhelming obstacle. Please also keep in mind Essential Fact #1: There is no such thing as a genetically perfect person!

DNA Testing

DNA Testing is rapidly becoming more widely available and less expensive. The more parents know about their own genomes, the better will be their chances of having healthy children. A person's genome is just the sum total of that person's DNA. We don't yet have the technology to affordably sequence a person's entire genome, but we can perform many useful tests at modest expense.

I personally, recommend that people try to learn a little about their genomes each year through DNA testing. Unlike other types of health information, DNA sequences do not change over a person's lifetime. A test performed on a baby's DNA is completely valid and useful when that baby is 90 years old. Even better, since DNA sequences are passed on from parents to their children with almost no change, DNA testing in parents is directly and immediately relevant to their children and to other family members. DNA sequence information can therefore be accumulated gradually over an entire lifetime. DNA sequence information is a legacy that each person can pass on to their heirs. My company, PreventionGenetics, was the first to offer general, relatively inexpensive annual testing.

Other Considerations

The age at which people reproduce is important. The risk, for example, of having a child with the chromosomal disorder Down's Syndrome (characterized by three copies of chromosome 21 instead of the normal two), increases dramatically with increasing age of the mother. The risk is about 1/800 at maternal age 30, 1/400 at age 35, 1/100 at age 40, and 1/25 at age 45. Ideally, careers and other lifelong activities should be planned around reproduction.

Available evidence indicates that most mutations occur in fathers rather than mothers, and that the mutation rate increases with paternal age. Therefore although the age of the father at the time of reproduction is less crucial than the age of the mother, advanced paternal age is also a risk factor.

Both prospective mothers and fathers need to avoid environmental mutagens, such as mutagenic chemicals, and especially radiation. People whose jobs substantially increase their risk of exposure, such as X-ray technicians and nuclear power plant workers, need to take special precautions.

I highly recommend DNA Banking for all people. DNA Banking is just the long term storage of a person's DNA. The availability of parental DNA, even after a person's death, dramatically increases the efficiency of DNA testing in the children and other family members. Birth is a particularly convenient time to Bank DNA from a person. DNA can readily be extracted from the umbilical cord blood or from the placenta after the cord is cut without any possible discomfort or harm to the baby.

Options for Couples at Especially High Genetic Risk

If you are among the relatively few couples who are at especially high genetic risk of having a child with a severe health problem, then there are several options available to you. The most common options are briefly listed and described in the following table. Other, more exotic options also exist. A professional geneticist can explain the options to you in detail.

I attach no value judgments to these options. Note that only one of the options involves abortion. Therefore, even for those adamantly opposed to abortion, there are still several other ways to avoid having a child that is severely ill or disabled.

Option	Brief Description
Genetic Selection of Reproductive Partner	Although the practice is very rare today, in the future it may become much more common for people to select reproductive partners based on their DNA sequences. For example, people may avoid reproducing with partners who carry the same dysfunctional gene for recessive disorders.
Prenatal DNA Testing	After a woman becomes pregnant a small sample of fetal tissue may be removed through the processes of amniocentesis or chorionic villus sampling. DNA from the fetus can then be tested in the lab. The parents and health care providers can use the information to prepare for the care of a sick or disabled child, or the parents may decide to terminate the pregnancy through abortion and to try again to have a healthy child in the next pregnancy.

Adoption	Couples may decide to have no children of their own, but rather to adopt. Parents, for example, who carry dysfunctional genes for severe dominant disorders may find this option attractive.
Pre-implantation Genetic Diagnosis	In this technically demanding and expensive option, egg cells are removed from the mother, fertilized <i>in vitro</i> (outside the body) with sperm from the father, and allowed to divide to the 8 or 16 cell stage. A single cell is then removed from the embryo through micro-dissection, and the DNA in this single cell tested. Only healthy embryos are implanted back into the mother.

Concluding Remarks

In the past, when we didn't have any appreciable DNA testing capability, there was little that prospective parents could do to increase their genetic chances of having a healthy child, and therefore little reason for parents to even think about genetics. But over the last few decades this situation has changed dramatically. I'm sorry that this additional burden has been placed on your shoulders. Young adults already have enough problems and challenges. But old, experienced people don't have babies. Nature works the way it works, and we can't change it.

The purpose of this letter was not to frighten you, nor to make you shy away from reproduction. Rather, the purpose was to make you smarter and stronger. As I wrote at the beginning of the letter, reproduction is one of the most wonderful experiences in life. I hope you will be able to experience the birth of children of your own.

Love,
Dad

PS

This letter is just an elementary introduction to the topic of genetics and reproduction. I simplified some of the information. Much more detailed information is of course available. The list of education links on the PreventionGenetics web site is a nice starting place for those who would like to learn more.