The purpose of this article was to review many research articles to find an answer to the following question. “Is Autism Spectrum Disorder (ASD) inherited or are there other non-heritable factors that might increase the chances of having a child with ASD?” The authors use the term “heritable factors” to refer to what is “inherited” from parents—also called “genetic factors”. The authors used the term “non-heritable” to refer to factors which are not inherited—what some researchers call “environmental” factors. The authors reviewed many articles (genetic and environmental). They wanted to understand what we know about these factors and conditions which might explain why some children have ASD and others do not.

This study is a “review” article. The authors evaluated 200 published research and clinical articles on autism. They looked at articles starting 50 years ago up to the year 2002. All of the articles described possible genetic causes of autism, changes in the brain of people with autism, and environmental factors. Environmental factors are things that people are exposed to that may cause a negative reaction in their body. Common research methods that were used in the 200 articles the authors reviewed are described below.
Pathophysiology of ASD
Many research studies have tried to understand what biological and physical changes occur in the body of a person with ASD. They want to find out why people with ASD behave the way they do. This type of research is called “pathophysiology”. Researchers have looked at the brains of people with ASD who have died. People with ASD (or their families) give permission to doctors to study their bodies. Autopsies used to be the only way doctors could look at the brains of people with ASD. Brain-imaging technology has improved over the last 10-20 years and now it is possible to measure structures of the brain (neuro-anatomy) and brain activity (neuro-physiology) when the person with ASD is doing something. Researchers take pictures of the brain while people with ASD are communicating, interacting with each other, or doing repetitive behaviors. Some studies have looked at bio-chemical differences in the brains of people with ASD.

Documenting Autism Phenotype
A lot of important research has tried to describe the characteristics of people with ASD. The scientific term for the characteristics of people is phenotype. Research on Autism phenotype has focused on physical features and behaviors you can see. Studies of Autism phenotype also studied things you cannot see such as the characteristics of the individual’s body organs (anatomy) and how well they function (physiology). Clinical researchers carefully study the phenotype of individuals to help diagnose ASD or other illnesses people with ASD might have. Research on autism phenotype also tries to see what characteristics people with ASD have in common and what kinds of differences they have.

Genetic Studies
Because most of the characteristics in an individual are genetically inherited from birth parents a number of researchers have tried to find a genetic cause of Autism. The genotype of an individual is a term which describes what genetic instructions the individual inherited from his/her parents. Every person has a unique genetic code. Not all people with the same genotype look or act the same way. The way a person looks and acts are also influenced by the environment—where the person lives and what they are taught. Similarly, not all people who look alike have the same genotype. Doctors learn about the genotype of an individual when they do a medical history and ask questions to find out if other family members have ASD or related characteristics. When a clinician takes a complete history they ask about immediate family, extended family, and may go back many generations if needed. This is called a “pedigree”. A pedigree helps researchers see if there is a pattern of inheritance which runs in a family.

Looking for a genetic cause may involve tests such as chromosome analysis. Every person has 22 pairs of chromosomes and one pair of sex chromosomes. See Figure 1. Each chromosome
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carries many genes which provide specific genetic instructions for some part of the individual’s body and functions. There are genetic conditions like Down syndrome, where the person’s chromosomes are damaged or missing. Scientists can test for differences in the chromosomes of people. Autism scientists compare genetic findings from people with ASD to other people without ASD to look for similarities and differences in chromosomes. Autism scientists also can use more sophisticated tests to try to find other locations in the genetic code of people with ASD.

Another group of articles the authors looked at used a common research design known as “twin studies”. In twin studies, researchers study the genetic code of twins to see if they can find “markers” in the genes of children with ASD. They look to see if the same markers are present in twins who don’t have ASD. Twin studies can also look at possible environmental causes for ASD. This type of study has been very important in the search for causes of ASD.

Twin studies use “identical” twins because they have almost the same genetic code.

Identical twins are called monozygotic. Identical twins happen when one egg is fertilized by one sperm and then the egg splits into two fetuses. See Figure 2. Because each fetus has the same genetic code, the twins are “identical” in most of their features. Most of these studies looked at the concordance between the twins. Concordance is the chance that a pair of people will both have the same features. Because monozygotic twins are almost genetically identical, any genetic change seen in one would also be seen in the other. So, if ASD is caused by genetics and if it is identified in one twin, then the other twin should also have ASD. If the other twin does not have ASD, then this may be evidence that the environment might be more of a cause of ASD.

This type of research also looks at the differences between identical twins and “fraternal” twins. Fraternal twins are called dizygotic twins. This happens when two eggs are fertilized by two separate sperm. See Figure 3. Dizygotic twins grow together in the mother’s womb, but each fetus has its own genetic code. So, if the cause of ASD is genetic only, it is not likely that both fraternal twins will have ASD. It is possible that one twin may have ASD and the other won’t. Their “concordance” would be low. Researchers also compare data on twins with ASD with twins who don’t have ASD (as controls).
Studies of nonheritable (environmental) factors
The authors reviewed articles which looked at environmental factors that seemed to be related to the development of ASD. Environmental factors are things that people are exposed to. These nonheritable factors can range from what people eat to whether they are exposed to radiation because they live in a house that is built on a toxic waste dump. Environmental factors may affect the fetus when it is growing in the mother’s womb. These are called “prenatal” factors. Environmental factors may also affect children after they are born.

Results
(What did the Researchers find?)

Pathophysiology of ASD
Researchers believe that ASD is a result of abnormal changes in the brain of people with ASD. The authors found there was no section in the brain or change in the brain that was the same in all people with ASD they studied. They reviewed articles that found some evidence that brain volume (how big and heavy the brain is) may be larger for some people with ASD. Not every person with ASD had this same characteristic. It is not clear exactly how this affects the development of ASD in individuals who have larger brain volume. Other studies found the amygdala, a section of the brain, is abnormal in people with ASD. This is interesting because this part of the brain is believed to have a key role in the social behavior of people and primates. There have been functional imaging studies which show this part of the brain may be important to people with ASD in recognizing faces. Some autism researchers feel this might be part of the problem people with ASD have when interacting with people.

Other promising studies have looked at the relationship of bio-chemicals in the brain and inappropriate behaviors of people with ASD. Studies have reported higher levels of serotonin in the blood of people with ASD. This is interesting to autism researchers because serotonin is a brain chemical that helps people regulate their behavior. Too much serotonin may lead to inappropriate behaviors seen in some people with ASD. To confirm this idea, some clinical studies reported giving a medication that would reduce serotonin levels in people with ASD. The behaviors of these subjects improved. More studies in this area are needed.

The authors looked at studies that tried to identify abnormal changes in the brain which might explain why ASD develops. These studies found many potential abnormalities. However, no single change or abnormality has been found in all people with ASD. They feel this is evidence that there are probably multiple causes of ASD.

ASD subtypes and High-Risk Groups
Because ASD can vary in many ways (it has a broad phenotype), scientists have tried to be more systematic in grouping children with similar patterns of ASD behaviors (different autism phenotypes) into “subtypes”. Some of the groupings they used include (1) children who have cognitive impairment (mental retardation) or not, and how severe it is; (2) children
who have normal development up to 15-19 months and then regress, and individuals with ASD who have developmental delays since birth; (3) children with a variety of physiologic abnormalities (GI problems, seizures, differences in facial features). These sub-types are the reason researchers are now thinking that ASD has more than one cause.

Is ASD a genetic or inherited disorder?
The findings of a number of studies suggest there is a genetic component to ASD. Some studies are trying to identify “high-risk” groups. The only known group which has a higher risk for having ASD is siblings of individuals with ASD. This does not mean all siblings will have ASD, but their chances of having ASD are greater than in a family where there are no children with ASD.

Twin studies have looked at the ASD in identical (monozygotic) and fraternal ( dizygotic) twins. This is called the “concordance” rate for ASD. In four studies of twins, the percentage (%) of both twins having ASD is much higher in the twins that are identical. See Figure 4. These studies lead the researchers to believe that ASD is partially due to genetic inheritance.

Multiple Genetic Causes of ASD
Researchers have looked for every kind of genetic marker that could be identified as the “Autism Gene”. Not one gene or site has been found to be the cause of ASD. Several possible genetic contributors have been identified. Some studies suggest multiple genes combine, add to each other, and possibly change each other to create a genetic “susceptibility” to ASD. This means that under certain conditions an individual with specific gene combinations is more likely to develop ASD than someone who does not have the same gene combinations. We do not know exactly what genes are involved, in what combinations, and under what circumstances.

Chromosomal Abnormalities
In addition to the multi-gene model, rare chromosomal abnormalities have been found needing more research. Three chromosomes in particular have come up in these studies: Chromosome 7, 15, and the X chromosome (which identifies whether the child with be male or female). One of the most commonly reported is deletions (loss of parts) or duplications (added parts) to the end of chromosome 15. See
Environmental (nonheritable) Factors

Several articles were reviewed which suggest that environmental factors may play a role in the development of ASD. There is general agreement that environment by itself does not cause ASD without some genetic susceptibility. Like genetic studies, no single environmental factor or clusters of factors have been identified in the development of ASD. For example, a study in Sweden in 1994 reported a significantly greater number of children with ASD born to mothers who took Thalidomide (a drug for nausea) very early in pregnancy—20 to 24 days. This is the time when the neural tube develops which eventually becomes the brain and spinal cord for the fetus. Many researchers believe that exposure to environmental factors during the prenatal period can be especially harmful because the brain is developing. However, infections during pregnancy do not seem to be a direct cause of ASD. Studies looking at the relationship between the MMR vaccine and children developing ASD in early childhood have generally found that the MMR vaccine by itself is not likely a cause of ASD. However, scientists are looking at the possible role of mercury which is in food and in many vaccines as a possible environmental toxin related to ASD. More research is needed to better understand how these and other environmental factors play a part in causing ASD.

What does this mean for my child and my family?

Although researchers are exploring nearly every possible cause for autism, the results of decades of research suggest that ASD is a complex disorder with many causes. Both genetic and environmental factors seem to have a part in increasing the risk that a person will develop ASD. Future research will focused on understanding the combination of genetic and environmental factors which lead to the various sub-types of ASD. Your participation in this type of research may help a great deal to make these important discoveries.

If you are worried about being exposed to environmental toxins you should talk with your doctor.
**Glossary of Terms**

**Heredity** – The genes for a certain trait that are passed down in families from parents to children.

**Pathophysiology** – the study of the biological and physiological changes which occur because of a disease or resulting from an abnormal syndrome. Pathology is the study of the nature and cause of disease. Physiology refers to normal bodily functions.

**Neuro-pathology** – The study of diseases of the nervous system tissue (like the brain).

**Phenotype** – The physical, behavioral, biochemical and physiological characteristics of of an organism (individual) which can be observed or measured. Phenotypes are expressions of the genes of an individual.

**Genotype** – Describes the underlying genetic makeup of an individual. The genotype is the complete description of an individual’s genetic traits.

**Genes** – A unit of the genetic code. Genes are found on chromosomes within every cell and give specific instructions for what chemicals and proteins the body should make which guide how people look, behavior, and the functioning of their organs.

**Amygdala** – A small oval structure in the brain that plays a role in the sense of smell, motivation, and emotional behavior or feelings.

**Serotonin** – A type of brain chemical (neuro-transmitter) that is involved in behavior and mood regulation.

**Neuro-transmitters** – Chemicals in the brain that act as messengers relaying directions for thoughts, language, movements, and emotions in an individual.

**Genetic Susceptibility** – An inherited increase in the risk of developing a disease. Also referred to as a “genetic predisposition”.

**Chromosomes and Chromosomal Abnormalities** – Chromosomes are the structure within every cell that hold the genetic code for an individual. Abnormalities within chromosomes can be caused by an abnormal number of chromosomes or structural defect that can give rise to disorders and diseases within humans.

**Twin Studies** – A type of study used in scientific research to allow scientists to isolate genetic effects and environmental effects.

**Monozygotic Twins** – Also known as “identical twins”. Monozygotic twins are genetically very similar because they are the product of one egg fertilized by one sperm, which splits in two to form two fetuses. “Mono” means one.

**Dizygotic Twins** – Also known as “fraternal twins”. Dizygotic twins share some of the same genetic code because they are siblings, but they are not identical. Dizygotic twins are the product of two separate eggs fertilized by two separate sperm. “Di” means two.
Concordance – A measure used in genetics to show that both members of a pair of twins have a certain trait in common.

X-linked Abnormalities – Physical conditions/disorders related to genes that can only be found on the X-chromosome. The X-chromosome is one of the sex chromosomes passed on by parents (females have two X’s, while males have an X and a Y).

Interaction – A research term that refers to a factor which has a different effect depending on another factor.

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