Spina Bifida: A Review

An Honors Thesis (HONRS 499)
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ABSTRACT

Spina bifida is a birth defect of the neural tube that results in an incomplete closure of the spinal column. There are four distinct forms of spina bifida, and depending upon the form, there is an extensive range in the severity of the spinal injury, as well as the secondary conditions that often accompany spina bifida. Treatments for the disorder range from intensive surgical methods to the simple use of medications to treat secondary complications. Although contingent upon the severity of the physical and cognitive dysfunction, those suffering from spina bifida experience similar, though delayed, independence and growth from adolescence to adulthood. Though a vast amount of knowledge has been gained in recent decades, much knowledge is still needed in order to fully understand the molecular and genetic pathways, which lead to the development of spina bifida, and as this knowledge is gained, better treatment methods will result.
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INTRODUCTION AND HISTORY OF SPINA BIFIDA

Spina bifida is a congenital disorder that is inherited through a variety of different means that is characterized by an incomplete closure of the spinal column. Occurring in 3.4 of 10,000 live births in the United State, spina bifida is the most prevalent deficiency of the central nervous system birth defects (Children’s Hospital of Philadelphia, 2011). While the defective region can be found anywhere within the spinal column, spina bifida is most commonly observed effecting the lower thoracic, lumbar, and sacral portions of the spine (Sandler, 1997). Although not completely understood, spina bifida is thought to be inherited by way of familial genetic means, as well as a molecular response to fetal nutrition.

Figure 1. “A terracotta figure from Colima, Mexico (circa 200 A.D.), revealing findings classic for a child or adult with a spinal dysraphism. The forward posture with hands resting on the knees and the severe kyphosis of the lumbar spine are classic findings” (Ozek et al., 2008).

Though the exact cause and effective treatment methods of spina bifida have only recently been discovered, there is evidence of spina bifida documented dating back to ancient history, with sculptures depicting spina bifida dating as far back as 1500 B.C. (Figure 1). Fredrick Ruysch, Dutch surgeon, conducted the first extensive case studies on spina bifida in 1691, and these studies included an accurate assessment of the physical
description of the disorder, while stating that the condition was completely untreatable (Ozek et al., 2008). While there are a few examples of medical documentation of the disorder, there is a much smaller amount of historic literature that the disease's prevalence would suggest, indicating that the disease was considered to be "hopeless" and therefore not significant (Ozek et al., 2008).

Because little was known about the specific pathogenesis of the disorder, the most common method of surgical treatment involved the amputation of the external neural sac (Figure 2). The result of this method of treatment was nearly always fatal, due in large part to the leakage of cerebrospinal fluid from the sac, in addition to continued degeneration of the untreated hydrocephalus, a condition commonly associated with spina bifida in which the ventricles of the brain begin to fill and swell with an accumulation of cerebrospinal fluid (Ozek et al., 2008). It wasn't until the late nineteenth and early twentieth centuries when surgical and medical treatment methods began to offer hope of quality of life to patients with spina bifida, specifically with the work of Julius Arnold on the presence of brain stem anomalies associated with spina bifida (Ozek et al., 2008).

Figure 2. "An example of the "Rizzoli enterotome" for removing a myelomeningocele. The Instrument was applied and then "slowly" closed, causing the sac to necrose eventually fall off" (Ozek et al., 2008).

PHYSIOLOGY AND PATHOGENESIS
The central nervous system is the key component to life in many organisms, especially that of humans. The central nervous system is not only the source of all motor reactions within the body, but it also initiates and partially regulates the functioning of all systems within the body, including the cardiovascular and digestive systems. The source of the tissue, which eventually gives rise to the central nervous system, lies in the neural plate, which is initially adjacent to the ectodermal tissue. In order for the dorsal neural tube to properly close, the expression of several genes, as well as the presence of various signals, must be present, and, if these factors are present and active, the neural plate is able to elevate, eventually forming a neural tube, with the neural crest forming at the position of fusion of the original margins of the neural plate (Sanes et al., 2006).

Figure 3. “A: Four phases of primary neurulation in neural tube closure… Panels a–c are dorsal views, whereas panel d is a lateral view. a–c…B: Stages of neural tube closure in a transverse section” (Bloom et al., 2006).
However, due to the delicate nature of the spinal column, the slightest error in the events associated with its formation can lead to devastating results, as is the case with spina bifida. Although there are several distinguishing features between the different forms of the disease, all four types of spina bifida are associated with an incomplete closure of the neural tube, leading to a wide-range of associated effects, depending upon the severity of the opening (Chao et al., 2010). The incomplete closure of the neural tube generally occurs approximately between the twenty-sixth and twenty-eighth day of gestation, and can range from a slight opening in the bones of the spinal column, to a complete opening of the spinal cord (Tecklin, 2008), (Figure 4).

**Figure 4.** The incomplete closure of the neural tube occurring during the third and fourth weeks of gestation is the foundation of the central defect associated with spina bifida (Mayo Clinic, 2008).
Generally considered to be the least perilous form of spina bifida, and occurring in approximately ten percent of the population, spina bifida occulta is characterized by an imperfect closure of the vertebrae of the spinal column (Saluja, 1988). However, the meninges of the spine are not herniated and there is no exterior cyst associated with spina bifida occulta (Menkes et al., 2006). Most often, X-ray examinations are utilized as the chief diagnostic tool in cases of spina bifida occulta (Sandler, 1997). Commonly occurring in the sacral regions of the spinal cord, with the highest rate of individuals retaining the ability to walk, both with and without support, are those with injuries to the lower lumbo-sacral regions (Amari et al., 2010). Though little exterior evidence of the disorder is readily observable, there are a multitude of possible internal abnormalities, which may be present. These malformations range from fusion of the vertebral bodies, abnormal bone mass within the spinal canal, and an overall widening of the spinal canal, to serious malformations of the spinal cord such as the absence of nerve roots, shortening of the filum terminale (the sheath that continues subsequent to the final spinal nerve), and diastematomyelia, or the sagittal divide of the spinal cord (Menkes et al., 2006), (Kent and Carr, 2001). While there is a lack of external malformations due to the condition, often patients suffering from spina bifida occulta will have the presence of a dimple or a tuft of hair near the affected area of the spine (Ehlers, 1992).

Spina bifida occulta is commonly referred to as a “closed” spina bifida because the spinal cord is completely housed by the spinal column. Due to this feature of the condition, the symptoms, though ranging from patient to patient, can appear to be extremely mild. Neurological side effects may be present from birth, though many with the condition experience no adverse effects of the spinal malformations and therefore
may remain undiagnosed. It is, however, important to discover the presence of the condition in non-symptomatic children because the adolescent growth spurt could potentially lead to progressive loss of neural performance (Menkes, Sarnat, and Flores-Saranat, 2006). In the case of symptomatic patients, the most common form of treatment is through surgical means to repair the bone irregularities of the spinal column, in an effort to regain neural function; nevertheless, many patients whose symptoms are not severe enough to interfere with daily functioning are encouraged to forgo any surgical reparative measures, at least until the patient reaches adulthood (Medical Devices, 2010).

Spina bifida cystica, also referred to as myelomeningocele, is the most common central nervous system malformation, and is a direct result of the failure of caudal neurulation during the fourth week of gestation, resulting in the protrusion of the meninges through the vertebral column, leading to the development of a cerebrospinal fluid containing sac on the exterior of the back (Bruner et al., 1999), (Figure 5C). The level at which the spinal lesion occurs determines the effects of the deformity, as well as the extent of the effects, to a large extent. Eighty percent of all myelomeningocele occurrences appear in the lumbosacral region of the spine, and they produce a variety of symptoms, in accordance to their specific location within the lumbosacral region (Menkes et al., 2006). For example, patients who have lesions located at the S3 vertebrae and below typically possess normal function of the lower extremities, and a variable degree of renal and rectal incontinence, while those patients with lesions located at the L3 vertebrae and above experience complete incontinence, paraplegia, and are considered nonambulatory (Menkes et al., 2006).
Additionally, spina bifida cystica is widely associated with the development of hydrocephaly, which is characterized by the dilation of the ventricles of the brain, leading to the accumulation of excess cerebrospinal fluid (Leestma, 2008). This hydrocephalic condition is a direct result of the Chiari II malformation, a structural deficiency of the cerebellum characterized by the extension of brain tissue past the skull, through the foramen magnum, in addition to the incomplete structure of the cerebellar vermis, which is a nerve that joins the two halves of the cerebellum (NIH, 2011), (Bruner et al., 1999). After birth, effected infants typically undergo surgery in order to lessen the degree of severity of the spinal lesion. However, this surgical treatment typically results in the adverse progression of the hydrocephaly, necessitating the implantation of a ventricular shunt in order to drain the excessive amounts of cerebrospinal fluid accumulating in the patient (Bruner et al., 1999).

The third form of spina bifida, myelocystocele is the protrusion of the spinal cord through the incomplete closure of the spinal column, resulting in an external sac that contains both meninges and neural tissue (Menkes, Sarnat, and Flores-Saranat, 2006), (Figure 5B). Though a portion of the spinal cord is contained within the dorsal sac, the spinal cord can potentially continue below the location of the lesion. In cases of Myelocystocele, there is typically the presence of spinal-nerve paralysis, and as with other forms of spina bifida, myelocystocele is associated with hydrocephaly due to downwardly displaced hindbrain resulting from a Chiari II malformation (Bianchi, Crombleholme, and D’Alton, 2000).

Meningocele is the final and least prevalent form of spina bifida, accounting for only five percent of all cases of spina bifida (French, 1990). Characterized by the
protrusion of only the meninges and not neural tissue through the incompletely closed spinal column, meningocele is rarely associated with central nervous system deformities, and therefore rarely results in neurological dysfunction (Menkes et al., 2006), (Figure 5A). However, as is the case with the other three forms of spina bifida, the location of the lesion is in direct correlation to the severity of the symptoms accompanying the disorder. For example, though rare, in the case of meningocele occurring in the thoracic region of the spinal column, subarachnoid pleural fistula (an atypical linkage of the subarachnoid space and the pleural cavity) can occur following the rupturing of the meningocele into the pleural cavity, either by spontaneous or traumatic means (Kumar et al., 2010).

**Figure 5.** Diagrams of the four distinct forms of spina bifida: “(A) Meningocele. Through the bony defect (spina bifida), the meninges herniate and form a cystic sac filled with spinal fluid... (B): Myelomeningocele. The spinal cord is herniated into the sac and ends there or can continue in an abnormal way further downward. (C): Myelocystocele or syringomyelocele. The spinal cord shows hydromyelia; the posterior wall of the spinal cord is attached to the ectoderm and is undifferentiated. (D): Myelocele. The spinal cord is araphic; a cystic cavity is in front of the anterior wall of the spinal cord” (Menkes et al., 2006).
PATTERNS OF INHERITANCE

The development of condition of spina bifida is exceedingly multifaceted due to the varied means by which the disorder can be inherited. Although we now understand means by which spina bifida can occur, the exact mechanism of inheritance and subsequent affliction is not completely understood. One aspect, which complicates the complete understanding of the mechanism of inheritance of spina bifida, is the complex interactions, which are thought to occur between genetic and environmental factors. Much more research needs be performed before the medical community can declare with confidence the precise source of spina bifida.

The inheritance of spina bifida is partially associated with the genetic mutations. In several genes, specifically expressed in the dorsal neural tube at the early stages of development, particularly the SLUG and SNAIL genes, are significant for the specification of neural crest cells and the ultimate formation of the neural tube (Sanes et al., 2006). SLUG is a gene, which encodes a zinc finger protein transcription factor protein that is involved in the production and migration of the neural crest cells and the mesoderm, which becomes expressed in response to a key dorsalizing signal in the neural tube (Stegmann et al., 1999), (Jiang et al., 1998). The SLUG gene is also a zinc finger protein, but it acts as a repressor in transcription, and in organisms in which SLUG is absent, significant defects in the production of the mesoderm, which gives rise to the notochord and bones among many other things (Carver et al., 2001). Therefore it can be possible to either inherit a mutation in these particular genes for parental chromosomes or have a random mutation occur through the process of cellular division. However, it is possible to inherit the mutated genes, and remain unaffected by spina bifida due to a lack
of signaling factors. In the same fashion, it is possible to inherit a non-mutated genome, yet become afflicted by spina bifida due to environmental triggers (Genetics and Spina Bifida, 2009).

Another large risk factor in the development of spina bifida directly relates to the lifestyle choices of the mother both during the pregnancy as well as prior to conception. The use of folic acid has been verified to decrease the risk of neural tube defects by approximately fifty percent, with the key exposure period being four weeks prior to conception to eight weeks of gestation (Jentink et al., 2010). Although folic acid has been shown to decrease the baseline risk of inheriting spina bifida, inadequate data is present to prove a further decreasing effect on the conditions prevalence (Jentink et al., 2010). Currently, research is underway with the end-goal of determining additional dietary supplements which have the potential of further reducing the risk of spina bifida (Jentink et al., 2010).

In addition to genetic factors and the composition of the diet of both the mother and developing embryo, the overall health of the mother, both before and during the pregnancy also lays a very key role in the potential development of spina bifida. For example, women with pregestational diabetes are two to ten-fold more likely to give birth to a child with spina bifida, and while the exact mechanism is not understood, this increased risk is thought to be in direct correlation to the blood-glucose levels during the first trimester of pregnancy (Mitchell et al., 2004). Additionally, certain drugs, specifically those containing valproic acid, used to treat epilepsy, migraines, chronic pain, and bipolar disorder have also been linked to an increase in the risk of spina bifida by one to two percent, although the mechanism by which the malformation occurs has
not yet been established. A multitude of other factors, such as increase body mass, maternal diarrhea, and hyperthermia, have been associated with an increased risk of the development of spina bifida, though the associations are extremely loose and have not been fully investigated (Mitchell et al., 2004).
CLINICAL APPROACH

Diagnosis of spina bifida typically occurs with the utilization of sonograms for specific, distinguishing factors, as well as through the presence of alpha-fetoprotein in the amniotic fluid discovered through an amniocentesis (Brock, 1972). Alpha-fetoprotein is an embryo-specific protein that is normal in the early stages of fetal development but routinely dissipates in the typically developing fetus. However, elevations in alpha-fetoprotein are often detected in embryos with neural tube defects, and this elevation is believed to occur due to an absence of the SNAIL repressor, which typically appears in the final stages of embryonic life (Tomasi, 1977). One of the main treatments of spina bifida, depending upon the severity of the condition, is that of surgical closure of the spinal lesion. Typically, surgical closure of the effected area and ventricular shut placement, if necessary, occurs within forty-eight hours after birth. However, in addition to post gestational reparative treatment, spina bifida can also be treated via in utero surgical means (Mitchell et al., 2004).

Treatment of spina bifida is often a multifaceted undertaking, in that the foremost neural tube defect must be treated in conjunction with the treatment of the multiple side effects which often accompany spina bifida. Because spina bifida carries with it an extremely extensive range of severity and effects, based upon the location and extent of the spinal deformity, the treatment of spina bifida must be constructed on an individual basis, rather than the uniform treatment plan, which often accompanies other disorders. For instance, the removal of the external cyst present in many cases of spina bifida is a simple procedure that greatly adds to the quality of life of the patient. However, in some cases, the external cyst contains some portions of the spinal cord, and therefore removal
of this external structure has the potential of leading to further spinal dysfunction.

In some cases of spina bifida, the neural tube defect can be corrected, either in utero or shortly after birth. Recently, improvements to the process of spinal defect correction have been made, vastly increasing the success rate and recovery time. Denise Arajo Lapa Pedreira has developed a two-step approach to fetoscopic correction of spina bifida in which the main goal of the surgery is to protect the medulla from contact with the amniotic fluid, which is significant because a constant exposure of the spinal cord and medulla is associated with progressive neurological injury (Children’s Hospital of Philadelphia, 2011). The first step in the process involves the use of “gasless fetoscopy”, while using both air and fluid medium, with the objective of enveloping the medulla with tissue grafts. The second step occurs subsequent to birth, and entails a much more complicated surgical technique (Pedreira, 2010). This two step approach offers vast improvements in success rate as compared with the previously utilized, more complex “open” prenatal surgeries, in which the entirety of spinal corrections were performed on the fetus.

Depending upon the extent of neuronal dysfunction and spinal deformation, urinary and fecal incontinence is often associated with more severe cases of spina bifida. One means by which fecal and urinary incontinence are experimentally being treated is through a surgical means of nerve re-routing. Specifically, fully functional lumbar nerves are redirected to the sacral regions of the body, specifically targeting the bladder and colon (Peters et al., 2010), (Figure 6). Currently, the nerve reinnervation of the bladder and bowel has seen wide success, with 78% of American patients exhibiting a reproducible increase in bladder pressure and bowel function, while the nerve rerouting
has reached a success rate of 75% in China (Peters et al., 2010). A decrease in strength of the lower extremities is the most common complication associated with the surgical procedure, but this decrease in functionality has been found to primarily be a self-limiting side effect. While the rerouting of the lumbar nerves does appear to be extremely beneficial for those suffering from spina bifida, more research must be done, particularly in the areas of sphincter control and the definition of success, in order for the treatment to become more widely accessible.

Figure 6. A diagram of the lumbar to sacral nerve rerouting. In this specific instance, the L5 left ventral lumbar nerve has been diverted to the S2 sacral nerve and sequentially to the bladder in an effort to repair urinary incontinence (Peters et al., 2010).
While the most prevalent forms of spina bifida lead to neurological dysfunction of the limbs, the disorder is also commonly accompanied by secondary musculoskeletal aberrations, which can be tremendously problematic due to the primary neurological deformities of the limbs. These secondary musculoskeletal deformities include but are not limited to, general muscular and skeletal degeneration, general instability of the joints, bony torsional deformities, which are characterized by an excessive anatomical rotation of the proximal portion of a bone in relation to the distal most portion (Kelley et al., 2010), (Subburaj et al., 2009). Prior to operative correction of the malformation, in order to fully analyze the extent of the deformity, three-dimensional gait analysis is often utilized. There are multiple methods by which these secondary musculoskeletal deformities are corrected, including the conventional limb reconstruction, as well as the Ilizarov technique, in which an external apparatus of pins, rods, or fine wires are used to stabilize and reform the afflicted limb after surgery. The Ilizarov technique offers a desirable alternative to conventional surgical methods in that it provides a gradual correction of the abnormality, allowing for a less stressful transition for the nerves, vascularization, and soft connective tissues of the area. While the high level of pain associated with the Ilizarov technique is often viewed as a disadvantage of this method of reconstruction, the neural dysfunction associated with spina bifida often leads to a complete or partial liberation from pain (Kelley et al., 2010).
The transition from youth to adulthood is dependent upon maturation in several aspects of life in addition to the obvious physical development, including emotional growth, cognitive development, and behavioral autonomy (Friedman et al., 2009). Due to the extensive range in severity of spina bifida, both physically and cognitively, the effect that the disorder has on the afflicted individuals' lives can range quite dramatically from absolutely no hindrance to posing a complete obstacle to normal day-to-day functionality. Although, generally, increases in emotional, social, and behavioral independence and growth was observed in adolescents afflicted with spina bifida and peers of the same age with normal functionality, individuals with spina bifida generally lagged behind their peers in all aspects of autonomy development. The area in which individuals with spina bifida most significantly differed from their peers was that of independent decision-making (Friedman et al., 2009). Overall, males with spina bifida exhibited a lower rate of emotional independence than females, in addition to a lower rate of independent decision making from both their mothers and fathers. As would be expected, those individuals with lower than normal cognitive and verbal abilities appear to be at the greatest risk for a severe delay in the development of autonomy in the cognitive, behavioral, and emotional aspects of maturation (Friedman et al., 2009).

The many physical and mental problems that are commonly associated with Spina bifida has led to an overall limitation in the social participation of individuals afflicted with spina bifida, particularly in the case of young adults. This overall restriction is associated with a multitude of areas of life, including occupational, and social. For example, only twenty-eight percent of twenty-one year olds with spina bifida are living...
independently, whereas twenty-one is the mean age at which healthy adults begin living independently. Additionally, the unemployment rate of those with Spina bifida is fifty-three percent, versus the twenty-eight percent unemployment rate for the general U.S. population. The most common perceived cause of the limitations in interactions was the actual or perceived physical hindrance of the given activity, in addition to a lack of accessibility (Barf et al., 2009).
Although preventative measures cannot completely elevate the incidence of spina bifida, many measures can be taken to greatly decrease the risk of spina bifida in children. For instance, in 1997 Canada instated federal mandates for the fortification with folic acid of many cereal-based foods, as well as pasta, cornmeal, and white flour with folic acid (Wals et al., 2007). While there was no significant alteration in the prevalence rates of spina bifida between 1993-1997, there was a dramatic decrease in the conditions prevalence between 1997-2001. Furthermore, in Ontario, the blood folate levels of women of child bearing age increased by an average of one hundred fifty micrograms, though such a dramatic increase was not observed in all provinces (Wals et al., 2007).

It has been clearly documented that the use of folic acid, whether through supplementation or dietary intake, in the diet of women prior to conception and during pregnancy greatly reduces the risk of the development of neural tube defects. In fact, it has been estimated that nearly half of all cases of spina bifida could be prevented by the intake of folate supplements by pregnant women (Gilbert, 2010). The mechanism by which folic acid reduces the prevalence is not entirely comprehended; however, through the study of mice models, it has been suggested that there is expression of a folate receptor protein located on dorsal regions of the neural tube directly prior to fusion of the neural tube (Gilbert, 2010).

Due to this knowledge, the United Stated Food and Drug Administration mandated that folic acid be included in all enriched grain products by 1998; this following the 1992 recommendation by the FDA for all women of childbearing age to daily consume at least four hundred micrograms of folic acid. In the year following the
folic acid supplementation mandate, a thirty-one percent decrease in spina bifida's prevalence was observed. Furthermore, an additional ten percent decrease in the prevalence of spina bifida was observed in the six years following the mandate (Boulet et al., 2008). Although the decline in spina bifida was noted immediately after the FDA's mandate on the supplementation with folic acid, it has been observed that nearly two-thirds of all United States women of childbearing age receive less than the recommended four hundred micrograms of folic acid, which may be due to a variety of factors, such as the trend of dietary avoidance of carbohydrates, as well as an overall alteration in the use of dietary supplements (Boulet et al., 2008).

The prevalence of children suffering from spina bifida between the ages of four and seven was higher in non-Hispanic black children than among non-Hispanic white children; additionally, among children from zero to nineteen years of age, it was found that a lower prevalence of spina bifida is observed in non-Hispanic black children than in non-Hispanic white children (Shin et al., 2010). This is most likely tied to a socioeconomic issue in which there is a lower birth rate for spina bifida afflicted children, as well as a lower survival rate due to an overall lack of readily-available healthcare. Though the prevalence study was published in 2010, the data presented is from 1991-2002. Thus it could be easily concluded that as healthcare becomes more accessible to all demographics, the prevalence of spina bifida will likely become more equal among all socioeconomic groups.
CURRENT RESEARCH AND FUTURE PROSPECTS

Through scientific inquisition, much knowledge has been gained on the cause and pathogenesis of spina bifida. However, in order to more comprehensively treat and eventually eradicate the disorder, much more research must be done to gain further information as to the specific genetic triggers and molecular pathways that lead to the development of spina bifida. Though a wide variety of research has been recently published and is currently underway, the foremost component of these studies appears to be the genetic aspects of the development of the disorder. However, the majority of the research currently underway is being conducted with the utilization of animal models rather than progressing to human spina bifida patients, due in large part to the highly experimental nature of the research.

The Sonic Hedgehog signally pathway is essential for the natural development and patterning of multiple organs, such as the nervous system. Therefore, the inappropriate activation of the pathway has the potential to cause a wide variety of neural tube defects, including spina bifida. Through experimentation, Patterson et al. recently discovered that the Tulp3 gene often acts as a downstream negative regulator of the sonic hedgehog pathway, and therefore its presence is associated with the presence of spina bifida. A new mouse mutant named hitchhiker, which exhibits several developmental aberrations including neural tube defects, was analyzed and a strong hypomorphic mutation in the Tulp3 gene, which exhibited ventralization of the caudal spinal cord, was characterized (Patterson et al., 2009). This new information regarding the association between neural tube defects and the mutation of the Tulp3 gene has the potential of leading to effective treatments of the defects by way of specifically targeting the mutated
gene, possibly *in utero*.

Additionally, as the significance and subsequent prevalence of genetic research progresses, more information is being discovered as to the potential specific genetic triggers of spina bifida. Recently a study performed by Brouns *et al.* investigated the correlation between spina bifida and the *grainyhead-like 2* (*Grhl2*) gene, which encodes a specific transcription factor. In the mouse model, spina bifida is commonly observed in *Axial defects*, characterized by the phenotype of a curled tail; however the exact cause of the correlation between spina bifida and the *Axial defects* is unknown. Through genetic mapping of the defected area of the genome, it was determined that an increase in the expression of *Grhl2* lead to an increase in the occurrence of spina bifida. Additionally, when there was a complete loss of the functionality of the *grainyhead-like 2* gene, there was an increase in the prevalence of neural tube defects, including spina bifida. Thus, it appears that any slight imbalance in the expressivity of the *Grhl2* gene has the potential to lead to neural tube defects, specifically spina bifida (Brouns *et al.*, 2011). While currently found within the mouse model, these findings of the correlation between an imbalance in *Grhl2* gene and neural tube defects have the potential to greatly increase the knowledge of the development of human inheritance of spina bifida. Furthermore, as the definitive causes of the disorder are discovered, treatments, which more precisely target the cause of the disorder, are becoming more conceivable.
SUMMARY AND CONCLUSION

Spina bifida is a devastating congenital disorder characterized by an incomplete closure of the spinal column, which, depending upon location and severity of the abnormality, can lead to a wide variety of side effects, including paralysis as well as cognitive dysfunction. Spina bifida can develop as a result of a genetic inheritance, a deficiency in various nutrients necessary for normal fetal development, including folic acid, as well as occurring due to a de novo mutation. The treatment of spina bifida typically involves surgical means either in utero or shortly after birth with the goal of closing the spinal column, and fully concealing the spinal cord. Additional treatments are utilized to combat the secondary effects of spina bifida, such as medications to combat secondary infections, and surgical procedures to correct musculoskeletal deformities, among many others.

While the immediate goal of the medical field is the treatment of those afflicted with spina bifida, a more comprehensive goal is the development of more individual-specific treatments based upon the specific method of the development of the disorder, with an ultimate goal of eradicating the existence of spina bifida. Through research, using both animal and human models, the specific molecular and genetic aspects involved in the development of neural tube defects are being discovered, and this knowledge can lead to a more complete treatment method for a multitude of neural tube defects, including spina bifida.
REFERENCES


Spina Bifida Occulta: Research from Kagoshima University, Department of Orthopaedic Surgery in the area of spina bifida occulta described. 2010. Medical Devices & Surgical Technology Week: 204.


