IMPACT

MAYO CLINIC
HEALTH SYSTEM

University of Wisconsin
Eau Claire

2019 IMPACT Symposium

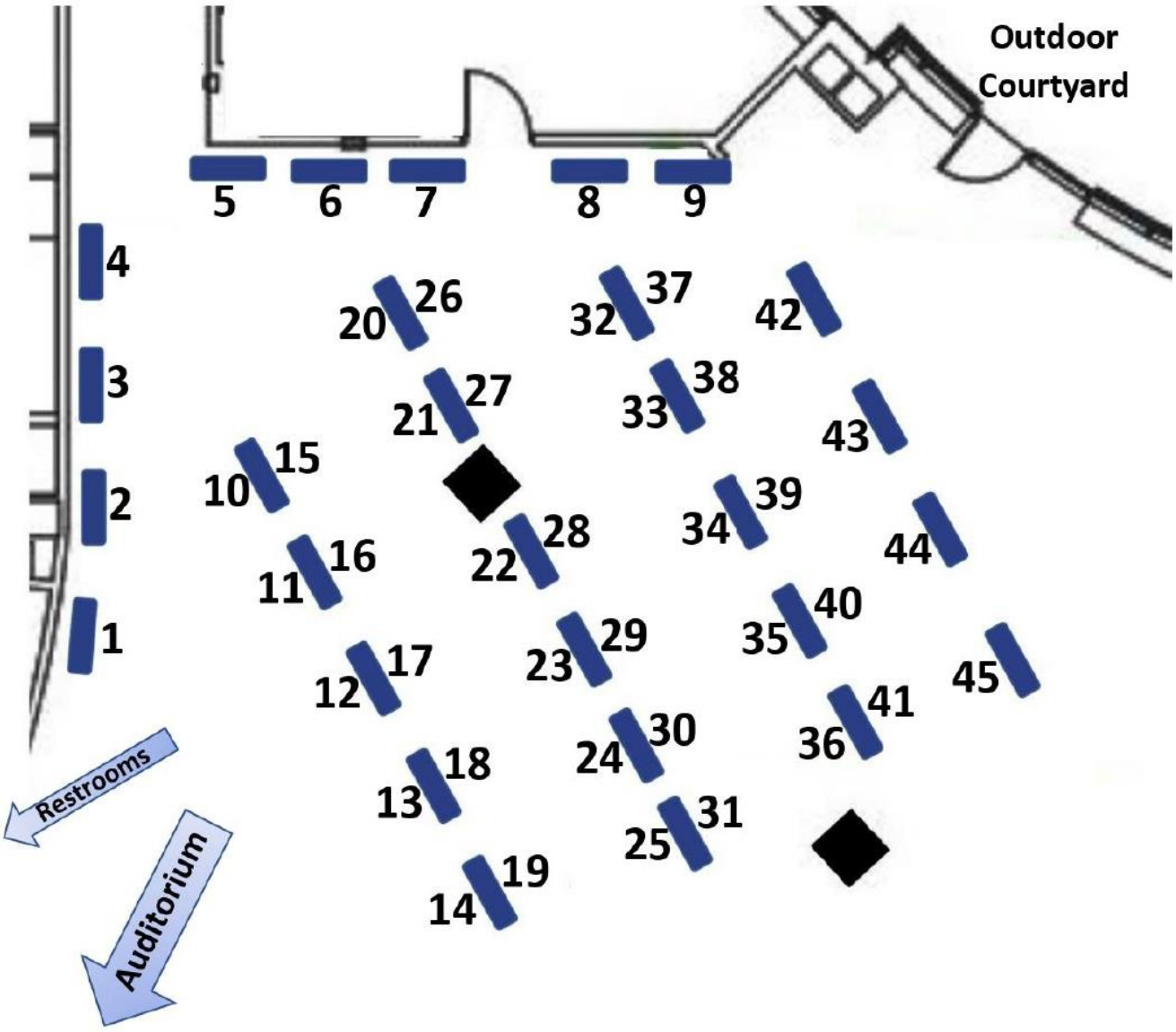
April 6, 2019

Hypotheses & Abstracts

All posters will be displayed in the Atrium through lunch.

Poster Session 1 will take place from 9:15 to 10:00am. Teams with posters at odd-numbered locations will be delivering poster presentations at this time.

Poster Session 2 will take place from 10:00 to 10:45am. Teams with posters at even-numbered locations will be delivering poster presentations at this time.



Team's hypotheses and abstracts are organized in this booklet by their poster location.

Student Poster Presentations

1 Epigenetic Changes Induce Mutations in TBX Genes and NKX2-5 Expression

Hannah Anderson, Benjamin Harrison, Emilie Hulse, & Samantha Wuebker
Simpson College // Faculty Sponsor: Jacqueline W. Brittingham, Ph.D.

HYPOTHESIS: We hypothesize that one or more epigenetic changes acquired in the parental generation impairs Tbx20, Tbx2, Tbx5, Nkx2-5 activation, causing Hypoplastic Left Heart Syndrome in future generations.

Hypoplastic Left Heart Syndrome (HLHS) is a congenital heart defect (CHD) that affects approximately 1000 children per year. As with many CHDs, the multifactorial etiology complicates identification of the underlying cause of HLHS in most patients and presents a challenge in developing effective prevention strategies. Innovative public health strategies designed specifically to identify and track factors in the maternal environment that lead to epigenetic changes may be the key to identifying novel causes of HLHS. Epigenetic changes in histone modification and methylation patterns in differentially regulated cardiac genes have been linked to other complex CHDs.[7] Previous research has identified the T-box family of genes and NKX2-5 as key regulators of the differentiation of ventricular myocardium and chamber specification, and have been implicated in many forms of congenital defects.[1] We hypothesize that one or more epigenetic changes acquired in the parental generation impairs Tbx20, Tbx2, Tbx5, Nkx2-5 activation, causing HLHS in future generations. These epigenetic changes may not be identified through traditional public health screening methods. A targeted epidemiological approach is necessary in order to identify underlying epigenetic causes of HLHS, along with other CHDs, and to develop effective public health actions to address specific stressors within communities.

2 Underlying Cause of HLHS: Biochemical Teratogens Lead to Mutations in Sap130 & Pchda9

Jeff Anders, Quincy Markham, Christine Puleo, & Alexandria Reinstein
Coe College // Faculty Sponsor: Cassy Cozine, Ph.D.

HYPOTHESIS: In the case a fetus is exposed to environmental or biochemical teratogens such as maternal hypoxia and abnormal amounts in the intake of caffeine and lithium, it will lead to mutations in Sap130 and Pchda9 which morphologically alter the heart. These attributions highlight the symptoms of HLHS and are found to be the causative factor of the congenital disease.

This research outlines the causes of HLHS and the biological changes the fetal offspring goes through as well as how to further understand how lithium, caffeine, and oxygen act as biochemical teratogens and the implementation of reversing HLHS affects using hiPSC's on Sap130 and Pchda 9 mutations.

3 Point Mutations Affecting the *cis*-Interaction of Jag-1 Leading to the Development of HLHS

Kervens Accilien, Nik Newville, Trysten Jensen, & Whitney Shegrud
Minnesota State University Moorhead // Faculty Sponsor: Adam M. Stocker, Ph.D.

HYPOTHESIS: We propose that a D1201A and/or N1124A mutation at the Mib1 binding sites of Jag1, in conjunction with its hypoxia induced up-regulation mediated by HIF-1α, results in the cis-inactivation of Notch. This prevents the differentiation of cardiac progenitor cells, decreasing the formation of cardiac fibers. This manifests as hypoplasia localized to the left side of the heart.

Hypoplastic Left Heart Syndrome (HLHS) is a rare congenital cardiac defect occurring in less than 0.04% of live births. HLHS comprises a spectrum of disorders classified by an underdeveloped left ventricle, atresia in the aortic or mitral valve, and other outflow tract disorders. Many studies have demonstrated the association of aberrant Notch signaling and cardiac defects; to the best of our knowledge, few have looked very far upstream of Notch regulation for potential causes of HLHS. We propose that a D1201A and/or N1124A mutation in Jagged-1 (Jag1), in conjunction with its hypoxia induced upregulation mediated by HIF-1α, results in the cis-inactivation of Notch. This prevents the differentiation of cardiac progenitor cells, decreasing the formation of cardiac fibers. This manifests as hypoplasia localized to the left side of the heart.

4 Underlying Cause of Hypoplastic Left Heart Syndrome in Relation to Yes-Associated Protein

Lourdes Anderson & Andrea Schaefer
Minnesota State University Moorhead // Faculty Sponsor: Sumali Pandey, Ph.D.

HYPOTHESIS: Premature phosphorylation of Yes-Associated Protein during heart development is associated with Hypoplastic Left Heart Syndrome.

Hypoplastic Left Heart Syndrome (HLHS) is a congenital birth defect that affects the normal blood flow through the heart. The underlying cause of HLHS, is not known. However, we hypothesize the underlying cause is due to premature phosphorylation of Yes-Associated Protein (YAP) during heart development. YAP is a nuclear protein kinase, which helps regulate the balance between cell proliferation and apoptosis. YAP is found within the Salvador-Hippo Warts (SWH) Pathway. YAP has been linked to growth regulation in the liver, lungs, and heart, however, little research has looked at the effects of YAP on HLHS. The growth regulation of YAP has been linked to its phosphorylation timing which leads us to believe the premature phosphorylation of YAP during fetal heart development to associated with HLHS.

5 Overexpression of DWORF and Increased Cardiac Contractility as a Plausible Constituent of HLHS

Rahma Ahmed, Mercedes Erpelding, Hlee Yang, & Shirly Yang-Lor
Northwestern Health Sciences University // Faculty Sponsor: Susan C. Lawrenz-Smith, Ph.D.

HYPOTHESIS: Overexpression of DWORF (dwarf open reading frame) protein in fetal heart causes ventricular wall thickening and an increase in cardiac contractility leading to HLHS.

We propose that researchers study the correlations of genetics and DWORF (dwarf open reading frame) to assist in understanding the underlying causes of HLHS. DWORF is a muscle specific micropeptide found in myocytes within the soleus muscle, heart, ventricles, and diaphragm [2]. Understanding the contributions of how DWORF operations in relation to HLHS will allow researchers to determine populations that are at high risk making screening both costeffective and efficient. Nonetheless, while in the womb and in the early stages of development, the fetus can be screened for overexpression of DWORF and, in doing so, prepare for in utero operations.

6 Hypoxia-Induced Survival of HIF-1α Causing Increased Activation of Proapoptotic Genes: A Mechanism Leading to HLHS

Rachel Astashinsky, Kyla Hagen, Mackenzie McDonald, & Leah Novik
University of Minnesota Twin Cities // Faculty Sponsor: Jop van Berlo

HYPOTHESIS: Severely low oxygen saturation in the placenta, due to enhanced maternal hypoxia during SHF development, leads to the manifestation of HLHS. Severe hypoxia greatly reduces hydroxylation of the HIF-1α protein and lowers its degradation by the pVHL ubiquitin ligase; this results in increased HIF-1α activated gene expression during cardiogenesis, where proapoptotic gene transcription outcompetes cardioprotective gene transcription, leading to the cardiac abnormalities characteristic of HLHS.

HLHS is a rare congenital defect with an obscure underlying etiology. Recent research pertaining to the role of the heart-placental axis in cardiac development may point to HIF-1 transcriptional activity as a central link to HLHS manifestation. Hypoxia in utero *elevates HIF1 transcriptional activity due to unreactive PHD enzymes reducing the degradation of HIF-1α. This transcriptional activity typically expresses as both cardioprotective and proapoptotic proteins. We propose that the severity of the hypoxic environment favors proapoptotic genes, impacting cardiogenesis of the early embryo. If further supported and explored, this provides promising implications for the future understanding and prevention of HLHS.*

7 EMILIN-1 and TGF-β1 Pathway Triggers Cardiac Fibrosis as A Pathophysiologic Mechanism That Leads to The Phenotypic Expression of HLHS

Ahminata Bah, Ricardo Becerra-Ruiz, Klondy Karina Canales, & Elizabeth C. Pasch
Northwestern Health Sciences University // Faculty Sponsor: Susan C. Lawrenz-Smith, Ph.D.

HYPOTHESIS: Deficiency of EMILIN-1 expressed in valvular endothelial and interstitial cells upregulates TGF-β1 signaling, promoting myofibroblast activation and transformation of the cell-matrix in mitral valve tissue that contributes to hypoplastic left heart syndrome.

A common characteristic of hypoplastic left heart syndrome (HLHS) is reduced blood flow inhibiting further growth of the left ventricle

(LV) resulting in hypoplasticity of the left heart structures. Dysregulation of biochemical signals causes remodeling of the extracellular matrix (ECM) in valvular endothelial cells (VECs) and valvular interstitial cells (VICs). This leads to a loss of most of the mitral and aortic valve's mechanical properties. Elastin microfibril interface located protein 1 (EMILIN1), an essential ECM protein in valve cells, plays a crucial role in transforming growth factor-β1 (TGF-β1) regulation, which activate VICs to undergo cardiac fibroblast to myofibroblasts transformation in myxomatous valves. We propose that genetic inactivation of EMILIN1 in response to disruption of ECM composition of mitral valve cells lead to dysregulation of EMILIN-1, inducing upregulation of TGF-β1, and triggering VIC activation to invasive myofibroblast. Our hypothesis could help explain valvular reprogramming in the immature heart and fibrosis affecting the development of the mitral valve configuration, impeding LV development.

8 HLHS: A Proposed Role for Retinoic Acid Abnormality and Primary Cilia Signaling in the Sonic Hedgehog Pathway

Justine Bersonda, Kimberly Her, & Taylor Olsen
Northwestern Health Sciences University // Faculty Sponsor: Susan C. Lawrenz-Smith, Ph.D.

HYPOTHESIS: We hypothesize that HLHS is caused by abnormal levels of retinoic acid in the developing fetus, resulting in precocious differentiation of primary cilia that will have a cascading effect on embryonic heart development through the Sonic hedgehog pathway (Shh).

Hypoplastic left heart syndrome (HLHS) is a congenital heart defect characterized by an underdeveloped left ventricle and structural abnormalities to the mitral valves, aortic valves, and the ascending portion of the aorta (Galindo, A, et al., 2009). The similar roles of primary cilia and retinoic acid in patterning heart fields and the heart defects observed when either factor is disrupted suggest a relationship between the two (DukeMedicine, 2011). Thus, we investigated the possible interplay between retinoic acid's influence on the formation of primary cilia through the sonic hedgehog pathway (Shih).

9 Group A *Streptococcus* Induced Rheumatic Fever Acts as a Teratogenic Agent of HLHS via Two Pathways

Alisha P. Chaudhry, Meserete H. Hatte, & Amrita Bhagia
St. Olaf College // Faculty Sponsor: Anne Walter, PhD

HYPOTHESIS: We propose that maternal exposure to Group A *Streptococcus* (GAS) bacteria during the first trimester of pregnancy can lead to the manifestation of rheumatic fever in the mother, producing GAS IgG autoantibodies that cross the placenta and can cause the HLHS phenotype in two ways: firstly, by inducing abnormal embryonic cardiomyocyte proliferation and differentiation and secondly, by damaging the embryonic mitral and aortic valves resulting in stenosis.

Previous literature has shown that Hypoplastic Left Heart Syndrome (HLHS) is hypothesized to be the result of both genetic and environmental factors, though no single causative pathway has yet been identified. Prior studies have also reported a known seasonality of the disease; thus, we propose that maternal exposure to Group A Streptococcus *(GAS) induces maternal rheumatic fever, resulting in the HLHS phenotype in infants via two pathways. Through these two pathways, we propose that damage occurs to the left ventricle (LV) myocardium and the mitral/aortic valves as the result of molecular mimicry induced by an autoimmune response.*

10 A Proposed Hypothesis of Three Mutated Genes Mediating HLHS: *SAP130*, *PCDHA9*, and *NKX2-5* Alter the Regulation of Transcription During Embryonic Heart Development

Brandon Ciak & Anh Nguyen
Concordia College (Moorhead, Minnesota) // Faculty Sponsor: Dr. Krys Strand, Ph.D.

HYPOTHESIS: During the development of the embryonic heart, gain-of-function mutations in *SAP130*, *PCDHA9*, and *NKX2-5* negatively impact regulation of transcription in cardiomyocytes, mediating HLHS.

Congenital heart diseases (CHDs) are the most common types of birth defects, affecting over 2.5 million people [1]. Hypoplastic left-heart syndrome (HLHS) accounts for nearly 25% of deaths in children suffering from CHD [2]. The underlying cause of HLHS is still unknown, but results of recent research suggest correlations with certain gene mutations as a probable cause. In mice, mutations in Sap130 *and* Pcdha9 *have resulted in an underdeveloped and less efficient left side of the heart [3]. The* NKX2-5 *gene has been studied more extensively and its protein is a DNA-binding transcriptional activator in cardiomyocytes. We hypothesize that* NKX2-5 *regulates the transcription of* SAP130 *and* PCDHA9*, which function as transcription repressors in cardiomyocytes [4]. Therefore, the mutations of these three genes are potentially the underlying cause of HLHS. Further investigation should focus on these three genes and their roles*

in the embryonic heart. Functional studies in mice with mutations in Sap130*,* Pcdha9*, and* Nkx2-5 *may lead to better understanding of HLHS and potentially inform new pharmaceutical interventions and gene therapies.*

11 Protocadherin Dysfunction Leads to the Overexpression of miR-99a Triggering a Gene Cascade Involving BAZ2A, NKX2.5 and GATA4 Resulting in Hypoplastic Left Heart Syndrome

Caylin Crawford, Meghan Lovegren, & Darlene Zemke
Metropolitan State University // Faculty Sponsor: Cindy Harley, Ph.D.

HYPOTHESIS: Protocadherin dysfunction leads to the overexpression of miR-99a triggering a gene cascade involving BAZ2A, NKX2.5 and GATA4 resulting in Hypoplastic Left Heart Syndrome.

HLHS is a congenital heart defect with a suspected multigenic origin. The heart is the first organ formed during embryogenesis and proper development relies upon precise levels of gene expression and regulation. We are proposing that protocadherin mutation and dysfunction lead to low blood flow in the developing heart, triggering epigenetic changes in the developing cardiac tissues. These changes increase expression of miR-99a and begin a cascade of events that result in ventricular hypertrophy and overgrowth of the left ventricle cardiomyocytes. The interactions between miR-99a and the genes BAZ2A, NKX2.5 and GATA4 are the focus of our research.

12 Viral Infection *in utero* Leads to Delayed and Impaired Myogenesis in Fetal Development

Delaney Cairns, David Scott, & Henry Thompson
Madison Area Technical College // Faculty Sponsor: Katie Kern, M.S.

HYPOTHESIS: Epstein-Barr Virus (EBV) infection, or other herpesvirus infection, of the fetus during the first trimester of pregnancy results in a dysregulation of the hypoxia response factors resulting in delayed and impaired myocyte differentiation and proliferation.

HLHS is a congenital heart disease characterized by the underdevelopment of the left ventricle in utero. This causes poor systemic circulation and typically requires surgical innovation. EBV is a virus known to rarely cross the placental barrier to the fetus. Primary infection of the fetus results in increased oxygen consumption by fetal myocyte progenitor cells, due to inflammation, resulting gin hypoxia of myocyte cells. These factors upregulate viral miRNAs which downregulates the normal cellular HIF1a response during hypoxia. This results in upregulation of NOTCH1 and HEY2 decreasing cell differentiation and proliferation in the left ventricle, as well as decreasing VEGF in the aorta, all resulting in HLHS pathology. If true this will result in the ability to screen for EBV naivety of the mother at the start of pregnancy, with potential treatment with antivirals.

13 Effects of the Notch Pathway and Nitric Oxide Deficiency on Hypoplastic Left Heart Syndrome

Larissa Clennon, Jacob Opatz, Mambo Che, & Lum Cheboh Emmanuela
Century College // Faculty Sponsor: Joann Pfeiffer, Ph.D.

HYPOTHESIS: The Notch pathway plays a critical role in cardiac fetal development. This pathway, and more specifically the NOTCH1 gene, may be mutated due to nitric oxide (NO) deficiency caused by multiple factors, including age and dietary intake of NO and/or bio synthesizers of NO. The mutation of the Notch pathway has been shown to lead to an increased chance of HLHS developing in newborns.

The purpose of this research was to examine the NOTCH1 gene, it's functioning in fetal heart development while analyzing possible mutations on the gene in relation to NO deficiency. Then evaluating the two factors together interpret their role in the development of hypoplastic left heart syndrome. Hypoplastic left heart syndrome is a heart defect that stems during prenatal development of a fetus, the defect results to an underdeveloped left sided heart thereby leading to abnormal heart functioning. Methods included doing research on the expression of the NOTCH1 gene within the Notch signaling pathway, production of nitric oxide in our bodies. Nitric oxide is an important signal molecule in the body, and it is produced in our bodies in two ways majorly: they include an enzyme isoforms pathway and a non-enzymatic pathways. Insufficient production of the molecule affects how the NOTCH 1 gene is expressed in the genome; and research has shown that a mutation in the NOTCH 1 gene increases the probability of one being affected by hypoplastic left heart syndrome.

14 Early Gestation IGF-II Analog Treatment to Prevent Placental and Cardiac Abnormalities in HLHS

André Flatt, Galen Gist, Carley Irlmeier, & Ellen Willhoit
Simpson College // Faculty Sponsor: Jacqueline W. Brittingham, Ph.D.

HYPOTHESIS: Infusion of an IGF-II analog during early- to mid- gestation allows for proper maternal-fetal nutrient exchange, thereby antagonizing excessive hypoxia. This induces normal development of the placenta and the heart, thus preventing the onset of HLHS.

Hypoplastic Left Heart Syndrome (HLHS) is a severe congenital heart defect associated with fetal growth abnormalities. Since the heart and the placenta develop simultaneously, abnormal cardiac development is associated with abnormal placental development. One possible mechanism for abnormal development of both systems is a decrease in transcription of insulin-like growth factor II (IGF-II). Studies have shown that IGF-II is crucial for regulation of cell proliferation, growth, migration, differentiation, and survival during normal cardiac development and may lead to placental abnormalities such as improper trophoblast implantation. In turn, this results in reduced delivery of nutrients and oxygen necessary for proper heart development, contributing to the onset of HLHS. Therefore, we suggest the novel idea of treating women with IGF-II analog early in pregnancy to prevent the development of HLHS in the fetus.

15 The Deletion of the Gene Nkx2.5 Leads to an Under Expression of the Hand1 Gene, Causing the Development of Hypoplastic Left Heart Syndrome

Brey Fure, Byde Enoh Ashuarrah, & Abshir Mohamed
Century College // Faculty Sponsor: Michelle LeBeau, Ph.D.

HYPOTHESIS: The Hand1 gene plays a critical role alongside Nkx2.5in the proliferation of the left ventricle during the ballooning process in a human embryo. Therefore, if a deletion of Nkx2.5 occurs, the Hand1 gene will not be expressed leading to the development of Hypoplastic Left Heart Syndrome.

The ballooning process of the left ventricle is due to the expression of the Hand1 gene. The gene Nkx2.5 is also associated with the development of the left ventricular chamber. The deletion of this Nkx2.5 gene influences the expression of the Hand1 gene which leads to the proliferation of the left ventricle causing Hypoplastic Left Heart Syndrome.

16 Dysregulation of Long Non-Coding RNAs as an Underlying Cause of HLHS

Kayla Finnegan, Morgan Johnson, Zahra Sharif Mohamed, & Milada Vannarath
Northwestern Health Sciences University // Faculty Sponsor: Susan C. Lawrenz-Smith, Ph.D.

HYPOTHESIS: During embryonic heart development, dysregulated long noncoding RNAs trigger polycomb-repressive complex 2 attenuation of the cardiac transcription factor GATA-4 and the underdevelopment of left heart structures characteristic of Hypoplastic Left Heart Syndrome.

Although there is no current definitive cause of Hypoplastic Left Heart Syndrome (HLHS) numerous studies have supported a genetic origin. Over the past decade, non-coding RNAs (ncRNAs) have emerged as significant upstream regulators, including long non-coding RNAs (lncRNAs). We hypothesize that by interacting with polycomb repressive complex-2 (PRC-2), dysregulated lncRNAs attenuate GATA-4 transcriptional activity, and ultimately, the regulation of genes responsible for the development of left heart structures as it relates to the phenotype of HLHS. LncRNAs could transform clinical practice with the potential to improve patient outcomes not only in Hypoplastic Left Heart Syndrome but the population at large.

17 Exosomes as Vehicles for Delivering Paracrine Signals to Remediate Cardiomyocyte Death in HLHS

Daniel Goldsmith, Hannahlynn Heinen, Amanda Stadtlander, & Ethan Woodruff
Simpson College // Faculty Mentor: Aswati Subramanian, Ph.D.

HYPOTHESIS: **Causation:** Impaired diastolic filling affects TGF-β signaling in cardiomyocytes thereby reducing cardiomyocyte proliferation, leading to the further development of HLHS. **Treatment:** In an effort to address inadequate cardiomyocyte proliferation in the developing HLHS heart, we hypothesize that *in utero* delivery of exosomes purified from cardiac progenitor-like cells derived from HLHS patient stem-cells, will protect cardiomyocytes from oxidative stress and promote cardiac regeneration, increasing the performance and viability of the affected heart.

The goal of this study is to identify the underlying cause of hypoplastic left heart syndrome and develop novel treatment options. This disorder is characterized by underdevelopment of the left ventricular myocardium, which can lead to altered hemodynamic forces in the

ventricles during diastole. In the absence of normal physiological stretching during diastole, we propose that the TGF-β signaling pathway is dysregulated in developing cardiomyocytes. Altered TGF-β regulation results in a reduction of cardiomyocyte proliferation and an increase in oxidative stress and apoptosis. Combined, these molecular and cellular mechanisms result in deoxygenated myocardium observed in HLHS. Our innovative proposed intervention is to send growth signals to cardiomyocytes which will stimulate ventricular growth and reverse oxidative stress. In utero *delivery of these paracrine signals will be carried out with exosomes isolated from cardiac progenitor-like cells, derived from the patient's reprogrammed amniotic or chorionic villus stem cells.*

18 The Interaction of HAND1 & TBX5 on HLHS Formation

Jake Gervais, Cameron Hayes, & Emily Schroeder
University of Northwestern—St. Paul // Faculty sponsor: Gary Mumaugh, DC, FACO

HYPOTHESIS: We hypothesize that Hypoplastic Left Heart Syndrome could be caused by a mutation of HAND1 and TBX-5 over producing collagen and elastin fibers during cardiac fetal development leading to Endocardial Fibroelastosis (EFE) and HLHS.

TBX-5 and both HAND1 & 2 genes contribute to cardio morphogenesis. Amongst cardiac morphogenesis, mutations are possible due to environmental factors, a minor nucleotide error, a combination of the two, or other unknown contributors. We hypothesize that a mutation within the transcription or translation of these genes poses the possibility of ventricular malformation, and insufficient blood supply to the fetal heart. The genetic interactions of TBX-5 and HAND are not mutually exclusive, however, interactions between them may show a pattern of causation and and consequence of their mutations, individually or complementary. Studying a protein-protein interaction between a mutant TBX-5 gene expression (which is involved in the first heart field) with a regularly expressed HAND gene (and vice versa) in mice. If a mutation is consistent in both presence and nature, a new pathway of research could be opened. Science has shown no significant correlation between environmental effects on the genes mentioned thus far and Hypoplastic Left Heart Syndrome. However, studying Endocardial Fibroelastosis in relation to HLHS could possibly give a new avenue of research. EFE is the "pronounced, diffuse thickening of the ventricular endocardium and presents as unexplained heart failure in infants and children. The disease can be primary or secondary to various congenital heart diseases, most notably hypoplastic left heart syndrome, aortic stenosis, or atresia" (8). Stenosis of the heart valves and walls leads to insufficient blood flow throughout the body and particularly back to the heart itself. Significant anemia and hypoxia could be preventing the cells from going through mitosis and regular cellular growth as we would see in a healthy fetal heart. The stenosis and brief thickening of the heart wall, represented by EFE, could be a temporary state which is followed by a stunning lack of formation of the left side of the heart shown in HLHS.

19 HLHS: Hypoxia Induced Over-Expression of miRNA and the Subsequent Under Expression of SAP130

Getachew Hundera, Tan Ngo, Chidiogo Orakwue & Zamzam Shalle
University of Minnesota Rochester // Faculty Sponsor: Rachel Olson, Ph.D.

HYPOTHESIS: We hypothesize that underexpression of SAP130 caused by hypoxia leads to hypoplastic left heart syndrome due to fetal cardiac underdevelopment of the left ventricle.

20 X-linked HLHS: Mutated FLNA of the X-Chromosome and Its Correlation to HLHS

Amanda Hansmann, Melissa Haseman, & Sunanda Rajput
University of Minnesota Morris // Faculty Sponsor: Rachel Johnson, Ph.D.

HYPOTHESIS: We hypothesize that a mutation in the FLNA gene present on the X chromosome is one of the underlying causes of HLHS, which is in addition to other genetic mutations as part of the multigenic property of HLHS.

Hypoplastic Left Heart Syndrome (HLHS) is a birth defect in which the fetus' left portion of the heart does not develop during pregnancy.1 The underlying mechanistic cause of HLHS is unknown. The current treatment of HLHS is surgery, which is not a permanent cure. Due to the male: female ratio of HLHS cases, we hypothesize that a mutation in the FLNA gene present on the X chromosome is one of the underlying causes of HLHS. Gene therapy or the use of siRNAs and antisense oligonucleotides dispensed using myocardial injections to a subset of patients are the innovative methods with this X-linked mutation we propose.

21 Exposure to Toxin 2,3,7,8-Tetrachlorodibenzo-P-Dioxin (TCDD) in the Environment Leads to HLHS

Napat Intarachumnum & Helen Vu
St. Olaf College // Faculty Sponsor: Kimberly Kandl, Ph.D.

HYPOTHESIS: Maternal exposure to toxin 2,3,7,8 –tetrachlorodibenzo-p-dioxin (TCDD) in the environment leads to Hypoplastic Left Heart Syndrome (HLHS). TCDD leads to activation of Aryl Hydrocarbon Receptor (AHR), which then dimerizes with Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) and represses NKX 2.5 gene expression which is essential in heart development.

Maternal exposure to toxin 2,3,7,8 – tetrachlorodibenzo-p-dioxin (TCDD) in the environment leads to Hypoplastic Left Heart Syndrome (HLHS). TCDD leads to activation of Aryl Hydrocarbon Receptor (AHR), which then dimerizes with Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) and represses NKX 2.5 gene expression which is essential in heart development.

22 Attack of the Antibodies: Maternal Antibodies Causing Hypoplastic Left Heart Syndrome

Gabrielle Jordahl, Savannah Mosier, & Bailey Onken
University of Minnesota Rochester // Faculty Sponsor: Andrew Petzold, Ph.D.

HYPOTHESIS: Hypoplastic Left Heart Syndrome (HLHS) occurs due to the presence of antibodies in the maternal immune system which attack proteins causing improper fetal heart development and looping.

Hypoplastic Left Heart Syndrome (HLHS) is a congenital birth defect with prohibits normal blood flow through the heart. HLHS first presents itself in week six of fetal development. Using anti-protein antibodies can counteract the protein antibodies attack Claudin-1, the vital protein associated with heart looping.

23 Altered Placental DNA Methylation and Impaired Hemodynamics: Hypoplastic Left Heart Syndrome Pathophysiology

Joohyun Grace Jin, Seohyun Park, Seth Ramin, & Daniel Traverzo
Northwestern Health Sciences University // Faculty Sponsor: Susan C. Lawrenz-Smith, Ph.D.

HYPOTHESIS: We hypothesize that altered placental DNA methylation gives rise to placental and fetal cardiac abnormalities, which subsequently impairs cardiac hemodynamics, giving rise to a variety of HLHS phenotypes.

Hypoplastic Left Heart Syndrome (HLHS) describes a spectrum of rare congenital cardiac disorders with a prevalence rate of approximately two in every ten thousand live births. These cardiac anomalies include aortic stenosis, valvular atresia, and a hypoplastic left ventricle. While the etiology of HLHS is not well understood, research has reveals complex genetic influences that may give rise to altered cardiac morphology and hemodynamics, which leads to HLHS manifestations. The discordance of HLHS phenotypes among genetic variants is suggestive of epigenetic control, which has been implicated in other congenital cardiac anomalies. We propose that the fetal placenta influences fetal cardiac gene expression during cardiogenesis, leading to valvular malformation, which impairs hemodynamics and stunts growth of the left ventricle as observed in HLHS cases and their matched controls can be used to examine placental DNA methylation. Simultaneously, fetal genome sequencing and fetal cardiac phenotypes will be assessed. If a relationship between placental DNA methylation, fetal cardiac DNA methylation, and fetal cardiac phenotype is established, placental sampling during gestation may prove useful in predicting HLHS. Additionally, if modifiable influences (environmental or maternal exposure) of DNA methylation are identified and associate with HLHS risk, then measures could be taken to prevent this disease.

24 The Specialization Pathway of Cardiomyocytes: In Obese Mice vs Normal Mice in *SAP130* Gene and *PCDHA* Gene Mutation

Luzan JadKarim, Wenxia Sweeney, & Ethan Hong
Coe College // Faculty Sponsor: Cassy Cozine, Ph.D.

HYPOTHESIS: HLHS shows penetrance in offspring with a combination of homozygous *SAP 120* gene and *Pcdha9* gene mutations. We believe that this combination of mutations is more common in the fetuses of obese mothers (BMI of 30 of above). This means that obese heterozygous mothers are more likely to pass on the mutated form of the two genes causing HLHS to their child than mothers with lower BMI.

Both genetic factors and environmental factors are most likely present in the development of HLHS in fetuses. These factors have been identified as mutations of the Sap130 *gene and* Pcdha9 *gene in addition to an obese maternal body mass.*

25 Notch Signaling Pathway & Environmental Factors Lead to Increased Risk of HLHS: Notch1 and Factors: Obesity, Lipopolysaccharides, Folic Acid & Phenylalanine

Abubakarr S. Konneh, Alex B. Wolner, Alexi S. Wall, & Andree L. Blackburn
St. Olaf College // Faculty Sponsor: Cynthia Book, Ph.D.

HYPOTHESIS: We hypothesize that a mutation in the NOTCH1 gene, in combination with increase in pre-pregnancy levels of obesity, lipopolysaccharides, and phenylalanine, and a decrease in folic acid results in a higher risk of developing HLHS.

The development of Hypoplastic Left Heart Syndrome (HLHS) is not solely based on genetics but requires looking at environmental factors. The decrease in folic acid levels and the increase in Body Mass Index (BMI), levels of phenylalanine, and lipopolysaccharides all lead to an increased risk of HLHS. These factors all have a relation to the NOTCH1 signaling pathway, so each will be discussed independently and with regards to genetics.

26 Hypoplastic Left Heart Syndrome: A Multigenic and Genetically Heterogeneous Condition

Ian Kretzmann, John Loepfe, Anna Lance, & Kelly Wichmann
St. Olaf College // Faculty Sponsor: Kimberly Kandl, Ph.D.

HYPOTHESIS: We hypothesize that the genetics behind HLHS are multigenic and genetically heterogeneous. Different mutant gene combinations lead to different variations and symptoms of HLHS. Specifically, we propose that *Sap130* and *Pcdha9* play a key role in the hypoplasia of the left ventricle. However, unless there are accompanying mutations in protective modifier genes, such as *Sin3A* and *Snai1*, the fetus will fail to survive full term." Other genes, such as *NKXY2.5*, *HAND1*, and *HAND2* also influence the manifestation of HLHS.

This project aims to hypothesize the cause of Hypoplastic Left Heart Syndrome (HLHS), a common neonatal condition that is potentially fatal. We hypothesize that the genes Sap130 *and* Pchda9 *play a significant role in its development. Understanding this condition and its etiology can help physicians not only treat but possibly prevent infant deaths.*

27 The Role of MicroRNA in HLHS: How the X Chromosome's Production of MicroRNA Can Effect the Development of the Fetal Heart

Joshua B. Krueger, Jordan D. Sauve, & Caleb J. Anderson
University of Northwestern—St. Paul // Faculty Sponsor: Gary Mumaugh, DC, FACO

HYPOTHESIS: We hypothesize that the root cause of HLHS resides in the X chromosome, specifically in its production of microRNA regulatory segments. The microRNA segments are mutated and unable to properly regulate the genes for normal cardiac development (ex. NOTCH1, SAP130, PCDHA9).

The underlying cause of hypoplastic left heart syndrome (HLHS) is thought to be primarily genetic. We hypothesize that the root cause of HLHS may reside in microRNA regulatory segments due to evidence that already shows malfunctioning microRNA is linked to a decline in heart development.11 Considering that 70% of HLHS patients are male and one third of people with Turner's Syndrome (XO) have HLHS, we hypothesize that HLHS stems from the inability to circumvent a mutated X chromosome via the expression of an alternative one.3,10 Our hypothesis explains that the faulty microRNA segments being produced by the X chromosome misregulate the genes that are responsible for fetal heart development. The specific microRNAs on X can be identified based upon their complementary base pairing with the mRNAs that are responsible for normal fetal heart development.

28 Maternal Exposure to PM2.5 During Embryonic Cardiac Development Leads to HLHS

Madisyn Kephart, Shawna Helmuth, & Summer Peoples
University of Wisconsin—Eau Claire // Faculty sponsor: Jeanette Olsen, Ph.D., R.N.

HYPOTHESIS: Hypoplastic left heart syndrome (HLHS) is caused by maternal exposure to high levels of $PM^{2.5}$ in the atmosphere during embryonic cardiac development.

Particulate matter has dangerous effects during embryonic cardiac development. $PM^{2.5}$ is small enough to enter the bloodstream, cross the placenta, and access fetal circulation. High levels of $PM^{2.5}$ in the blood cause biomarkers of oxidative stress, which are similar to those found in HLHS. $PM^{2.5}$ levels are highest in urban areas, especially during the winter months. Seasonal trends indicate the incidence of HLHS is higher during the summer months. Blood levels of $PM^{2.5}$ should be tested during pregnancy and compared with postpartum blood analyses. With a high mortality rate and costly hospital stay, our hypothesis focuses on a preventative action for hypoplastic left heart syndrome (HLHS).

29 The Effects of Benzothiazole and PORCN Activity on the Development of Hypoplastic Left Heart Syndrome

Pooja Kandikonda & Priya Periakaruppan
University of Minnesota Twin Cities // Faculty Sponsor: Matthew Ambrose, M.D.

HYPOTHESIS: Environmental factors, such as air pollutants released during home renovation, have been associated with a higher incidence of CHD. Benzothiazole (BZT) is a volatile organic compound commonly released during home renovations, likely due to vinyl flooring assemblies. BZT can inhibit the porcupine protein (PORCN) from binding to *wingless/integrated* (WNT) by fitting into the binding site of PORCN. This relationship was determined because evidence suggests that BZT is the antagonistic portion of a small class of molecules which can inhibit PORCN activity (IWPs). These IWPs are laboratory synthesized small molecule inhibitors of the WNT pathway. The PORCN gene, found on the X chromosome, has various levels of regulation in individuals, thereby influencing the PORCN protein's activity. Because of genetic variations, likely due to mutations that can alter the PORCN protein activity, the PORCN protein could have differing levels of susceptibility to BZT inhibition. Without the binding of PORCN, WNT is not acylated or secreted and the canonical WNT pathway is inhibited. Typically, after acylation and secretion, WNT binds to the frizzled receptor. This binding results in the inhibition of the beta catenin degradation complex. In a normal cell, this causes an accumulation of beta catenin in the cytoplasm of the cell since it is not being broken down. This excessive amount of beta catenin activates gene expression and cell-cell adhesion which is related to the formation of heart structures. However in a cell that inhibits PORCN activity, a lack of beta catenin results in the underdevelopment of left heart structures, eventually resulting in HLHS.

Hypoplastic left heart syndrome (HLHS) is thought to be due to a combination of genetic and environmental factors. Benzothiazole and PORCN genotype influence the activity product of the PORCN gene, the PORCN protein. If the PORCN protein's activity is reduced, the WNT protein is not catalyzed to its active form. This causes a lack of beta catenin accumulation in the cell which leads to less cell proliferation and cell-cell adhesion. This hypothesis takes environmental causes and genetic causes of HLHS and explains the mechanism of interaction between these two factors. There is opportunity for experiments at multiple stages.

30 Hypoplastic Left Heart Syndrome: The Underlying Cause of this Congenital Heart Disease

Caterra Leavens, Maddy Marasch, Seth Subiaga, & Lizzy Keena
University of Wisconsin—Eau Claire // Faculty Sponsor: Winnifred Bryant, Ph.D.

HYPOTHESIS: The underlying cause of Hypoplastic Left Heart Syndrome is undiagnosed levels of elevated blood glucose in a pregnant woman which reduces the level of glutathione, increases the levels of reactive oxygen species, and impairs GATA4 and GATA5 expressions. In turn, these factors affect the fetal development of the left side of the heart.

Hypoplastic left heart syndrome, also known as HLHS, is a congenital heart defect that affects the left side of the heart. In a study conducted on mice by researchers for cardiovascular diabetology, it was found that important antioxidant levels were decreased and mutative enzymes (ROS's) were increased in a pregnancy with elevated blood glucose. The mice treated with N-Acetylcysteine saw significant improvements with their offspring. CHD's were lowered from 58.1% to 16.3%.

31 Affects of Smoking on Sperm DNA: Inherited Mutations in Sperm as a Potential Cause for HLHS

Grace M. Laudenbach, Kailee L. Medved, & Jessie L. Ericson
College of Saint Benedict & St. John's University // Faculty Sponsor: Katherine Furniss, Ph.D.

HYPOTHESIS: Smoking tobacco, as well as ingesting second hand smoke, acts as an environmental teratogen inducing harmful mutations and therefore damage to sperm DNA which results in the formation of offspring exhibiting the prenatal medical defect known as Hypoplastic Left Heart Syndrome.

The majority of Hypoplastic Left Heart Syndrome research has focused on genetic influences and maternal factors. Our research of sperm DNA damage due to smoking detracts from the popular topics. The mutations may derive from first or second hand smoke which then cause this particular congenital heart defect.

32 The Transcription Factor FoxC2: A Key Transcriptional Regulator in Left Heart Development

Howard Leuschen, Cyrus Nouraee, Vivek Prasad, & Dylan Ross
University of Minnesota Twin Cities // Faculty Sponsor: Jeffrey Simon, Ph.D.

HYPOTHESIS: We hypothesize that mutations in both alleles of *FoxC2* in the DNA binding domain lead to a loss of function of the protein, leading to downstream effects that cause the signs and symptoms found in hypoplastic left heart syndrome.

Hypoplastic Left Heart Syndrome (HLHS) is a developmental abnormality of the fetal heart characterized by underdevelopment of left heart structures, including hypoplasia of the aorta, aortic atresia, mitral valve stenosis, underdevelopment of the left ventricle, and ventricular septal defect. FoxC2 *is an essential transcription factor for cardiac neural crest cell migration and other transcription factors involved in heart development. Additionally, the cells in the cardiogenic area express* FoxC2 *during embryogenesis. Part of the rationale of this hypothesis was derived from research in the disease Lymphedema-Distichiasis. In studies regarding* FoxC2*, complete knockout of the gene* (FoxC2$^{-/-}$) *in mice models leads to phenotypes associated with HLHS. Our hypothesis proposes that* FoxC2 *is an upstream factor of numerous genes:* Hey2*,* Hand1*, and* Tbx5*.*

33 Examining the Role of the Chordin-Bone Morphogenetic Protein Pathway Signaling Pathway in the Etiology of Hypoplastic Left Heart Syndrome

Anab Mohamed, Subban Hassan, & Isra Addani
University of Minnesota Rochester // Faculty Sponsor: Peter Larsen, Ph.D.

HYPOTHESIS: We hypothesize that an increase in Chordin inhibition will decrease the typical molecular activity of bone morphogenetic proteins, inducing subsequent underdevelopment during ventricular and atrial cardiomyocyte development, resulting in hypoplastic left heart syndrome.

34 Teratogenic Effecting of Exogenous Retinoic Acid Found in Prenatal Supplements May Be the Underlying Cause of HLHS

Mikael Mir, Jake Malkani, Kaila Bergman, & Ibtisam Rauf
Northwestern Health Sciences University // Faculty Sponsor: Susan C. Lawrenz-Smith, Ph.D.

HYPOTHESIS: Exogenous retinoic acid (RA) metabolized from vitamin A found in prenatal supplements causes an aberrant increase in the amount fetal RA exposure during the first few weeks of gestation, similar to the side effects seen with isotretinoin (Accutane) use during pregnancy. The teratogenic effects from high levels of RA alter the expression of cardiogenesis-specific transcription factors via transcriptional regulation in the developing left ventricle and affect the migration of cardiac neural crest cells to the aortic-pulmonary septum, thus causing HLHS.

Hypoplastic left heart syndrome (HLHS) is a congenital birth defect characterized by an underdevelopment of the left ventricle (LV), mitral valve, aortic valve, and ascending aorta, with some infants being born with atrial septal defects (ASDs). We hypothesize that vitamin A found in prenatal supplements causes an aberrant increase in fetal retinoic acid (RA) exposure during the first few weeks of pregnancy. Excess RA exposure causes a teratogenic effect that alters the expression of cardiogenesis-specific transcription factors in the developing left ventricle and affects the migration of cardiac neural crest cells to the aortic-pulmonary septum, thus causing HLHS. Many prenatal supplement brands contain large amounts of vitamin A and mothers may be at risk if they go over their recommended daily dose. If our hypothesis is supported, preventative therapies can be identified and intervention can be administered at the early stages of development. Routine prenatal testing for the mother's and fetus's serum RA levels, as well as Doppler ultrasound techniques for detecting abnormal increases in uteroplacental blood flow during gestation, could prove effective for detecting early signs of HLHS.

35 Hypoplastic Left Heart Syndrome Caused by Premature Closure of the Foramen

Sicheng Mo, Dongjie Tu, Warren Williams, & Carson Derousseau
University of Wisconsin - Eau Claire—Barron County // Faculty Sponsor: Wufeng Tian, Ph.D.

HYPOTHESIS: Premature closure of the foramen ovale during the fetal period may cause the hypoplastic left heart syndrome.

In this poster, we have reviewed the background of the Hypoplastic left heart syndrome and made a bold but reasonable assumption

that if the foramen ovale closes prematurely, the blood that is transported to the left atrium by the right atrium will be restricted, resulting in hypoplastic left heart syndrome. We have also proposed to use the odds ratio model to statistically verify our hypothesis. However, we have showed an example of how to use our model to test our hypothesis.

36 The Histone Acetyltransferase p300 is Associated with Signaling, Epigenetics, and Abnormalities Found in the HLHS Phenotype

Anna Olson, Isaac Lynch, Ben Milhaupt, & Greta Prokosch
St. Olaf College // Faculty Sponsor: Jean Porterfield, Ph.D.

HYPOTHESIS: We hypothesize that p300, a histone acetyltransferase that is critical in the activation of the NOTCH signaling pathway, could epigenetically cause an HLHS phenotype in similar ways that NOTCH1 mutations do. Abnormal p300 activity could result in altered cell differentiation patterns and calcium signaling, leading to the observed phenotype of HLHS.

Hypoplastic Left Heart Syndrome (HLHS) is a congenital heart condition that is characterized by an underdeveloped left ventricle. We hypothesize that p300, a histone acetyltransferase, alters the NOTCH signaling pathway, which in turn influences cell differentiation and calcium signaling, leading to the phenotypes characteristic of HLHS. NOTCH1, a gene in the NOTCH signaling pathway, regulates calcium signaling and cell proliferation. NOTCH1 mutations have been found to contribute to the increased Ca^{2+} signaling and aortic atresia found in patients with HLHS. Calcium plays a critical role in the human heart, and calcium levels are controlled by gated calcium channels called ryanodine receptors. We also propose the consideration of epigenetic factors such as acetylation and methylation of histones and DNA in the analysis of HLHS. p300 is involved in the transcriptional activation of NOTCH. Therefore, altered p300 activity could lead to impaired cell differentiation and signaling found in HLHS. As there has not yet been extensive research performed on the connection between p300 and HLHS, we propose that this is the missing puzzle piece to finding the underlying cause of this complex disease.

37 Mutations in HAND1 and NKX2.5 Genes in combination with Air Pollution Exposure Reveal Potential Cause for HLHS

Elise Patchett & Kiley Robertson
St. Olaf College // Faculty Sponsor: Cynthia Book, Ph.D.

HYPOTHESIS: Mutations within the NKX2.5 and HAND1 genes, in combination with exposure to air pollution during gestation, results in abnormal development of the left ventricle, ultimately causing Hypoplastic Left Heart Syndrome.

Hypoplastic Left Heart Syndrome is caused by mutations within the NKX2.5 and HAND1 genes, along with exposure to air pollution during pregnancy. Since not all HLHS patients have these mutations, it is likely that exposure to air pollution during pregnancy also plays a role in embryonic heart formation. In order to prevent the onset of HLHS, gene therapy can be used by inserting normal copies of the mutated genes into the placenta via placental injection.

38 Folic Acid and the Developing Heart: Effects of Folic Acid Deficiencies on Homocysteine Levels, Nitric Oxide Signaling, and the NOTCH1 Pathway

Ryan Peterson, Samantha Hammill, & Zachary Caldwell
University of Northwestern—St. Paul // Faculty Sponsor: Gary Mumaugh, DC, FACO

HYPOTHESIS: Deficient levels of FA in mothers before and during the first trimester of pregnancy leads to high levels of homocysteine as well as an insufficient availability of NO. Through this, low levels of NO
interrupt proper *NOTCH1* signaling leading to irregularities in the developing heart, specifically the phenotype of HLHS in newborns.

Hypoplastic Left Heart Syndrome (HLHS) is a relatively rare condition characterized by severe underdevelopment or hypoplasia of structures found in the left side of the heart. The the underlying cause of HLHS remains largely unknown, however, the importance of folic acid (FA) in prenatal health is well noted. Further studies have concluded that FA plays a major role in regulating homocysteine levels in the blood and biologically available amounts of nitric oxide (NO). Insufficient activity in NO signaling is shown to misreglate the NOTCH1 *pathway, which plays a major role in the proper development of asymmetrical heart structures, thus leading to the HLHS phenotype. The exact effects of FA and NO on myocardial development could be further examined by use of induced pluripotent stem cell (iPSC) cultures. Treatment of potential HLHS cases could be made extremely simple by readily available dietary folate supplements as well as public awareness campaigns on the importance of maintaining proper FA levels in women of childbearing age.*

39 Long Non-Coding RNA Sequences Repress MYH6 Expression in HLHS: A Novel MYH6 Long Non-Coding RNA Sequence Mechanism

Jenna R. Richter & Iya Abdulkarim
St. Olaf College // Faculty Sponsor: Laura Listenberger, Ph.D.

HYPOTHESIS: We hypothesize that HLHS is caused by reduced α-MHC due to one of two factors, 1) recessive mutations in the MYH6 gene prevent the translation of functional α-MHC or 2) lncRNA strands within or near the MYH6 domain repress MYH6 expression.

The etiology of hypoplastic left heart syndrome (HLHS) has been under investigation for years. There is a strong consensus that the disease is genetically linked, but the molecular underpinnings remain poorly understood. We hypothesize that the primary gene involved in HLHS etiology is MYH6, which codes for α-myosin heavy chain (α-MHC) protein and plays a vital role in facilitating cardiac muscle contractions. Furthermore, we believe that MYH6 expression may be reduced in some HLHS patients by a regulatory long non-coding RNA (lncRNA).

40 An Immunological Response in the Fetus Manipulates Calcium Signaling of Cardiac Rhythm thus Altering the Cyclic Stretch and Cell Migration

Jack T. Strotbeck & Elijah A. Williams
Saint Mary's University of Minnesota // Faculty Sponsor: Debra Martin, Ph.D.

HYPOTHESIS: This hypothesis proposes that improper cardiac rhythm, induced by defective calcium signaling pathways that are manipulated by an immunological response in the fetus, leads to pathophysiologic alterations to the cyclic stretch and cell migration, resulting in the subsequent hypoplasia of left heart structures.

Antibodies are known to cross the placental barrier. In the case of cardiac malformation, particular antibodies, anti-SSA and anti-SSB, have been linked to cardiac damage of the atrioventricular (AV) node. The damage to the AV node may impact intracellular calcium signaling pathways which may lead to fetal rhythm disturbances. This flawed electrical signaling may impact the electrotaxis of embryonic cardiac cells. With this in mind, this combination of factors accompanies hypoplasia of the left ventricle and mitral and atrial valve stenosis. To explain the hypoplasia of the ascending aorta and aortic arch, the flawed cyclic stretch of smooth vascular endothelial (VSE) muscle cells has to be taken into account. When applied, this improper cyclic stretch, due to improper electrical conduction, explains the hypoplasia of the ascending aorta and aortic arch. This leads to the characteristics observed with Hypoplastic Left Heart Syndrome (HLHS).

41 Role of Nitric Oxide in HLHS Development

Pavina Soukamneuth, Abdiasis Abdilahi, Jed Kreuser, & Rehan Saber
Northwestern Health Sciences University // Faculty Sponsor: Susan C. Lawrenz-Smith, Ph.D.

HYPOTHESIS: A reduction in maternal leptin levels causes a decrease in nitric oxide (NO) production, down-regulating GATA4 and TBX5 expression and disrupting mitochondrial respiration in the left heart, leading to Hypoplastic Left Heart Syndrome (HLHS).

42 Exploring Viral Infection as the Underlying Cause of Hypoplastic Left Heart Syndrome

Richard Sam & Hugh Yeh
University of Illinois at Urbana-Champaign // Faculty Sponsor: Shawna Naidu, Ph.D.

HYPOTHESIS: Inspired by Zika virus induced microcephaly and type B coxsackieviruses association with cardiovascular complications, and the resemblance of patterns of occurrences of HLHS to viral infections, we propose that a possible underlying cause of a subset of HLHS may be due to viral infection from vertical transmission during pregnancy.

Currently, the underlying cause of hypoplastic left heart syndrome (HLHS) is believed to due to multifactorial contributions from genetic and environmental factors. Due the resemblance of HLHS to developmental abnormalities caused by Zika virus and in attempt to consider both environmental as well as genetic factors, we propose that the underlying cause of a subset of HLHS may be due to maternal viral infection transferred to the infant via vertical transmission. Furthermore, we showed that the pattern of HLHS diagnosis resembles that of infectious diseases due to viral infection. We conclude our study by exploring currently known viruses capable of

causing cardiovascular complications. By attempting to find a underlying cause of a subset of HLHS, we hope to promote the development of treatments to prevent HLHS before genetic abnormalities occur.

43 ECM Degradation by MPs in HLHS Patients

Elizabeth Valine, Anne Mills, Crystal Mua, & Antonia Fritz
University of Northwestern—St. Paul // Faculty Sponsor: Gary Mumaugh, DC, FACO

HYPOTHESIS: We hypothesize that an over expression of cardiac metalloproteinases induces the degradation of the extracellular matrix, causing the underdevelopment of the left ventricle, resulting in Hypoplastic Left Heart Syndrome.

Our research investigates the involvement of metalloproteinases (MPs) in the development of hypoplastic left heart syndrome (HLHS). MPs regulate the degradation of the extracellular matrix (ECM) and its components. We hypothesize that overexpression of MMP-2, MMP-9, MMP-14, ADAMTS1, or ADAMTS9 during embryonic development will result in HLHS.

44 Streptococcus infection and HLHS: The Possible Role of Immunity Following Streptococcal Infections as a Risk Factor of HLHS

Wei Wang & Jiaping Pan
St. Olaf College // Faculty Sponsor: Sarah Amugongo, Ph.D.

HYPOTHESIS: We hypothesize that a misguided immune response that intends to target GABHS can possibly lead to HLHS and that certain genetic components may increase the likelihood or severity of
the misguided immune response.

In our poster presentation, we discuss certain evidence that links Hypoplastic Left Heart Syndrome (HLHS) to seasonal infections caused by Streptococcus spp., specifically the group A b-hemolytic streptococci (GABHS). We compare the immunological response triggered by GABHS to HLHS symptoms and propose the possibility of said response as one of the causative agent of HLHS.

Student Index

Faculty Sponsor Index

Institution Index