Gastrointestinal functions in autism

Autism is defined by behavioral patterns and delays in language development, but chronic gastrointestinal (GI) problems are also seen, like abdominal pain, diarrhea, constipation, esophagitis, and gaseousness. The central hypothesis of this proposal is that altered handling of intracellular calcium ion by GI nerve and muscle causes some of these GI disorders. To study these disorders, we will use a genetically altered mouse that exhibits the rare disorder of Timothy Syndrome (TS). Individuals with TS have a genetic mutation in a cell membrane calcium ion channel, known as Cav1.2. Strikingly, over 80% of patients carrying this mutation have also been diagnosed with autism. No other human mutation shows this high degree of correlation. We hypothesize that this mutation in TS mice will cause nerve and muscle cells to be overloaded with calcium ion. Specifically, we will examine intestinal smooth muscle in TS mice to determine if intracellular calcium ion overload alters its ability to propel food. We will also determine if nerves of the intestine abnormally regulate the absorption processes. Next, we will use molecular biological techniques to identify mutant Cav1.2 channels in intestinal smooth muscle and nerves of TS mice and electro-physiological techniques to determine the mechanisms that lead to altered function of these channels. Study of this unique mouse will provide key insights into the cellular basis of autism and its relationship to GI disorders and will provide a model for testing new therapies.

Principal Investigator: Duffey, Michael
Funder: Department of Defense
Funding Amount: $0.00
Institution: University at Buffalo, The State University of New York
Fiscal Year: 2010

The MET signaling system, autism and gastrointestinal dysfunction

In this project, researchers will directly investigate relationships between co-occurring gastrointestinal dysfunction (GID) and autism spectrum disorders (ASD), testing a biological hypothesis regarding disruption of the tyrosine kinase receptor MET receptor and its associated intracellular signaling events as a common theme in ASD. Genetic polymorphisms in MET have been implicated in ASD, and MET plays a role in brain wiring and gastrointestinal epithelial cell repair. Researchers will follow a pediatric group with and without ASD, characterizing their GI function and genotyping for sequence alterations in the MET gene to connect the genetic risk findings with biological changes. The studies will provide unique epidemiological descriptions of the study population giving insight into stratification of the ASD subgroup that is characterized by the presence of GID. Identification of biomarkers such as pan-MET and phospho-MET protein levels may also benefit diagnosis and treatment for ASD.

Principal Investigator: Levitt, Pat
Funder: National Institutes of Health
Funding Amount: $277,299.00
Institution: University of Southern California
Fiscal Year: 2010

Biomarkers for autism and for gastrointestinal and sleep problems in autism

The hormone melatonin has an important influence on the sleep-wake cycle and daily rhythms, is involved in fetal development and neurodevelopment, is used in the treatment of sleep problems, and has a role in gut function. Thus, there is a strong theoretical basis for studying melatonin in autism. A compelling reason for investigating melatonin in autism also comes from several previous studies that have found lower melatonin levels or decreased urinary excretion of the main melatonin metabolite in individuals with autism. Melatonin production has not been examined in children with autism younger than 5 years old. Examination and characterization of melatonin production in toddlers with autism may lead to measures useful for early screening for autism risk, for predicting behavioral phenotype, and for guiding intervention.

The immediate objective of the proposed research is to compare the production of melatonin by young children with autism to typically developing children. Specifically, we will see if the nighttime excretion rate of melatonin sulfate is markedly lower in the children with autism, whether there is a subgroup of children with autism having very low excretion; whether low nighttime excretion of melatonin sulfate is associated with sleep problems; and whether low daytime melatonin sulfate excretion is associated with gastrointestinal problems. We also will determine whether other hormones with day-night variation are similar in children with autism and in typically developing children.

Establishing the presence and characterizing the extent and nature of altered melatonin production in young children with autism has several important implications: (1) the measure may prove useful in early screening for autism risk; (2) may provide an indication of which areas of behavior or functioning might be most affected (e.g., sleep problems, GI disturbances); (3) may serve to guide early intervention strategies; (4) may function as a useful predictor and surrogate marker of response to intervention; and (5) may provide leads to related neurobiological alterations and mechanisms, and may suggest specific candidate genes of interest in autism. Larger second phase studies are planned to establish more fully the initial findings, to replicate the expected behavioral associations, and to examine the genetic and biochemical basis of the altered secretion/excretion. National Institutes of Health funding will be sought for the follow-up studies that may well take a multi-center approach. The urine samples collected should also permit or facilitate future investigations examining day-night variation in other systems, levels of sex hormones, markers of oxidative stress, and environmental exposures in toddlers with autism.

The research has the potential to help families and children affected by autism by improving early detection/screening, by improving treatment, and by increasing basic understanding of the origins of autism.

By moving the research on melatonin in autism to younger children, the research has the potential to greatly improve the clinical utility of the measure. Characterizing the relationship of the alteration in melatonin to disturbances in sleep behavior and gastrointestinal functioning may lead to an improved understanding of the bases for these problems in autism.

Principal Investigator: Anderson, George
Funder: Department of Defense
Funding Amount: $0.00
Institution: Yale University
Fiscal Year: 2010

Identifying gastrointestinal (GI) conditions in children with autism spectrum disorders (ASD)

Gastrointestinal (GI) dysfunction is relatively prevalent in children with autism spectrum disorder (ASD), but is especially difficult to diagnose. Current clinical practice guidelines include neither routine GI evaluation nor diagnostic criteria or protocols that consider the special gastrointestinal needs of this patient population.

Therefore, the first objective of the proposed study is to develop and validate effective and appropriate diagnostic screening methods to detect symptomatic GI dysfunction in children with ASD. The second objective of the proposed research is to determine whether GI dysfunction contributes substantially to the expression of problem behaviors (PB) in children with ASD and to determine, if specific behaviors, including but not limited to PB, are increased in those children with gastrointestinal dysfunctions.
Analysis of the small intestinal microbiome of children with autism

Many children with autism spectrum disorders (ASD) experience gastrointestinal symptoms such as abdominal pain, constipation, diarrhea, and bloating that exacerbate their behavioral problems. These symptoms may be related to alterations in microbial flora in the intestine. Evidence on the effect of gut flora on children with autism is very limited; however, even in healthy humans intestinal microflora is largely unexplored. Modern culturing-independent techniques allow studying complex microbial ecosystems (microbiomes) containing at least 100 times as many genes as human genome. The most informative is technique based on gene analysis of specific rRNA found in all microorganisms. This novel approach was successfully used for the analysis of colon mucosa and stool samples in healthy humans and patients with inflammatory bowel disease. However, microbiota of the upper part of gastrointestinal tract in humans has been understudied in comparison to that of the colon. The objective of our study is to evaluate the entire microbial population in the upper gastrointestinal tract of children with autism to determine if there is an overgrowth of specific populations of bacteria. These data will be correlated with questionnaires on gastrointestinal symptoms and autistic behavior. The genomic data from this study might be of interest in terms of understanding the role of upper gut microorganisms in the etiology of autism and use of therapeutic strategies to alter intestinal flora.

Molecular pathways involved in oxidative stress and leaky gut impairment in autism spectrum disorders

The main aim of this research is to investigate the relationship between the gastrointestinal tract and autism and understand how gut, brain, nutritional, and toxic status are consistent with greater oxidative stress in autistic spectrum disorders (ASD). Researchers will perform detailed analysis on peripheral blood mononuclear cells (PBMCs) and in the intestinal mucosa of ASD patients to identify several proteins and genes involved in inflammatory and cellular stress response as well as the innate and adaptive immunological response. In particular, researchers will study the molecular pathways responsible for apoptosis, inflammation, and cell damage or suffering of ASD-PBMCs.

Growth and maturation in children with autism

While the cause of autism is unknown, children with autism and autism spectrum disorders (ASD) have been noted in several studies to have a high prevalence of accelerated head growth, appear to be taller on average than the general population, and may have gastrointestinal co-morbidities for which gluten- and/or casein-free diets are prescribed. Growth patterns and markers of maturation in autistic children have not been studied in detail, and other methods of assessing maturation in autistic children, such as hormone analyses and bone age, have not been explored. This cross-sectional study aims to determine if children with autism or ASD have patterns of childhood growth, development, and hormonal levels that differ from that of a group of normal control children.

Evaluation of altered fatty acid metabolism via gas chromatography/mass spectroscopy and time-of-flight secondary ion mass spectroscopy imaging in the propionic acid rat model of autism spectrum disorders

Researchers hypothesize that propionic acid (PPA) and related enteric short chain fatty acids are likely molecular candidates linking the disparate dietary, gastrointestinal, neuropathological, behavioral, metabolic, and metabolic disturbances seen in autism. In this study, live rat exposure to propionate and other short-chain fatty acids will be followed by an animal-model demonstration and organ analysis. The brains and tissues of the rats will be analyzed with Time of Flight (ToF)-SIMS imaging, which will enable rapid anatomical determination of key biomarkers in ASD pathology and relate these markers to available human samples such as gut or blood. These animal studies will provide further evidence that behavioral, neuropathological, electrophysiological, and biochemical abnormalities with PPA exposure can be reduced by treatment (such as diet, costridial eradication, probiotics, etc.), which are our long term goals.

Treatment of medical conditions among individuals with autism spectrum disorders

The life-long impairments in communication and social function for those with autism are often complicated by the presence of medical comorbidities, including epilepsy, gastrointestinal disturbances, and sleep disorders. Little is known about the pathophysiology of these comorbid conditions and even less about treatment of the symptoms among individuals with autism. Sleep disorders in ASD are of particular interest and can be reliably investigated using polysomnography (PSG), a non-invasive recording of a variety of sleep parameters. A previous study showed that children with autism spend an abnormally short time in the Rapid Eye Movement (REM) stage of sleep, which is thought to play a key role in learning and memory, compared to total sleep time. Donepezil hydrochloride is a drug that has been shown to normalize REM sleep, and treatment with donepezil could benefit the quality of sleep in children with autism as well as enhance their ability to learn and remember. This pilot study aims to determine the dose of donepezil that reliably increases the percentage of REM sleep and to assess any potential side effects in children ages 2-11. If donepezil is effective in normalizing REM sleep, and the drug’s side-effects profile is favorable, then a placebo-controlled trial will be initiated to assess the effects of long-term donepezil administration on REM sleep and on autistic symptoms, learning, memory, and overall behavior.
Are autism spectrum disorders associated with leaky-gut at an early critical period in development?

Although there is general consensus of greater prevalence of gastrointestinal (GI) distress in individuals with autism spectrum disorders (ASD), the nature of the link is unknown. There is preliminary evidence to suggest that GI distress in ASD may be associated with “Leaky-Gut” (i.e., increased permeability of the intestinal mucosal barrier due to either delayed or abnormal development), as shown by a study showing higher-than-normal prevalence in ASD children 4 - 16 years of age (e.g., D'Eufemia et al., 1996). During normal digestion, the mucosal barrier is responsible for keeping digestive enzymes out of the intestinal wall. Recent evidence shows that if these powerful degrading enzymes enter the wall of the intestine, they will cause major damage to the intestinal wall as well as inflammation in the brain. Investigators hypothesize that ASD may be associated with Leaky Gut early in development, which combines, or interacts, with diet (breast-milk, formula, solid foods) leading to intestinal wall damage and inflammation in: 1) the intestine, which could explain the GI distress, and 2) in the bloodstream, which could reach and damage the developing brain, thus contributing to the onset of ASD itself. In this study, researchers will track key aspects of GI function in Low-Risk and “High-Risk” infants (i.e., infants who have an older sibling diagnosed with ASD); including: 1) signs of Leaky-Gut, 2) symptoms of GI distress (e.g., diarrhea, reflux, constipation), 3) diet (breast-milk vs. formula), and 4) evidence of digestive enzymes and inflammatory markers of cell death in the bloodstream. They will correlate GI diet, and inflammatory measures with results from cognitive, visual, and behavioral tests, including standard ASD diagnostic tests, at two and three years of age to determine if Leaky-Gut is associated with the development of ASD.

Principal Investigator: Dobkins, Karen; Schmid-Schoenbein, Geert
Funder: National Institutes of Health
Funding Amount: $309,000.00
Institution: University of California, San Diego
Fiscal Year: 2010

A prospective multi-system evaluation of infants at risk for autism

This study proposes to learn about the early biological and medical features of autism. Our reasoning for doing this is as follows. We observe that autism starts in infancy or early childhood. We observe that children who are diagnosed early and receive intensive early intervention do better. We also observe that many children with ASD have medical problems, such as gastrointestinal problems, or immune problems (such as frequent infections or allergies). But researchers and clinicians do not at present look for medical early warning signs of autism. If we could identify early medical and laboratory signs of ASD or high ASD risk, we might be able to reduce the severity of ASD or even prevent it entirely.

But in order for this to be possible, we need to understand the earliest medical changes that occur in ASD, even before the autistic behaviors begin. Because autism has been considered a behavioral disorder, researchers have looked for early behavioral signs of the onset of autism. To do this they have studied infants who are at high risk for autism because they have an older sibling who has already been diagnosed with this condition. The goal of research into early behaviors predicting autism is to get early intensive behavioral intervention started sooner.

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In this project we are testing the idea that the biological features of autism may come on line before the behavioral features do, and may allow us to help the child earlier than if we wait for the behavioral features.

We are also operating on the belief that the biomedical and medical problems of young children at risk for autism may be a big part of the cause of autism. Even if these factors do not cause the autism—if the autism is caused independently of these medical problems—then the medical problems may still make the quality of life worse.

We are therefore choosing measurements to focus on medical and metabolic problems that may closely relate to the underlying reasons why the child is having trouble with brain functioning. For example, we will study immune system functioning and see whether it changes in relation to brain or behavior functioning. And we will measure cells in the blood for signs of oxidative stress, which is a change in metabolism that happens in the cells of our bodies when we are exposed to environmental or emotional stressors. Inflammation and oxidative stress have been measured in children and adults with autism, but they have never been studied by researchers by measuring children who don't have autism yet but are at high risk of developing it.

We expect that the medical and metabolic problems that researchers have been finding in older children will start to appear early in the life of a child with autism. We think that when these problems appear, they interfere with the normal functioning of the brain and, possibly, also (especially if these problems persist for a while) with the way the brain develops. We will measure this by tracking the development of medical problems at the same time as we track the development of brain signaling using EEG measures. If we see that these changes are related to each other, it will offer more ways to catch these problems early, and this may give us opportunities to correct them through treatment, and particularly through medical treatment, before they contribute to the child having more severe problems. Even if the problems don't happen for the same reasons, the body problems may be good early warning signals. Our goal therefore is to see whether we can find early biomedical predictors of autism.

This study will lay the foundation for a systematic medical evaluation of every infant at risk for autism or showing signs of autism. Moreover, it will help us expand what we consider to be risk factors for autism to include problems, such as recurrent infection or early gastrointestinal problems, that may either signal that the child is vulnerable, or weaken the child and make him or her more vulnerable to later challenges—or both.

If the patterns we predict turn out to be the patterns we actually find, we may be able to move rapidly to use the information to suggest that children who show warning signs on tests such as the ones we will use should get special attention and help so we can get an early start on preventing deterioration and keeping them doing well. This study will also help other researchers know where to start in investigating the early onset of autism and in looking for medical treatments that may help.

Principal Investigator: Herbert, Martha
Funder: Department of Defense
Funding Amount: $0.00
Institution: Massachusetts General Hospital
Fiscal Year: 2010

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Once we expand our view of autism to include its biomedical and metabolic features, then we can realize the importance of looking for early biomedical and metabolic signs of autism. The goal of research into early biomedical and metabolic signs of autism is to know enough to start early medical support and treatment that may improve the well-being of the child and head off some of the difficulties that child may face if left untreated.

To bring us closer to the time when we understand the biomedical features of autism as much as the behavioral features, in this research project we will add biomedical approaches to the study of infants at risk for autism. We will do medical exams, measure electrical activity in the brain (through EEG), and study substances in blood, urine, and saliva to understand the chemistry and metabolism of autism.

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Principal Investigator: Dobkins, Karen; Schmid-Schoenbein, Geert
Funder: National Institutes of Health
Funding Amount: $309,000.00
Institution: University of California, San Diego
Fiscal Year: 2010
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**Behavioral and physiological consequences of disrupted Met signaling**

A number of risk genes for autism spectrum disorders have been identified thanks to the intensive efforts of the Simons Foundation and other genetic consortia. This is just the beginning, however. A major goal of future research is to translate these genetic findings into a more in-depth understanding of how such risk, combined with environmental factors, disrupts the formation of brain architecture that leads to autism. This information is essential to designing better prevention, diagnostic and intervention strategies for the disorder.

To that end, Pat Levitt, of the University of Southern California, is leading a collaborative effort by four laboratories to understand the functional implicatons of mutations in the autism risk gene MET, which codes for a receptor that is involved in the wiring up of important brain circuits. The researchers' previous study of three large collections of families with members with autism found a mutation in MET that more than doubles the risk for autism and reduces the amount of MET protein in the brains of people with the disorder. Three other research laboratories, using five different family collections around the world, have reported similar findings regarding MET as an autism risk factor. What's more, basic research in mice has shown that altering MET expression leads to problems in the formation of synaptic circuits—the junctions between neurons—which ultimately affects the ability of the cells to communicate with each other to process complex information.

Levitt's team is working on clinical follow-up studies to determine the correlation between the MET mutation and disrupted brain and gastrointestinal functions in autism, a project also supported by the Simons Foundation. To understand why this gene may be a key risk factor for autism, Levitt and colleagues are investigating how the MET gene controls the development of synapses in circuits that control social and emotional behaviors and learning. In addition, Levitt and his colleagues will investigate the impact of a 'double hit'—a genetic mutation of MET, combined with exposure to a common pollutant that by itself negatively impacts developing brain architecture. This is being done by using genetic tools and new methods for measuring neuron activity in key brain circuits that include the cerebral cortex, a structure that is responsible for complex functions, such as processing social and emotional information. Their experiments will test the popular hypothesis that in autism, local and long-range connections in the brain do not assemble properly, leading to the core behavioral features of the disorder.

The team of scientists are performing a number of studies. The development of new complex cognitive tests in mutant mice are being led by Larry Rothblat (George Washington University). Darryl Hood (Meharry Medical College) is leading the efforts involving prenatal exposure to polyaromatic hydrocarbons, a common pollutant that appears to have a negative impact on the long-term expression of both MET and another key protein, SP4, that can control MET expression. Advances in the local and long-distance circuit analyses in MET mutant mice are being led by Gordon Shepherd (Northwestern University), who has already demonstrated hyperconnectivity in local circuits. The research findings from this basic research program, the continuing clinical studies, and the additional genetic replication in new family collections, strongly support MET as a biologically and genetically relevant risk factor for autism.

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**Novel probiotic therapies for autism**

Most research into autism and autism spectrum disorders (ASD) has focused on genetic, behavioral, and neurological aspects of the illness. However, a role for the immune system in the onset or progression of autism has recently gained significant attention. Striking alterations in the immune status of the brains of autistic subjects have been found. Moreover, many autistic children have been diagnosed with food allergies and are on special diets. There are a number of reports of inflammatory reactions in the gastrointestinal (GI) tract in ASD: a significant subset of autistic children display chronic inflammation of the colon; many ASD children have loose stool; diagnostic analysis of patients reveal elevated levels of inflammatory factors; the bacterial microbiota (the collection of beneficial bacteria within the intestine of humans) is altered in ASD; antibacterial treatments provide behavioral improvements in ASD. Thus, the connection between gut bacteria, intestinal inflammation and autism is a very promising area of investigation. However, a hypothesis-driven investigation in this area has not been attempted thus far.

Combining two laboratories with different but relevant areas of expertise, we propose to study the ability of beneficial gut bacteria to ameliorate ASD-like symptoms in a mouse model. We will test for improvements in behavioral, neuropathologic, and GI abnormalities by introducing a probiotic microbe that has already been shown to reduce intestinal inflammation. In recent years, the notion that beneficial bacteria can provide a remedy for digestive diseases is becoming accepted by the public (many grocery stores carry yogurt products supplemented with probiotics). The Mazmanian laboratory was the first to show how a human symbiotic microbe prevents harmful intestinal immune responses. Since GI inflammation can dramatically alter behavior in animal models and in
human disorders, our goal is to extend this connection to ASD. Combined with the expertise of the Patterson laboratory, which has developed an animal model for autism based on epidemiological research, we wish to validate the use of specific beneficial bacteria as a therapy for ASD. Namely, can we measure improvements in the ASD-like behaviors and neuropathology by curing intestinal symptoms associated with the disease?

We have recently demonstrated that symbiotic intestinal bacteria direct the development of the mammalian immune system and confer protection from GI inflammation. Bacteria in our intestines actively promote our health, and therefore losing these "good" bacteria may lead to disease. As the incidence of autism diagnosis has risen dramatically in recent years, many have speculated lifestyle changes to be the cause for this increase. Have societal advances (including sanitation, "Western" diets, hygiene, and anti-bacterial therapeutics) paradoxically affected human health adversely by reducing our exposure to health-promoting gut bacteria? We propose that by restoring the balance of beneficial microbes, we can correct the environmental factor(s) that may be contributing to the development of autism in so many children today. If successful, our approach could provide clinical benefits to a broad range of ASD patients, including children, adolescents, and adults. The use of beneficial bacteria that are found in most healthy humans should pose very little risk to patients. Furthermore, as these therapeutics are natural and harmless, the time frame to achieve patient-related outcomes will likely be shorter than for therapies using synthetic chemicals. Our hope is that by understanding the biological reasons why individuals develop autism, and if treatment with specific probiotic bacteria to ASD children can be beneficial, we can design novel and natural therapeutics to prevent and/or cure this devastating disease.

Principal Investigator: Patterson, Paul
Funder: Department of Defense
Funding Amount: $570,145.00
Institution: California Institute of Technology
Fiscal Year: 2010