**Investigating the role of the human exposome in Crohn’s disease**

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**Date submitted: May 14, 2019**

**Summary**

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD), the exact cause of which is unknown. The peak window of disease onset is between ages fifteen and thirty and currently there is no known cure. Epidemiological evidence suggests that environmental exposures contribute to the etiology of the disease, supported by its increasing incidence and prevalence world wide (Ng et al., 2017). Analyzing individual human exposomes for potential triggers in the development of Crohn’s disease is a novel approach to understanding disease pathogenesis. In this pilot study, we propose to investigate the role of environmental, biological, and chemical exposures in the onset and progression of the disease. We will introduce a wearable/portable, non-invasive device to monitor the longitudinal airborne environmental exposures of 75 young adult participants in a high risk and an affected population, along with a healthy control cohort. Biological and chemical exposure samples will be processed using non-targeted approaches using next generation sequencing and mass spectrometry, respectively. Integrated statistical and computational analyses, including machine learning algorithms, will be implemented to identify potential environmental exposure markers in the development of Crohn’s disease. In addition, participants will wear a smartwatch to continuously monitor heart rate, stress response and other physiological parameters. Metabolome, immunome and microbiome profiling will be performed from blood and fecal samples, respectively. By integrating environmental exposure samples and other real-time measurements collected by the pocket-size monitor, physiological measurements from smartwatches, metabolomics, immunome and microbiome profilings, we will 1) identify environmental exposures related to the etiology of CD; 2) environmental exposures correlated with disease flares 3) potential biomarkers indicative of disease state; 4) early detection physiological markers measured by smartwatches. Our study will not only improve our understanding of the environmental component of the Crohn’s disease but also provide a potential new frontier for disease prevention and treatment.

**Project Goal (max 50 words)**

We plan a pilot study to identify potential environmental exposure markers that may contribute to the development and progression of CD.

**Strategy (max 50 words)**

We will use a pocket-size personal environmental exposure monitor and a smartwatch, along with multi-omics approach,to closely monitor 25 gender-balanced CD patients and their siblings reside in the same household (25), and a cohort of 25 healthy individuals for a year.

**Outcomes (max 50 words)**

We expect that the results from our study will shed light on the impact of environmental exposures on the development of CD and flares associated with the disease and provide insight into potential novel approaches to disease prevention and treatment. Although this is a modest-sized cohort, it will serve as a pilot model to scale up to a larger study.

**Need**

CD is heterogeneous in genetic variations, epigenetic features and clinical phenotypes (Lee et al., 2017). Intensive efforts have been made to study the genetic predispositions of the disease, however, we lack a comprehensive understanding of how environmental factors contribute to disease incidence, and more importantly, how environmental factors interact with other factors, such as dysregulated immune system and dysbiosis (Legaki et al., 2016; Greenblum et al., 2012; Manichanh et al., 2012) in CD. We propose this study to start to close the gap in our knowledge of CD etiology by monitoring personal environmental exposure and their impact on CD in great detail.

**Significance**

Human health is affected by a diverse range of factors including genetics, environmental exposures, and their complex interactions. However, while intensive efforts have been made to measure and understand the impact of genomic variations on health, our knowledge about many environmental exposures and their impact remains remarkably limited. Existing evidence suggests certain types of environmental exposure (e.g. exposure to broad classes of air pollutants such as particulate matter) greatly affects our health, and is directly associated with numerous respiratory diseases, allergies, infectious diseases (Fujimura et al., 2014), and even cancer (Pfeifer, 2010; Tomasetti et al., 2017).

CD is a type of IBD, the underlying mechanisms of which are largely unknown. Epidemiologic studies have pinpointed risk factors such as family history (Shen et al., 2009), ethnicity (Bengston et al., 2009), geographic regions (Loftus et al., 2004), infections (Wakefield et al., 1995), antibiotic exposure (Wurzelmann et al., 1994), and smoking history (Seksi et al., 2009) in the etiology of the disease. These epidemiologic studies provide ample data that environmental factors could strongly contribute to the etiology of CD (Lakhani et al., 2019).

Evidence suggests that CD results from immune dysregulation triggered by the host environment in a genetically susceptible individual (Uhlig et al., 2018). The phenotype of Crohn’s disease has wide variation in age of symptom onset, region of gastrointestinal involvement, disease behavior and severity. Persistent inflammation of different areas of the digestive tract can cause abdominal pain, diarrhea, fatigue, weight loss and malnutrition. Untreated, the inflammation in CD may induce intestinal stricturing or penetrate through the bowel wall to cause pathologic connections between the intestines and other organ systems, the skin, or leak into the abdominal cavity (Vavricka et al., 2010 and 2011; Bernstein et al., 2005; Silverberg et al., 2005). This process can be painful, debilitating, and lead to irreversible and or life-threatening complications including the development of neoplasia. Unfortunately, there are no known cures for CD at this time. Current therapy relies on treatment with immunomodulatory and immunosuppressant therapies to suppress inflammation and bring about disease remission. These therapies increase the risks for certain infections and malignancies, and are ineffective in some patients to halt disease progression as evidenced by the fact that approximately 60% of people with CD will require surgery (Ballengee et al., 2018).

Meanwhile, scientists are beginning to recognize that environmental exposures during childhood could have a formative impact on the development of the immune system (Boule and Lawrence, 2016; Martikainen et al., 2018). Disruption of the immune system may lead to a diverse array of problems in early as well as later stages of life, including but not limited to allergy/asthma (Lambrecht and Hamida, 2014), autoimmune diseases, various types of psychological conditions (Leonard 2010), and potentially CD (Marks et al., 2006). Therefore, we propose to systematically investigate the role of environmental exposures, including both biotics and abiotics, in young adults with CD, along with an at risk cohort and a healthy control group. We hypothesize that patients who develop CD in young adulthood may have abnormal exposures to biological or chemical agents through air, direct contact, and food intake. Identification of these environmental triggers could lead to interventions to modify disease course, or prevent the onset of Crohn’s Disease.

**Preliminary Results**

Our recent research (Jiang *et al.* 2018) revealed that we are constantly bombarded by a dazzling array of abiotic and biotic environmental airborne microscopic particles in our daily lives, far beyond what was previously quantified and understood. In particular, we developed novel methods for measuring personal environmental exposure (PEE) and revealed the remarkable spatial-temporal dynamics and diversity of personal biological and chemical exposure, or what we term the environmental “exposome”. We reengineered wearable devices to collect biologicals onto a one micron filter and chemicals using a cartridge to monitor 15 people as they moved around the country and world for up to two years (Fig. 1 A and B). We found that individuals were exposed to more than a thousand of species and 3000 chemical features within three months. Overall, we identified at least 2560 species, 1265 genera and 44 phyla, with about 300 species per 3-7 day sample (Fig. 1C); at the same time we tentatively identified 972 (out of 2796) putative chemical compounds, the majority of which were potential toxins. Through our analyses we demonstrated that both location and seasons have a strong impact on both biological and chemical profiles resulting in dynamic changes in samples collected from the same person. Perhaps more importantly, we discovered that human exposomes differed substantially between individuals even located in the same general area (e.g Bay Area), demonstrating that traditional monitoring data on broad area cannot reflect the complexity and dynamics of individual environmental exposures in practice. Altogether, we describe a novel method and demonstrate its practicability in tracking personal PEEs in unparallelled detail.

The development of smartwatches allow for frequent measurement of physiological parameters, such as heart rate and blood oxygen level. In our recent publication (Li *et al.* 2017), we monitored 43 individuals for up to 2 years. We collected over 250,000 daily measurements of heart rate, blood oxygen levels, skin temperatures, and physical activity (Fig. 2A). We found personalized circadian differences in physiological parameters, especially in particular environments, such as flight. More interestingly, we detected early signs of Lyme disease and inflammatory responses using readings from biosensors, based on which we developed a personalized, activity-based normalization framework to identify abnormal physiology signals for early disease detection (Fig. 2B-D).

The development of our PEE tracking technology opens the door to directly address the gap in our understanding of the interaction between environment and human health. Specifically, for the first time, we have the ability to fully characterize PEEs with a wearable instrument that closely tracks different individuals, instead of relying on broad-scale data from fixed monitoring stations or satellite images. Early detection of inflammatory responses by our wearable sensors is expected to be extremely helpful in a disease such as CD where the immune system is heavily involved. We propose to deploy our technology to study the role of environmental exposures in the etiology and flare ups of CD in young adults by tracking diagnosed patients’ PEEs for a year. By coupling the environmental measurements with concurrent activity tracking with biosensors, as well as metabolome, immunome, gut microbiome sampling and diet tracking, we expect to correlate exposure with disease physiology, biochemistry and immunology, all at a personal level. Although the study cohort is small we believe the information learned will enable a larger future study.

**Research Strategy and Approach**

We hypothesize that patients who develop CD in young adulthood have exposures to biological or chemical agents through air or direct contact that contribute to their disease etiology and flare ups. To test this hypothesis, we propose to perform a pilot study in which we measure the biological and chemical exposures of 75 people along with continuous tracking of physiological data, and periodic measurement of metabolomic, immunome and microbiome of the host. 25 people will have CD, 25 will be a risk for CD and 25 will served as healthy controls. We will correlate exposure information with physiological and host information to better understand what particular exposures correlate with which host physiology and disease onset and flare ups. Specifically we propose the following aims (Fig 3):

**Aim 1: Longitudinal sampling of PEEs in young adults with Crohn’s diseases or at higher risk of CD by personal exposure monitors (PEMs), smartwatches and omics profiling; data generation.**

Rationale

Though the exact cause of CD is unknown, the general consensus is that CD results from abnormal immune response triggered by environmental stimuli in a genetically susceptible individual. Intensive genome-wide association studies have identified more than 200 loci associated with IBD (Furey, et al. 2019), yet the effect size of most individual loci is small (McGovern, et al.2015, Mirkov, et al. 2017 ), suggesting that multiple loci, together with environmental factors contribute to the multifactorial nature of CD pathogenesis. To better our knowledge on the impact of environmental exposures, we propose a pilot study to closely monitor personal environmental exposures of participants who are at risk for or have the disease. We will test the feasibility of executing a study such as this one and attempt to correlate biological and chemical exposures with disease onset and acute flare ups.

Experimental Strategy

In this pilot study, we propose to monitor 25 young adults with CD; 25 siblings, who lack the disease but presumably are at high risk of CD and reside in the same household, and 25 healthy controls in families lacking CD with PEMs and smartwatches.The participants will wear PEMs and smartwatches for one year to closely monitor their PEEs and physiology. To better correlate with human physiology, we will analyze metabolomics and environmental compounds from blood samples, and as well as the microbiome from stool samples collected on a monthly basis. Participants will be asked to keep a food log as well to follow correlations with diet.

**Participants**

Participants of each sex along with age and sex matched controls will be recruited locally by Dr. Sarah Streett, at the Stanford Hospital who has a large registry of CD patients. Age matched healthy controls will be recruited through advertisements.

**PEMs**

PEMs collect airborne particulate matters (PMs) and toxic substances from personal environments, in particular, the air. Other features of the PEM include measuring temperature, humidity, airflow rate and reporting GPS coordinates. The PEM is also equipped with Bluetooth technology to connect with smartphones to allow real-time reporting and monitoring through a mobile app. The PEMs contain a hydrophilic (polyethersulfone) filter to capture the PMs, potentially consisting of viral particles, bacteria, fungal spores, animal debris, plant pollens, and other types of biological particles, ranging from 50 nm to 100 µm in size. The PEM is also equipped with a cartridge hosting adsorbents that collects both hydrophobic and hydrophilic aerosol chemicals.

**Smartwatches**

We will use a SensOmics smartwatch that continuously measures 1) physiological parameters, including heart rate, heart rate variability, peripheral capillary oxygen saturation (SpO2); 2) activity-related parameters, such as sleep, steps, and calories; and 3) galvanic skin response (GSR) which measures electrical resistance on the skin due to increased sweat gland activity when stressed. This measurement is expected to be of great value when CD patient experience acute episodes of the disease, and thus can be potentially used as an early detection marker.

Specific Methods

Subjects will be asked to wear a smartwatch, and carry the PEMs within their breathing zone to monitor their PEEs for a year. Sampling periods will be for two weeks (i.e. 26 samples per year). Fresh devices will be given to participants every two weeks. Individuals with CD will be equipped with a spare device, which will be turned on during periods when they experience an acute phase of the disease (flare ups). Clinically, this can be quantified using C-reactive protein (CRP) kits and other immune measurements. When special circumstances such as disease occurrence or relapse happens, samples will be taken every 4 to 7 days.

Exposure samples will be sent to Stanford for biological and chemical analysis where the devices are opened and processed in a sterile hood chamber. The biological samples are extracted from the filter and subjected to DNA and RNA Sequencing using our Illumina NovaSeq sequencer (depth 50M 150 bp paired end reads). The chemical samples are extracted from the chemical absorbent and processed for mass spectrometry analysis using our LC-Q Exactive plus which is run in a positive and negative mode; both reverse phase (for hydrophobic molecules) and HILIC (for hydrophilic molecules) LC systems will be used (Contrepois et al., 2015). We will be able to generate the most comprehensive environmental exposure database for CD patients to date.

To gain information concerning the participant immune, metabolome and microbiome response, in parallel with the exposure samples 20 mls of blood will be drawn every 4 weeks (13 samples per year) as well as during flare up every four days. Plasma samples will be analyzed for cortisol, CRP, as well as the metabolome (including chemicals) using untargeted metabolomics and our Q exactive HF (as above), and cell counts using standards assays and CyTOF. Stool samples will be analyzed for the microbiome. Urine samples will be banked for future use. To reduce expense,for the microbiome samples, it is likely that we will only analyze samples taken just before, during and just after flare ups with similar numbers of samples analyzed for the controls. The other assays are relatively inexpensive and can be run on all samples.

All samples and final aliquots will be collected in barcoded tubes and tracked using our lab information management system (LIMS).

Potential difficulties

1. Recruitment of study participants

The difficulty in recruitment of study participants is that not only the participants have to live locally in the Bay area to allow bi-weekly clinic visits, which requires a lot of effort itself, but also have to have a sibling who reside in the same household and willing to participate. We envision the requirement of the sibling would greatly reduce the number of eligible volunteers thus lengthening the recruiting period, yet is crucial to the study as siblings dramatically reduce the confounding genetic factors and easily tease out environmental factors that contribute to the disease development. To enable this we will modify our existing IRB approved study to include 16 years olds and higher (Presently it is 18 year olds and higher).

1. Loss of study participants and devices

Bi-weekly clinic visits requires a lot of efforts from participants, which results in participants dropping out in the middle of the study. Participants or their sibling may move to other geographic locations which makes the participant unavailable for clinic visits, contributing to the loss of participants. Carrying a device 24 hours a day for a year requires a lot of attention and efforts, which may not seem as overwhelming at the beginning, but may become tedious, leading to dropping out of the participant. Devices may be easily lost or stolen as well. We anticipate loss of patients and devices along the course of the study.

3. Sample size

As a pilot study the sample size is small and we are at most likely observe one CD onset and perhaps 0-2 flare ups in CD patients. Multiple flare ups is enough to build personal models of disease. Regardless, this is intended as a pilot study to test the feasibility of capturing biological and environmental samples from the same person.

Expected Outcomes

We expect to determine the feasibility of dense sampling of environmental and biological samples from the same person over time. We will also build a pilot LIMS system to allow hassle-free sample tracking. By closely monitoring the PEE of study participants for a year, collecting thousands of PEM, along with millions of readouts from smartwatches, we will use the collection of data to depict the most comprehensive exposome cloud of CD patients to date.

**Aim 2: Integrated analyses of the PEEs and multi-omics data between the diseased and healthy individuals to identify potential mechanisms underlying CD etiology and prognosis.**

Rationale

We will determine if we can correlate environmental exposures with disease flare ups and perhaps etiology by correlating the exposure data with these events. Importantly we will also determine if compounds detected in the environment can be found in the bloodstream of participants.

Experimental strategy

Once samples are collected and subjected to experimental analysis, the data will be processed and analyzed for environmental and host exposures, as well as their correlation with disease etiology and flare ups, as well as physiological and omics measurements. Correlations will be performed at the level of molecule/feature as well as pathway analysis.

Specific methods

**Environmental exposure analysis**

PEE, metabolome, microbiome and physiological measurements will be analyzed using our in-house pipeline from our published work (Jiang *et al.* 2018). Assembled contigs will be queried against our custom built database, which contains more than 40,000 species, and classified using the lowest common ancestor (LCA) algorithm. C means clustering will be used to detect seasonal patterns. For chemical exposures, compounds will be annotated using accurate mass/charge ratio. Patterns of chemical features will be evaluated using clustering and PCA analysis. We will also correlate chemical and biological exposures with one another as biologicals have been found that both correlate and anticorrelate with chemical exposures (e.g. pyridine, a chemical found in paints, anti-correlates with fungi exposure (Jiang et al 2018)). Most importantly, we will specifically compare differential exposures 1) between siblings; 2) as well as before, during and after flare ups to gain insight on disease etiology and conditions that associate with acute flare up.

**Metabolome**

For metabolome data, plasma specimens will be processed and analyzed by our Q exactive HF (Contrepois et al., 2015). Metabolic features will be identified with multivariate statistics given the correction of an appropriate false discovery rate. We will identify metabolites in general, as well as environmental chemicals that are found in plasma, and compare differential metabolome profiles from patients and siblings, as well as before and after flare ups. This will reveal for the first time which environmental compounds transfer to the blood at a large scale. Such information is important to understanding which airborne toxins penetrate the human body.

**Immune profiling**

Immune profiling will be performed on samples collected from patients and controls during and after flare ups. Human cytokines assay and CRP tests will be performed at the Stanford Human Immune Monitoring Center. We will compare the differential cytokine and CRP level before and after flare ups. Moreover, we will compare the differences in the accuracy of predicting disease state using CRP test and metabolome profiling, the result of which will shed light on potential disease state biomarkers to be used clinically.

**Microbiome**

For microbiome data, we will use Metaphlan 2 and Centrifuge for taxonomy analyses, and in-house pipelines for functional and population genetics analyses*.* Since it is well known that gut microbiome in CD is dysregulated, we expect to see differential microbiome profiles in CD patients compared with controls. We will focus on characterizing the differences in gut microbiome during and after flare ups.

**Physiological measurements**

Heart rate, heart rate variability, GSR, activity and SpO2 measurements acquired from the smartwatches will be correlated with disease etiology and flares relative to healthy periods.

**Integration of PEE and multi-omics profiling**

We use supervised clustering to 1) distinguish the differential PEE and multi-omic profiles between healthy and diseased people; 2) pinpoint a subset of PEEs that correlate with changes in disease states, such as occurence and remission, and multi-omics profiling; 3) correlate disease related exposures to changes in physiological parameters collected by smart watches, thus potentially providing early detection physiology markers for CD. 4) After normalization and correction for BMI and age, we will search for coassociations between metabolites, environmental exposures and physiological parameters. In addition to analyzing individual features we plan to analyze associations at the pathway level (see Rose et al for methods).

Potential difficulties and solutions

1. Small number of participants

In this pilot study the number of participants is necessarily small and there may be no events for onset of CD even in this at risk population. However, some individuals with CD may develop 2-3 disease flares during the study period. In these circumstances we will evaluate environmental exposures, seasons and physiological and omics measurement with disease flares. Minimally, we should be able to detect correlations that will generate hypotheses that can be pursued in follow up studies.

2. Integration of multi-omics data

The difficulty in integrating multi-omics data lies in the fact that each -omic data is high-dimensional, and when analyzing large numbers of features we may be underpowered to make significant associations. Nevertheless, the power of using omics profiling is that we should be able to make correlations at the pathway level where disease flares associate.

Expected Outcomes

We will provide a comprehensive report for each study participant of their PEE, metabolome, immunome, gut microbiome, and their interactions and impact on the course of CD. Together with immunome, metabolome and gut microbiome profiles, the results will not only inform the participants of what they were exposed to, but more importantly, associate exposures that trigger changes in other -omes that contribute to change in disease states. By comparing the data from before/after disease incidence and remission, the results from this study will shed light on the etiology and prognosis of CD. Moreover, with the integration of physiological data collected by smartwatches, the results from our study allow early detection of disease occurrence and remission by changes in parameters picked up by non-invasive wearable sensors.

**Plan for sustainability**

The results from our study will demonstrate feasibility of measuring personal exposome in Crohn’s patients and potentially improve our knowledge on multiple aspects of CD, including environmental exposure, etiology, prognosis, clinical biomarkers, and early detection physiological markers. Despite our small sample size, this innovative proof-of concept study will demonstrate the feasibility of capturing biological and exposure samples from the same person. The study can be easily scaled to investigate environmental exposures with CD patients at a population scale with economical devices and more targeted strategies using information garnered from this study. We will actively seek funding from both public and private sources, such as National Institutes of Health (NIH), specifically National Institute of Diabetes and Digestive and Kidney diseases (NIDDK), the mission of which aligns with our study well--to provide support for scientists investigating complex interactions of genetics, environmental, immune, microbial and other factors that contribute to the development of IBD. On the private sector, we will pursue support from foundations dedicated to IBD, such as Crohn’s and Colitis Foundation and Kenneth Rainin Foundation.

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