Resident Scholarly Project

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Title of Project Investigation of Genetic Causes of Severe Early Childhood Onset Obesity

1. **Study Purpose and Rationale**
   Obesity is increasingly prevalent in children and adolescents in the United States. It is associated with numerous and significant comorbidities including type II diabetes mellitus, primary hypertension, nonalcoholic hepatic steatosis and all-cause mortality. While commonly multifactorial in etiology, obesity is known to have significant heritable component though currently identified variants do not account for much of the known heritability. Sampling at phenotypic extremes (severe obesity) and focusing on early onset disease is an effective way to increase the probability of identifying highly penetrant risk alleles and reduce etiologic heterogeneity, respectively. Many monogenic variants associated with obesity pathogenesis have been identified, including the well-studied Melanocortin 4 Receptor (MC4R). Understanding the frequency of mutations of monogenic obesity in a general pediatric population and uncovering new possibly pathogenic variants associated with obesity may lead to insight into pathophysiology and novel interventions.
   Aims:
   a. Identification of known of novel genetic variants in genes that underlie obesity.
   b. We will test the hypothesis that 1-3% of early onset obesity could be explained by carriage of mutation of monogenic obesity such as melanocortin receptor 4 in a mixed pediatric population.
2. **Study Design and Statistical Procedures**
   Participants with severe early onset obesity will be identified by screening of the clinical database or referred to the study. Subjects will be invited to participate in the study. After obtaining informed consent, the investigators will obtain history on the proband and the family, and perform a brief examination in addition to collecting genetic material. Targeted sequencing of genes associated with monogenic and syndromic forms of obesity will be performed using next-generation sequencing. In selected individuals with favorable family history, exome or whole genome sequencing will be performed with Illumina HiSeq 2000. Alignment of whole exomes to a large reference genome will be done using Burrows-Wheeler Aligner (BWA). Variants, or differences in proband exomes from reference genome, will be called using Genome Analysis Toolkit (GATK). Variants will then be annotated (loci, gene) using SnpEff and filtered for rarity (population frequency <0.01), frequency in cohort < 10, and effect of variant (missense, nonsense, frameshift, etc.) Functional analysis of newly identified variants will be performed where possible.
3. **Study Procedures**
   NA
4. **Study Drugs or Devices**
   NA
5. **Study Instruments**
   NA

6. **Study Subjects**

   This study will enroll children with BMI > 99th percentile for age noted prior to 6 years of age. Current age of the child can vary from 0-21 years.

   a. Inclusion Criteria:

   BMI > 99th percentile documented at age < 6 years of age

   b. Exclusion Criteria:

   Known genetic causes of obesity
   Known Endocrine causes of obesity.
   Neurologic tumor, trauma or surgery
   Prior malignancy or transplant
   Known autoimmune diseases
   Edema of a known or unknown cause
   Prolonged steroid use.

7. **Recruitment**

   Potential subjects will be identified by screening the clinical database and by referral from primary physicians and endocrinologists.

8. **Informed Consent Process**

   Informed consent will be obtained by trained study staff after prospective subjects are identified though screening of the clinical database or referral by their primary clinician.

9. **Confidentiality of Study Data**

   Unique identifiers will be used for all data collected for the study. The samples sent for sequencing will be labeled with the unique study code and the individuals in the sequencing laboratory will not have access to the link to the subject identity.

10. **Privacy Protections**

    Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner.

11. **Potential Risks**

    The risks associated with the proposed project include loss of confidentiality and risks associated with venipuncture. All study personnel will be trained in accordance with HIPAA guidelines and blood draws will be done by trained CUMC staff.

12. **Data and Safety Monitoring**

    As this study is non-interventional and requires nothing more than obtaining data and blood/ saliva samples on study subjects, no safety events are expected to occur.

13. **Potential Benefits**

    Study participants are not guaranteed benefit from participation in this research study. It is possible that some participants may be provided genetic diagnoses unrelated to the disease process being investigated though there may not be benefit or change in clinical outcome in uncovering said genetic diagnosis.

14. **Alternatives**

    NA

15. **Compensation to Subjects**

    NA

16. **Costs to Subjects**

There will be no compensation or cost to subjects.

17. **Minors as Research Subjects**
    This study does not involve greater than minimal risk to the pediatric subjects involved. Assent will be obtained when enrolling subjects aged 7 and above. Permission of the parents or guardian will be obtained when enrolling all subjects.
18. **Radiation or Radioactive Substances**
    NA

References

Kumar, S., & Kelly, A. S. (2017). Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. Mayo Clin Proc, 92(2), 251–265.

Sadaf Farooqi, I., Keogh, J. M., Yeo, G. S., Lank, E. J., & Cheetham, T. (2003). Clinical Spectrum of Obesity and Mutations in the Melanocortin 4 Receptor Gene. n engl j med (Vol. 12)

Saeed, S., Arslan, M., & Froguel, P. (2018). Genetics of Obesity in Consanguineous Populations: Toward Precision Medicine and the Discovery of Novel Obesity Genes. Obesity, 26(3), 474–484.

Gill, R., Cheung, Y. H., Shen, Y., Lanzano, P., Mirza, N. M., Ten, S., … Chung, W. K. (2014). Whole-exome sequencing identifies novel LEPR mutations in individuals with severe early onset obesity. Obesity (Silver Spring, Md.), 22(2), 576–584.

Hendricks, A. E., Bochukova, E. G., Marenne, G., Keogh, J. M., Atanassova, N., Bounds, R., … UK10K Consortium, U. (2017). Rare Variant Analysis of Human and Rodent Obesity Genes in Individuals with Severe Childhood Obesity. Scientific Reports, 7(1), 4394.

Stitziel, N. O., Kiezun, A., & Sunyaev, S. (2011). Computational and statistical approaches to analyzing variants identified by exome sequencing. Genome Biology, 12(9), 227.

Kühnen, P., Clément, K., Wiegand, S., Blankenstein, O., Gottesdiener, K., Martini, L. L., … Krude, H. (2016). Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. New England Journal of Medicine, 375(3), 240–246.

Collet, T.-H., Dubern, B., Mokrosinski, J., Connors, H., Keogh, J. M., Mendes De Oliveira, E., … Van Der Ploeg, L. H. T. (2017). Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency. Molecular Metabolism, 6, 1321–1329.

Li, H., & Durbin, R. (2009). Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics, 25(14), 1754–1760.

McKenna, A., Hanna, M., Banks, E., Sivachenko, A., Cibulskis, K., Kernytsky, A., … DePristo, M. A. (2010). The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Research, 20(9), 1297–1303.

Yen, J. L., Garcia, S., Montana, A., Harris, J., Chervitz, S., Morra, M., … Church, D. M. (2017). A variant by any name: quantifying annotation discordance across tools and clinical databases. Genome Medicine, 9(1), 7.