composition of GnomAD and clinical trial subjects with *LMNA* mutations were significantly different (p=0.024) with the clinical trial cohort being more enriched for white patients (78 vs 21%) and less enriched for Latino patients (7 vs. 21%). There were no differences for other genes. The rates of synonymous mutations were different among patients of different ethnicities, p<0.001 for all genes.
Discussion: Partial lipodystrophy due to *LMNA* mutations may be underdiagnosed in Latinos, leading to reduced participation in clinical trials. The lack of differences in other genes suggests there is no overall cohort bias. Different rates of synonymous mutations suggest there may be evolutionary drivers to racial differences in inherited forms of lipodystrophy, such as founder mutations or heterozygote advantage. Future work will determine prevalence of pLOF variants in lipodystrophy-associated genes in other genetic data sets enriched for minority subjects.

Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Renal GLUT2 is Essential in Regulating Systemic Glucose Homeostasis by Glycosuria

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Diabetes increases renal GLUT2 levels and consequently, worsens hyperglycemia by enhancing glucose reabsorption. We recently demonstrated that renal GLUT2 is a primary effector of the central melanocortin system in regulating glucose homeostasis. Therefore, we hypothesized that renal GLUT2 is essential for maintaining systemic glucose homeostasis by regulating glycosuria. To test the hypothesis, we generated kidney-specific inducible *Glut2* knockout (KO) mice [$Glut2^{LoxP/LoxP}$ x $KspCad^{CreERT2}$ (inducible by tamoxifen)]. These mice exhibited 90% reduction in *Glut2* expression selectively in the kidneys, without affecting the expressions of other renal glucose transporters, such as *Glut1*, *Sglt1*, and *Sglt2*. To evaluate the physiological contribution of renal GLUT2 in systemic glucose homeostasis, we performed oral glucose tolerance tests (OGTT) in kidney-specific *Glut2* KO mice and their control littermates (Ctrl). We observed that the kidney-specific GLUT2 deficient mice exhibited improved glucose tolerance compared to their Ctrls (AUC for OGTT, 41,950 ±2,014 vs. 52,165 ±1,686 mg/dL.min). To measure glycosuria in the kidney-specific *Glut2* KO mice, we placed the mice in metabolic cages and collected 24h urine after acclimating the mice in the new cages. Indeed, the GLUT2 deficient mice had ~1,800-fold increase in urine glucose levels (53.5 ±11 vs. 0.03 ±0.005 mg/24h) and exhibited an increased urine volume (2.5 ±0.3 vs. 0.9 ±0.3 mL/24h) and water intake (7.6 ±0.7 vs. 4.9 ±0.7 mL/24h) compared to their Ctrl littermates. The improvement in glucose tolerance in the kidney-specific *Glut2* KO mice was independent of the insulin signaling because we did not observe any changes in insulin tolerance tests (ITT) (AUC for ITT, 10,982 ±414 vs. 11,275 ±583 mg/dL.min) and serum insulin levels (1.07 ±0.14 vs. 1.05 ±0.13 ng/mL) between the groups. Importantly, the kidney-specific GLUT2 deficient mice had normal serum creatinine (0.42 ±0.02 vs. 0.41 ±0.03 mg/dL), free fatty acid (0.43 ±0.14 vs. 0.53±0.14 nmol/μL), β-hydroxybutyrate (0.29 ±0.01 vs. 0.27 ±0.02 mM) and glucagon (14 ±4 vs. 10 ±1 pg/mL) levels. Moreover, the kidney-specific *Glut2* KO mice had normal glomerular area (4,190 ±119 vs. 4,219 ±186 μm^2) as measured by kidney histology and normal glomerular filtration rate (153 ±9 vs. 173 ±10 [μL/min/b.w.]/100) compared with their Ctrl littermates, indicating the absence of any known renal injury. Altogether, we have developed a new mouse model in which we can knockout *Glut2* selectively in the kidneys in adult mice. We show that loss-of-function of kidney-specific GLUT2 improves glucose tolerance due to elevated glycosuria without producing any known side effects. In conclusion, blocking kidney-specific GLUT2 has the potential to treat diabetes.

Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Scientific and Regulatory Considerations for the Approval of the First Generic Glucagon

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Glucagon for Injection (NDA 020928) is a polypeptide hormone identical to human glucagon approved 20 years ago for severe hypoglycemia in patients with diabetes mellitus. On Dec 28, 2020, the U.S. FDA approved the first generic version of glucagon for injection USP, 1 mg/vial packaged in an emergency kit. The generic and the reference listed drug (RLD) version, i.e., the innovator version, of glucagon were each produced through different manufacturing processes. The RLD version of glucagon is produced via recombinant DNA in yeast while the generic version of glucagon is produced by peptide synthesis. The FDA published its current thinking on how to ensure sameness between the generic and innovator peptide products prepared with different manufacturing processes in a Draft Guidance for Industry: Submission of Abbreviated New Drug Applications for Certain Highly Purified Synthetic Peptide Drug Products, which applies to five peptide drug products, including glucagon. In this presentation, we aim to provide an overview of the regulatory recommendations for submitting generic glucagon drug products for approval, as outlined in the aforementioned draft guidance. Although glucagon may be produced using different manufacturing processes, the sameness in glucagon can be adequately demonstrated using analytical methods, which involve demonstrating physicochemical properties, as well as primary and secondary structures, oligomers and aggregation states. Biological assays may also be used as part of the demonstration of active pharmaceutical ingredient sameness. Synthetic glucagon may have different impurity