1 diabetes mellitus (DM) (T1DM n = 6), type 2 DM (T2DM n = 24), and control (n=24). Neurodevelopment was assessed using two standardized tools: the Ages and Stages Questionnaire 3rd edition (ASQ-3), a parent questionnaire, and the Bayley Scales of Infant and Toddler Development, 4th edition (BSID-IV). The ASQ-3 is composed of five domains: Communication, Gross Motor, Fine Motor, Problem Solving, and Personal-Social. The BSID-IV is also composed of five domains: Cognitive, Language (Receptive and Expressive), Motor (Gross and Fine), Social-Emotional, and Adaptive Behavior. For this study, we assessed only the Cognitive and Language domains of the BSID-IV. We used the Cochran–Mantel–Haenszel (CMH) Mean Scores test to compare the mean scores across the three groups. RESULTS/ANTICIPATED RESULTS: The ASQ-3 showed no statistically significant differences between groups across all five domains. However, several children showed delays or were at risk for delays in multiple domains: Communication: (1 [1.85%]; 4 [16%] delayed), Gross Motor: (4 [7.4%] delayed), Fine Motor: (13 [24.1%] at risk; 7 [12.9%] delayed), Problem Solving: (9 [16.7%] at risk; 11 (20.3%) delayed, and Personal-Social: 8 [14.8%] at risk, 10 (20%) delayed). Similarly, the BSID-IV showed no statistically significant group differences in Cognition and Language. However, below-average performance was observed in both domains. For Cognition, 14 children (25.9%) scored below average (T1DM:1 [1.85%], T2DM: 7 [12.9%], Con = 6 [11.11%]). For Language, 12 children (22.22%) (T1DM = 1 [1.85%], T2DM = 4 [7.4%], and Con = 7 [12.9%]). DISCUSSION/SIGNIFICANCE OF IMPACT: Children from all groups had delays in fine motor, problem-solving, personal-social, cognitive, and language development. These findings suggest that maternal diabetes may influence neurodevelopment. We suggest that these children have continued neurodevelopmental follow-up with their pediatrician to improve these delays.

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Pumilio2 haploinsufficiency causes a neurodevelopmental disorder with ataxia

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OBJECTIVES/GOALS: Our goal is to determine whether insufficient Pumilio2 (Pum2) leads to neurological disorders. We identified predominantly young patients with mutations in PUM2 who suffer from developmental delays, motor incoordination, seizures, and so on. We will utilize Pum2 null mice to identify behavioral issues and neural degeneration. METHODS/STUDY POPULATION: We conducted several neurobehavioral assays with the Pum2 mutant mice (an estimated 40 mice) throughout their development. These assays measure learning and memory, motor coordination, spatial recognition, hyperactivity, and social cues. In addition to these experiments, we conducted immunofluorescence and Nissl staining to characterize brain morphology and Purkinje cells. Additionally, we collected patient-derived fibroblasts for qPCR and Western blot to measure the mRNA and protein levels of PUM2 in the different variants. Using both eCLIP and RNA sequencing, we will determine and rank targets bound by Pum2 in the murine brain. RESULTS/ANTICIPATED RESULTS: At 12 weeks, we discovered Pum2 mutant mice exhibit neurological phenotypes that worsen with age development, such as motor incoordination, muscle atrophy, hyperactivity, impulsiveness, and compulsiveness. We observed a decrease in dendritic density in the Purkinje cells at 10 weeks of age, but no neural degeneration. However, we observed a reduction in dendritic density and aggressive Purkinje cell degeneration much later in adulthood. We obtained patient-derived fibroblasts to conduct Western and qPCR. We found that the missense mutations lead to a decrease in PUM2 protein and mRNA levels. These findings exhibit phenotypes similar to those observed in PUM2 patients, suggesting that insufficient levels of PUM2 lead to neurodevelopmental disorders and ataxia. DISCUSSION/SIGNIFICANCE OF IMPACT: Pumilio2 is an RNA-binding protein from the PUF family that either promotes mRNA degradation or inhibits translation. It controls dendritic development and synaptic activity. PUM2 may be a novel ataxia gene that manifests neurodevelopmental problems.

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Discovering novel atrial fibrillation phenogroups: A multi-algorithm approach using real-world claims data

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OBJECTIVES/GOALS: To discover novel phenogroups of atrial fibrillation (AF) from a real-world claims database using a multi-algorithm unsupervised machine learning (ML) approach and to reveal clinical factors associated with each phenogroup using supervised ML. We aim to establish clinically meaningful AF phenogroups to advance precision medicine. METHODS/STUDY POPULATION: We will leverage the Merative MarketScan databases (2016–2024) of real-world claims data with an estimated >600,000 AF patients. Four unsupervised ML clustering techniques will be employed to identify phenogroups: k-means, Gaussian mixture models, agglomerative, and HDBSCAN. Following cluster generation, the algorithms will be evaluated through internal validation via the Davies–Bouldin Index which calculates cluster compactness and separation, and the Adjusted Rand Index to determine stability between algorithms. Then, supervised ML via SuperLearner, which will include advanced algorithms (e.g., gradient boosting machines and support vector machines), will identify clinical factors associated with each phenogroup and will be evaluated using k-fold cross-validation and Shapley values. RESULTS/ANTICIPATED RESULTS: We anticipate that the multi-algorithm approach will yield robust, distinct, and clinically meaningful AF phenogroups. SuperLearner will confirm the key clinical characteristics driving membership in each group (e.g., hypertension and heart failure). These data-driven classifications will provide a robust foundation for subsequent

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translational analyses. We will perform time-to-event analyses to assess the differential risks of stroke, coronary artery disease and myocardial infarction, heart failure, and rates of healthcare utilization across phenogroups. Next, we will employ the target trial framework to evaluate the comparative effectiveness of anticoagulant therapies on stroke incidence across phenogroups. DISCUSSION/SIGNIFICANCE OF IMPACT: This work demonstrates a highly rigorous, multi-algorithm approach to characterize a large, real-world database of AF patients. By constructing novel AF phenogroups, we aim to move beyond the limitations of current AF classifications and advance precision medicine by providing the foundation for individualized therapeutic strategies.

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Genetic clues to blurred vision: A multi-ancestry GWAS of diabetic macular edema*

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OBJECTIVES/GOALS: Identify genetic variants associated with the development of diabetic retinopathy (DR) and its advanced complication, diabetic macular edema (DME). Despite DME being a leading cause of vision loss among people with diabetes, genetic findings have been limited by small sample size, underrepresentation of diverse populations, and poor study design. METHODS/STUDY POPULATION: Genome-wide association studies (GWAS) were conducted to identify genetic variants linked to DME. GWAS were conducted separately by ancestry (African, European, and Admixed American) in the Million Veteran Program and All of Us cohorts, adjusted for age, sex, BMI, diabetes duration, mean HbA1c, and 10 principal components. We then combined population groups to perform a multi-ancestry meta-analysis (Multi) using a software called METAL. Analyses included autosomes and chromosome X for DME versus DR controls (14,211 cases and 47,005 controls). Gene expression analyses were performed using S-PrediXcan across 49 tissues to identify genes whose predicted expression is associated with DME risk. APOL1 variant and haplotype analyses were conducted to assess ancestry-specific associations with DME and type 2 diabetes. RESULTS/ANTICIPATED RESULTS: Genome-wide significant loci included G6PD (Multi and African), previously reported to influence diabetes diagnosis, and APOL1 (Multi and European), previously linked to kidney disease in African ancestry. Gene expression analyses revealed 32 significant gene–tissue pairs (Multi 18 and African 18), corresponding to 9 unique genes. In APOL1, E150K was strongly associated with DME in Europeans (OR=1.22, $P=2.9\times10^{-8}$) and modestly in Africans (OR=1.18, $P=5.3\times10^{-4}$). N264K also showed significant effects in Europeans (OR=1.42, $P=9.8\times10^{-4}$) and weaker but consistent effects in Africans (OR=1.04, P=0.025). The high-risk G1/G2 haplotype demonstrated a modest association in African ancestry (OR=1.15, P=0.048). DISCUSSION/SIGNIFICANCE OF IMPACT: This is the largest genetic study of DME, uncovering genetic risk factors that could potentially be driving risk, such as APOL1, a gene historically tied to kidney disease among individuals of African ancestry. Our results indicate its involvement may extend to diabetic complications more generally.

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Characteristics of HbA1c subgroups of young adults with type 1 diabetes

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OBJECTIVES/GOALS: The objective of this study was to identify subgroups of young adults with type 1 diabetes (T1D) defined by HbA1c measured 12 months after participating in a randomized controlled trial for a behavioral intervention. METHODS/STUDY POPULATION: This study is a secondary, exploratory analysis of 76 young adults with T1D with complete data who enrolled in the DiaBetter Together RCT. A regression tree model is used to identify subgroups of participants according to HbA1c measured 12-month post-enrollment. Predictors include baseline participant characteristics, questionnaire scores, and clinical characteristics. Model fit is informed by restricted sum of squares, pruned using cost complexity assessment, and number of observations per node. RESULTS/ANTICIPATED RESULTS: The final regression tree predicting 12m HbA1c included two branches and five leaves defined by baseline HbA1c, Diabetes Distress: Friend/Family (DDFF), and Diabetes Strengths: Getting help with diabetes management (DSGMH). Participants with baseline HbA1c <6.87% had the lowest mean 12m HbA1c (M=6.5, SD=0.7). Two unique subgroups were identified among patients with baseline HbA1c between 6.87 and 9.91 defined by DSGMH. The mean 12m HbA1c was 8.13 (SD=1.1) and 10.0 (SD=2.6) for DSGMH ≥6.06 and <6.06, respectively. Among patients with baseline HbA1c>9.91, two unique subgroups were defined by DDFF. The mean 12m HbA1c was 9.99 (SD=1.5) if DDFF <3.55. The highest 12m HbA1c was observed among participants with baseline HbA1c ≥9.91% and DDFF≥3.55 (M=13.0,

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