Genetic variation in mouse islet Ca^{2+} oscillations reveals novel regulators of islet function

Christopher H. Emfinger[1#], Lauren E. Clark[1#], Kathryn L. Schueler[1], Shane P. Simonett[1], Donnie S. Stapleton[1], Kelly A. Mitok[1], Matthew J. Merrins[2,3], Mark P. Keller[1], Alan D. Attie*[1,2]

[1]Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, 53706, USA

[2] Department of Medicine, Division of Endocrinology, University of Wisconsin-Madison, Madison, WI, 53705, USA

[3]William S. Middleton Memorial Veterans Hospital, Madison, WI 53705 USA

[#]These authors contributed equally to this work

*corresponding author

For inquiries, please address correspondence to:

Alan D. Attie

543A HF DeLuca Biochemistry Laboratories, 433 Babcock Drive, Madison, WI 53706

(608) 262-1372

adattie@wisc.edu

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ABBREVIATIONS:

COBLL1	Cordon-Bleu-like Like 1
ACP1	Acid phosphatase 1
GALNS	galactosamine (N-acetyl)-6-sulfatase
PSMC3	Proteasome 26S subunit, ATPase 3
GWAS	Genome-wide association study
SNP	single-nucleotide polymorphism

ABSTRACT:

Insufficient insulin secretion to meet metabolic demand results in diabetes. The intracellular flux of Ca^{2+} into β-cells triggers insulin release. Since genetics strongly influences variation in islet secretory responses, we surveyed islet Ca^{2+} dynamics in eight genetically diverse mouse strains. We found high strain variation in response to four conditions: 1) 8 mM glucose; 2) 8 mM glucose plus amino acids; 3) 8 mM glucose, amino acids, plus 10nM GIP; and 4) 2 mM glucose. These stimuli interrogate β-cell function, α-cell to β-cell signaling, and incretin responses. We then correlated components of the Ca^{2+} waveforms to islet protein abundances in the same strains used for the Ca^{2+} measurements. To focus on proteins relevant to human islet function, we identified human orthologues of correlated mouse proteins that are proximal to glycemic-associated SNPs in human GWAS. Several orthologues have previously been shown to regulate insulin secretion (e.g. ABCC8, PCSK1, and GCK), supporting our mouse-to-human integration as a discovery platform. By integrating these data, we nominated novel regulators of islet Ca^{2+} oscillations and insulin secretion with potential relevance for human islet function. We also provide data for identifying appropriate mouse strains in which to study these regulators.

INTRODUCTION:

The majority of gene loci responsible for the genetic variation in type 2 diabetes (T2D) susceptibility affect the function of endocrine cells of pancreatic islets, primarily β-cells (1, 2). Variation in β-cell mass and β-cell function place boundaries on the capacity to respond to acute and chronic demands for insulin, such as those in overnutrition and insulin resistance (1, 2). Therefore, metabolic challenges are useful in genetic screens because the increased demand for insulin promotes the progression from normal blood glucose to diabetes in individuals with genetic variants that affect β-cells.

The collection of inbred mouse strains currently available provides us with a wide repertoire of genetic and phenotype diversity, comparable to that of the entire human population (3). Yet, the majority of mouse studies have been confined to a small handful of highly inbred strains (3, 4). It is becoming widely appreciated that gene deletions, nutritional interventions, and drug effects vary widely between mouse strains as they do in humans (3, 5). Thus, characterization of the basis for this high level of phenotype variation is a way to gain deeper insights into the pathophysiology and genetics of a wide range of physiological processes.

The pancreatic β-cell is a nutrient sensor. In response to particular nutrient stimuli (e.g. glucose, amino acids), the cells generate ATP and close ATP-dependent K^+ channels (K_{ATP}), resulting in plasma membrane depolarization. This leads to an oscillatory influx of Ca^{2+} ions, triggering insulin secretion. The process of secreting insulin and re-compartmentalizing Ca^{2+} ions consumes ATP, and the drop in the ATP/ADP ratio reopens K_{ATP} channels, repolarizing the membrane, and closing membrane Ca^{2+} channels. Consequently, oscillations in metabolism, insulin secretion, and Ca^{2+} are intrinsically linked (6-9), and the capacity to maintain functional Ca^{2+} handling has been suggested to be critical for islet compensation (10).

In this study, we utilized the extraordinary genetic and phenotypic diversity represented in the eight founder mouse strains (which we subsequently refer to as founders) used to generate the Collaborative

Cross (CC) recombinant inbred mouse panel and the Diversity Outbred (DO) stock (11, 12). These strains capture the majority of the genetic diversity of all inbred mouse strains (11, 12). While studies of these mice have provided significant insight into genetic regulators of islet function (13), determining the appropriate model system for evaluating genes of interest is often difficult as most deletion models are made in only a small number of strains such as the C57BL/6J.

We explored the diversity of nutrient-evoked islet Ca^{2+} responses across the eight founder mouse strains, revealing a remarkable diversity of Ca^{2+} oscillations. Our prior proteomics studies showed that the protein abundance from islets of the founder mouse strains is also highly diverse, as is their insulin secretory response to different stimuli (14). By correlating the strain and sex variation in protein abundance with the variation in Ca^{2+} oscillations, we identified a subset of islet proteins that are highly correlated with islet Ca^{2+} oscillations. The human orthologues of many of these proteins are encoded by genes with nearby SNPs linked to glycemic traits (e.g., fasting blood glucose, see **Table 2** for terms), as revealed in genome-wide association studies (GWAS). By integrating these data, we nominated novel regulators of islet Ca^{2+} oscillations and insulin secretion with potential relevance for human islet function. We also provide proteomic, secretory, and Ca^{2+} data for identifying appropriate mouse strains in which to study these regulators.

RESULTS

Genetics exerts a strong influence on islet Ca^{2+} responses

Glucose metabolism, β-cell Ca^{2+} flux, and insulin secretion are pulsatile, and have been found to oscillate in both humans and mice (6, 7, 15-17). Because they are interconnected, understanding the factors governing oscillation patterns can inform about the mechanisms that regulate insulin secretion (9, 18-20). To specifically explore the influence of genetic background on Ca^{2+} oscillations, we measured Ca^{2+} in islets of the eight founder strains, that together harbor as much genetic diversity as humans: A/J, C57BL/6J (B6), 129S1/SvlmJ (129), NOD/ShiLtJ (NOD), NZO/HILtJ (NZO), CAST/EiJ (CAST), PWK/PhJ (PWK), and WSB/EiJ (WSB).

All mice were maintained on a Western-style diet (WD) high in fat and sucrose for 16 weeks, prior to isolating their islets for Ca^{2+} imaging using Fura Red, a Ca^{2+}-sensitive fluorescent dye (**Figure 1A**). Using a perifusion system, we measured Ca^{2+} dynamics in response to four conditions: 1) 8 mM glucose (8G); 2) 8 mM glucose + 2 mM glutamine, 0.5 mM leucine, and 1.5 mM alanine (8G/QLA); 3) 8G/QLA + 10 nM glucose-dependent insulinotropic polypeptide (8G/QLA/GIP); and 4) 2 mM glucose (2G) (**Figure 1B**). There was a high degree of similarity between three of the five classical strains (A/J, B6, 129), which were dominated by slow oscillations (period 2-10 minutes) in 8G and 8G/QLA/GIP, and had relatively fewer islets reach plateau (continuous peak activity without oscillation) in 8G/QLA. Likewise, the wild-derived strains (CAST, WSB, and PWK) closely matched one another, while differing from the classic strains. The wild-derived mouse islets were dominated by fast oscillations (period <2 minutes) in 8G, resulting in plateaus for 8G/QLA and 8G/QLA/GIP.

Two strains stood out from the others. Islets from NOD mice showed characteristics from both the wild-derived and classic strains; slow oscillations in 8G and a sustained plateau in response to 8G/AA and 8G/QLA/GIP with fast oscillations superimposed. The NZO mice also differed from the other classic strains, likely because they were all diabetic (blood glucose >250 mg/dL). Their islets were minimally

responsive to 8G, but did respond with a strong pulse in 8G/QLA and Ca^{2+} remained elevated in 8G/QLA/GIP.

Many of the strain differences seen in the male mice were maintained in the females (**Supplemental Figure 1A**). The classic strains were once again highly similar to one another, as were the wild-derived strains. Furthermore, the NZO females, of which all but one were diabetic, mirrored the behavior of the male islets. One interesting observation that emerged from the female islets is that the NOD females displayed a greater variation in their Ca^{2+} oscillations than the NOD males (**Supplemental Figure 2**). Some of the islets maintained slow oscillations throughout the various conditions, while some demonstrated fast oscillations and plateaued similar to the wild-derived strains. Yet others appeared strikingly similar to the islets from diabetic NZO mice, despite none of the NOD mice being diabetic. Finally, the one non-diabetic female NZO displayed oscillatory behavior similar to that of the other classic strains, with clear, slow oscillations (**Supplemental Figure 1B**).

Dissecting islet Ca^{2+} dynamics

An understanding of the mechanisms regulating insulin secretion, including the roles of specific metabolic pathways, ion channels, and hormones, have been derived from the shape and frequency of islet Ca^{2+} oscillations (7, 9, 16, 18, 21-24). To elucidate strain differences in Ca^{2+} dynamics, we primarily analyzed six parameters of the Ca^{2+} waveform (**Figure 2A**): 1) peak (the top of each oscillation); 2) active duration (the length of time for each oscillation measured at half of the peak height); 3) pulse duration (the length of time for each oscillation where cytosolic Ca^{2+} is at its lowest); 4) period (the length of time between two peaks); 5) plateau-fraction (the active duration divided by the period, or the fraction of time spent in the “on” phase); and 6) silent duration (the period minus the active duration, or the length of time spent in the “off” phase). We also assessed the spectral density for every islet to extract additional information from complex oscillations where multiple components were visible (e.g. the trace in **Supplemental Figure 3A).** We analyzed each trace segment to determine the top two

frequencies contributing to the trace (1st and 2nd component frequencies, **Supplemental Figure 3B)** and their respective contributions (1st and 2nd component amplitudes). Because certain features, such as ion channels or metabolic enzymes, have known frequencies (25), extracting the top two frequencies may highlight additional information beyond that previously collected.

A representative Ca^{2+} dynamic from a female B6 islet is illustrated in **Figure 2A.** The transition from 8G to 8G/QLA resulted in an increased active duration, yielding a longer period and increased plateau fraction. For an islet that plateaued at the peak, as seen in 8G/QLA (**Figure 2B**), we computed a plateau-fraction of one, an active and pulse duration of 40 minutes (the measurement time), and a period of zero minutes. An islet that returned to baseline and ceased to oscillate, as seen in 2 mM glucose (**Figure 2B**), was determined to have a plateau-fraction, active duration, and pulse duration of zero, and a period of 40 minutes. Understanding the strain-dependence of these parameters is important for identifying underlying mechanisms, as illustrated in **Figure 2C**. While both traces have a similar active duration (blue bars), trace 1 has a longer period (red bars), resulting in an increased silent duration and a decreased plateau-fraction.

Examples of pathways altering specific components of Ca^{2+} oscillations have previously been established (**Figure 2D**) (9, 11, 18, 28, 29). For example, when K_{ATP} channels are pharmacologically closed with Tolbutamide, the silent duration is shortened, resulting in increased frequency without a change in pulse shape (upper panel). The addition of glucose leads to increased glucose metabolism and glucokinase (GK) activity (11). The resulting rise in ATP inhibits K_{ATP} channels and is used as a substrate for additional processes that affect Ca^{2+}, such as SERCA pumps (30, 31). Thus, glucose alters both the active and silent durations, resulting in a change in both frequency and shape of the Ca^{2+} oscillations (lower panel).

Average stimulated calcium levels do not correlate with insulin secretion

Average Ca^{2+} is commonly used for analyzing Ca^{2+} dynamics and is frequently assumed to be highly correlated to insulin secretion. To determine whether average Ca^{2+} is predictive of insulin secretion, we performed perifusions on islets from WSB and 129 male mice, two strains that showed similar average Ca^{2+} (**Figure 4B**), but exhibited vastly different Ca^{2+} oscillations (**Figure 1B**). WSB mice had significantly higher insulin secretion in each of the secretory conditions (**Figure 3A**), suggesting another Ca^{2+} parameter better predicts insulin secretion.

To identify parameters of the Ca^{2+} dynamics most strongly correlated to insulin secretion, we computed the correlation between the Ca^{2+} oscillation parameters and insulin secretion in similar conditions (8G, 8G/QLA, basal) for the same sexes and strains (**Figure 4A** and **Supplemental Figure 4**) (32). Consistent with our observations from the perifusion data in the WSB and 129 islets, we found that average Ca^{2+} was not strongly correlated to insulin secretion. Other metrics, such as active duration in 8G, and the silent durations in 8G/QLA, were more highly correlated to insulin secretion. Meanwhile, the 1st component frequency in 8G from the spectral density analysis was highly correlated with *decreased* insulin secretion. These metrics were also the most highly correlated with multiple clinical measures in the founder mice, particularly plasma insulin (**Figure 4B, Supplemental Figure 5**), for which silent duration in 8G/QLA/GIP had the strongest correlations.

Several parameters of the Ca^{2+} oscillatory waveform showed strong strain and sex effects. For example, basal Ca^{2+} (average Ca^{2+} in 2G, **Figure 4C**) was relatively consistent among the strains, except NZO where it was highest in islets from male mice. For the overall pulse duration (**Figure 4D**), the NZO mice were once again the highest, followed by CAST and WSB. A noticeable sex-effect was measured for the CAST mice, where male mice had a longer pulse duration than the female mice. The 1st component frequency (**Figure 4E**) is driven by the differences observed in the wild-derived strains, for which CAST has the highest frequency, followed by PWK and WSB. Finally, the trend for a sex

effect in the classic strains for silent duration (at 8G, 8G/QLA, and 8G/QLA/GIP) is absent in the NZO and wild derived mice with the former having greater silent duration in males and the latter frequently having islets plateau in response to these stimuli. These data demonstrate that genetics has a profound influence on key parameters of islet Ca^{2+} oscillations.

To explore this further, we took advantage of our previously published whole islet proteomic survey from the eight founder strains (14). To identify proteins that may underly the strain-differences in Ca^{2+} oscillations, we computed the correlation between islet protein abundance and Ca^{2+} dynamics across both sexes of the eight founder strains (**Figure 5** and **Supplemental Figure 6**). Our previous survey of islet proteomics included both sexes for all strains, except NZO males, resulting in a quantitative measure of ~4054 proteins (14). **Figure 5A** illustrates a heatmap of the correlation between islet proteins and several parameters of Ca^{2+} oscillations. Unsupervised clustering was used to show that groups of proteins showed strong positive or negative correlation to a given Ca^{2+} parameter and the correlation displays a distinct architecture. The proteins highly correlated to the 8G 1st component frequency, for example, tended to also be strongly anticorrelated to the silent duration conditions which were very similar to one another. The active and pulse durations for 8G had nearly identical correlation structure, and the conditions with the fewest highly correlated proteins were the average Ca^{2+} measures for 8G, 8G/QLA, and 8G/QLA/GIP, and the structure for these was largely inverted from the active duration conditions. Finally, despite the differences in the overall correlations between the different metrics, there were proteins that did overlap (e.g. the block of proteins with high correlation to both 8G A_D and 8G/QLA S_D) suggesting that while there were clusters of distinct proteins/pathways for any given metric some proteins may modify more than one metric.

Among the ~4045 islet proteins, 363 had high absolute correlation coefficients ($r > |0.5|$) to 3 or more of the parameters our data suggest most strongly correlate to insulin secretion and plasma insulin (Basal Ca^{2+}, 8G A_D, 8G P_D, 8G/QLA S_D, 8G S_D, 8G/QLA/GIP S_D). Interestingly, of the proteins

correlated to these traits, many have been previously implicated in islet biology, including PCSK1, GCK, SUR1, GLUT2, PDX1, and GLP-1 (26-34). Notably, the highly correlated proteins enriched for tissues, pathways, and transcription factors that support their role in insulin secretion (**Figure 5B**). For instance, proteins highly anti-correlated to active duration in 8G were enriched for components of oxidative metabolism and had their gene promoters enrich for binding to the islet transcription factor MAFA (33). These enrichment data provide a framework for discovering new genes of interest for their role in islet function.

Integration of mouse genetics with human GWAS to nominate novel players in islet biology

The data presented in **Figure 5A** illustrates the *correlation* between islet proteins and Ca^{2+} dynamics. Importantly, a protein strongly correlated to Ca^{2+} does not necessarily reflect a causal relationship; i.e., a change in protein abundance may or may not cause a change in the Ca^{2+} signal. To take our analysis beyond correlation, we integrated our data with human GWAS of glycemia-related traits.

First, we identified all human homologues for islet proteins strongly correlated ($r > |0.5|$) to one or more of the Ca^{2+} oscillatory metrics. We identified human homologues for ~2880 proteins that were correlated to Ca^{2+} in either direction for at least one of our parameters of interest. We then searched the Type 2 Diabetes Knowledge Portal (https://t2d.hugeamp.org/) for SNPs that are associated with one or more glycemia-related traits (see **Table 2**) with a P-value < 10^{-8}, and occur within ±100Kbp of the homologous gene (e.g. COBLL1, **Figure 6A**) or are on regions contacting the gene's promoter (determined using human islet promoter-capture HiC data (35)) as illustrated by ACP1 (**Figure 6B**). This yielded a list of 316 human genes strongly associated with diabetes-related SNPs, and 168 of these proteins have not been previously reported to play a key role in islet function (**Table 3**). In summary, our approach leverages the genetic diversity of the eight founder strains and human GWAS for diabetes-related traits to highlight genes that play a novel role in islet function.

Importantly, the relevance of these tools depends on the mouse model in which they are used to validate the roles of the candidate protein. To aid in the selection of mouse strain, we provide the proteomic, secretory, and Ca^{2+} data (**Figure 7,** https://doi.org/10.5061/dryad.j0zpc86jc). This will enable the user to identify proteins correlated to genes, proteins, or traits of interest, and from there, identify which strain(s) may be most appropriate for the study of their target. In the examples illustrated in **Figure 7C**, GALNS shows a high negative correlation to multiple traits including the active duration time in 8G/QLA. Strains at the extremes of this trait are also extremes with regard to protein expression for GALNS. Ones with high abundance (B6, for example) would be appropriate models for inhibition or knockout, while the CAST mice could be a comparison strain for validating the role of the protein, as they express less of it. By contrast, the silent duration traits (e.g. those expressed in 8 mM glucose) have strong influence of the NZO strain and consequently NZO may be the most appropriate strain to assess the role of some proteins (e.g. PMSC3) with regard to that metric (**Figure 7C**, lower panels).

DISCUSSION

Genetic variability drives islet function

While the development and progression of T2D is potentiated by environmental factors, an estimated 50% of disease risk is driven by genetic factors (1, 3, 36). Therefore, to study the genetic variation contributing to T2D, we utilized the eight founder mouse strains. These mice collectively contain a level of genetic diversity mirroring that seen in humans, making them an excellent model for studying genetic regulators of islet function (11, 12). We demonstrate that they also vary in their Ca^{2+} response to various insulin secretagogues, supporting the use of these mice to identify novel genes involved in regulating islet biology.

Calcium waveform analysis reveals pathways regulating islet function

Variations in Ca^{2+} dynamics are highly complex, and are the result of changes in metabolism, extra-islet signaling, and Ca^{2+} itself (6). We therefore selected stimulatory conditions to assess each of these components in islets of the eight mouse strains. 8 mM glucose was first used to survey glycolytic responses, because we have observed that several strains reliably oscillate at this glucose concentration. Furthermore, this glucose concentration remains close to the stimulatory threshold, thus reducing the possibility of oscillations plateauing if islet Ca^{2+} responses were left-shifted in any strains (21, 37, 38). We then added QLA as fuel to engage non-glycolytic mitochondrial metabolism and signaling from α-cells, providing a survey of alpha-to-beta cell communication in the islet (18, 39-41). Finally, we used GIP to interrogate the islet incretin responses and the cAMP amplification pathway (40), before returning to a low glucose concentration, enabling us to establish baseline Ca^{2+} levels.

The variation in Ca^{2+} response to these conditions can be better understood by examining the multitude of pathways regulating Ca^{2+} dynamics. As mentioned previously, altering ionic pathways involved in regulating Ca^{2+}, such as K_{ATP} channels, has a very different effect on Ca^{2+} oscillations compared to altering glycolysis. It is important to further dissect these pathways, as changing specific

components of glucose metabolism can elicit different effects. For example, increasing pyruvate kinase (PK), an enzyme involved in converting phosphoenolpyruvate (PEP) to pyruvate, and increasing GK activity both alter the active duration and the plateau-fraction. However, they do so in opposite directions (18). While both enzymes are involved in the glycolytic pathway, activating GK increases the active duration and period, while activating PK decreases those same parameters. This demonstrates the complexity of analyzing Ca^{2+} oscillations, and the importance of considering the changes in a variety of parameters, rather than focusing on just one.

The importance of analyzing a variety of Ca^{2+} parameters is further supported by the insulin secretion measurements in the male WSB and 129 mice. While average Ca^{2+} is a common metric used to predict insulin secretion, relying on only this metric would suggest that the two strains secrete insulin similarly. However, the WSB mice secreted significantly more insulin in 8G, 8G/QLA, and 8G/QLA/GIP (**Figure 3**). Based on our correlation analysis between Ca^{2+} parameters and insulin secretion across each sex and strain, active duration and pulse duration in 8G more accurately predicted insulin secretion and may be highly informative when used with other data (**Figure 4**). This is similar to results published by some other groups, suggesting that average Ca^{2+} does not correlate well with insulin secretion (42).

Strains segregate by their phylogenetic origins

Notably, several of the strains appeared to cluster together with similar responses. One such group is composed of three classical strains (A/J, B6, and 129) that had similar waveforms dominated by slow oscillations. These differed from a second group containing the wild-derived strains (CAST, WSB, and PWK) which closely matched one another and were dominated by faster oscillations.

The classic strains have been highly inbred (>150+ generations) and descend from related common ancestors, the “fancy mice.” They also have extremely low genetic diversity, with 97% of their genomes explained by fewer than 10 haplotypes (3, 43, 44). By contrast, wild-derived strains are each

independent in their parental origin, inbred for far fewer generations than the classic strains (although still at least 20), and include significant contributions from other subspecies of *Mus musculus* than the predominant subspecies (*M. m. domesticus*) in the traditional strains, particularly CAST (*M. m. castaneous)* and PWK (*M. m. musculus*) (3, 43, 44). It is thus unsurprising that the two primary Ca^{2+} response clusters were composed of the classic and wild-derived strains. Multiple loci have already been linked to islet dysfunction and differential metabolic homeostasis in the classic strains (3). Our work here highlights the promise in using wild-derived strains to unmask previously underappreciated islet phenomena, something we and others have previously shown (14, 45, 46).

While considered one of the classic strains, the NOD mice differed from the two primary clusters noted above. They displayed a combination of features from both groups and had a high degree of inter-islet variability, especially the female mice. NOD share common ancestors with the Swiss-Webster mice, which do not share parental origin with the other classic strains (43) and also display a “mixed” phenotype consisting of islet Ca^{2+} oscillations in response to glucose, with both slow and fast components (21).

Additionally, while all NOD were normoglycemic, a heterogeneous response was observed in islets from female, but not male, NOD mice. Female NOD mice are known to develop islet immune infiltration and subsequent autoimmune diabetes whereas males are largely protected from this (47). Male NOD islets were largely consistent in their Ca^{2+} waveforms. In the females, however, a high degree of heterogeneity in responses was observed across the female’s islets (**Supplemental Figure 2**). For any NOD female, some islets resembled those from NOD males in their clear oscillations, others largely lacked oscillatory behavior other than a strong pulse in response to 8G/QLA, and still others had an intermediate response. These observations may reflect varying degrees of dysfunction in the NOD female islets as the mice progress to diabetes, though we cannot say whether this results from variation in beta-cell intrinsic defects or islet immune infiltration.

The NZO mice also varied from the two clusters previously discussed. All of the male mice, and all but one of the female mice, were diabetic. The islets from the diabetic mice had reduced amplitude and oscillatory behavior, other than a single pulse in 8G/QLA. This pattern is similar to the patterns observed in many of the NOD female islets. On the other hand, islets of the one non-diabetic female NZO mouse demonstrated clear, slow oscillations (**Supplemental Figure 1B**) which was surprising given reports of low K_{ATP} abundance due to *Abcc8* mutations in the NZO (48) and the strong role of K_{ATP} channels in regulating islet Ca^{2+}(9, 30, 31, 49). While not of the same lineage as the NOD, the NZO do exhibit some autoimmune infiltration in the pancreas, and the marked difference between the non-diabetic and diabetic NZOs, along with the variation in female NOD islet responses, further suggests that intra-islet variability for the NOD mice may be the result of disease progression.

Understanding the genetic variation driving islet responses in the founders may be informative beyond these specific strains. Screens in the DO mice and similar outbred populations can track SNPs associated with trait variation to their parental inbred strain of origin. Our previous genetic screen for drivers of islet function observed that many of the quantitative trait loci (QTL) appearing for *ex vivo* islet traits had effects driven by the SNPs from the wild-derived strains as opposed to the traditional inbred groups (13). The QTL mediated by *Zfp148*, which drives Ca^{2+} and insulin secretion phenotypes in beta cells (38), also had strong strain effects from wild-derived strains (13).

Previous studies of islet Ca^{2+} have largely been confined to a handful of strains, and many studies by individual labs tend to use the strains with which they initiated their projects. While this does include a few outbred stocks (e.g. NMRI (50-52), CD-1 (7, 53, 54)), direct comparisons of these to the traditional inbred lines are rare (50), and studies of specific genes often use traditional inbred lines as wild-derived lines do not respond as well to the conventional assistive reproductive technologies required for genome editing and transgenesis (55, 56).

One study, comparing the outbred (NMRI) stock to the C57BL6/J and C57BL/6N strains (50), found that the NMRI displayed significantly lower frequencies than the C57 lines, particularly in physiological glucose ranges and had similar active periods. While highly informative, there were important differences between these studies and our studies here. Of note, the studies were done in acute slice culture, in only one sex, and the frequencies detected did not resemble the (at least for the C57 lines) the slow oscillations observed in isolated islets from these inbred strains (e.g. **Figure 1**, (18, 38)).

Integrating protein correlations to calcium and human GWAS nominates novel drivers of islet function

One limitation of our current study is that the association between islet proteins and Ca^{2+} waveforms is correlative and therefore cannot distinguish proteins that are causal for the differences in islet Ca^{2+} between strains from proteins changing as a result of these differences. One way to further dissociate the two, and to establish the relevance of likely candidates to human islet biology, is to identify whether genes encoding human orthologues of these proteins are associated with glycemic traits in humans. SNPs for glycemic traits (**Table 2**), particularly those involving insulin, suggest that alterations in these proteins may impart disease risk, which is less likely for proteins that do not play critical regulatory roles. Thus, the filter for glycemic trait association, while not definitive, suggests a likely causal role for these proteins in mediating differences in islet Ca^{2+} and therefore differences in secretion between strains. Integrating human GWAS data with the proteins most correlated to Ca^{2+} waveform parameters nominated over 647 protein candidates, of which approximately a third have been previously shown to have roles in some aspect of islet biology. These include well established drivers of insulin secretion responses, such as SUR1, GLUT2, and GNAS. Other previously unknown candidates show promise for validation, as they are already targets of small molecule compounds (e.g. ACP1 and others, (57-60)), are secreted (e.g. COBLL1 and others, (61-64)), or have been knocked out in mice, resulting in metabolic phenotypes (**Figure 7B**, **Table 3**, (65)).

Comparing Ca^{2+} dynamics across strains and sex offers one approach for designing future experiments

In addition to the candidate regulators with potential relevance to human islet biology, we offer access to our data where others can determine whether their gene of interest may have roles in islet biology. As noted above, multiple inferences regarding the roles of specific pathways are possible via analysis of Ca^{2+} oscillations in islets (6, 7, 16, 18) and our protein correlations provide a resource to identify which parameter most closely relates to a Ca^{2+} trait of interest. Additionally, it highlights the relevant extreme strains for a given trait and for the gene, giving guidance regarding the best mouse strain in which to explore that gene's role (e.g. **Figure 7C**). Newer technologies in reproductive assistance, transgenesis, and gene editing, together with more accurate genome sequencing and single mutations conferring docility, are quickly making utilization of the wild-derived mice more practical (55, 56, 66-68). As many of the QTL identified in DO-based studies often have strong driver SNPs from the wild-derived strains, a further understanding of which experimental questions might be best addressed by use of these strains will be important.

Our lab and others have previously provided databases for querying the expression of genes as a function of diet (WD vs chow, (69, 70)) and background (e.g. BTBR and B6, (69, 70)), correlation and QTL scans in F2 intercrosses of these mice (71), and where these may align with QTL in our DO studies (13). Many of our candidates are strongly altered by diet and have strong correlations in the F2 data for certain clinical traits including insulin and glycemic parameters (71). Here, we provide the correlation data for islet proteins against multiple parameters describing islet Ca2+ responses between strains (DOI: https://doi.org/10.5061/dryad.j0zpc86jc). These will enable researchers to better identify proteins or parameters of interest as well as appropriate background strains with which to determine the functions of these proteins.

MATERIALS & METHODS:

Chemicals:

All general chemicals, amino acids, BSA, DMSO, glucose, gastric inhibitory polypeptide (GIP,G2269), cOmplete Mini EDTA-free Protease Inhibitor Cocktail Tablets (11836170001), and heat-inactivated FBS (12306C) were purchased from Sigma Aldrich. RPMI 1640 base medium (11-875-093), antibiotic–antimycotic solutions (15240112), NP-40 Alternative (492016), Fura Red Ca^{2+} imaging dye (F3020), DiR (D12731), and agarose (BP1356-500) were purchased from ThermoFisher. Glass-bottomed culture dishes were ordered from Mattek (P35G-0-14-C). Fura Red stocks were prepared at 5 mM concentrations in DMSO, aliquoted into light-shielded tubes, and stored at –20°C until day of use (5 μM final concentration). DiR was prepared in DMSO at 2 mg/ mL, aliquoted to light-shielded tubes, and stored at 4°C until use. All imaging solutions were prepared in a bicarbonate/HEPES-buffered imaging medium (formula in **Table 1**). Amino acids were prepared as 100× stock in the biocarbonate/HEPES-buffered imaging medium, aliquoted into 1.5 mL tubes, and frozen at –20°C until day of use. Aliquots of GIP stock were prepared at 100 μM in water and kept at -20°C until day of use.

Animals:

Animal care and experimental protocols were approved by the University of Wisconsin-Madison Animal Care and Use Committee. Most strains (B6, AJ, 129, NOD, PWK, and WSB) were bred in-house, although two strains (CAST and NZO) were purchased from Jackson Laboratory (Bar Harbor, ME). All mice were fed a high-fat, high-sucrose Western-style diet (WD, consisting of 44.6% kcal fat, 34% carbohydrate, and 17.3% protein) from Envigo Teklad (TD.08811) beginning at 4 weeks and continuing until sacrifice (aged ~19-20 weeks for all strains except the NZO males). The NZO males were sacrificed at 12 weeks of age owing to complications from severe diabetes. For each strain, 3-7 males and females from at least 2 litters were analyzed. Animals were sacrificed by cervical dislocation prior to islet isolation.

In vivo measurements:

Fasting blood glucose and insulin levels were measured in mice at 19 weeks of age, except for the NZO males which were measured at 12 weeks of age. Glucose was analyzed by the glucose oxidase method using a commercially available kit (TR15221, Thermo Fisher Scientific), and insulin was measured by radioimmunoassay (RIA; SRI-13K, Millipore).

Islet imaging:

Islets were isolated as previously described (72) and incubated in recovery medium (RPMI 1640, 11.1 mM glucose, 1% antibiotic/antimycotic, 10% FBS) overnight at 37°C and 5% CO_2. Islets were then incubated with Fura Red (5 μM in recovery medium) at 37°C for 45 minutes. Imaging dishes were created from glass-bottomed 10 cm^2 dishes that had been filled with agarose. A channel with a central well was cut into the agarose with expanded ports on either side of the well for inflow and outflow lines. Prior to loading the chambers were perfused with the initial imaging solution (8 mM glucose in imaging medium). Islets were then loaded into these dishes. The imaging chamber was placed on a 37°C–heated microscope stage (Tokai Hit TIZ) of a Nikon A1R-Si+ confocal microscope. All solution reservoirs were kept in a 37°C water bath. Solutions were perfused through the chamber at 0.25 mL/min, with constant flow controlled by a Fluigent MCFS-EZ and M-switch valve assembly (Fluigent). The scope was integrated with a Nikon Eclipse-Ti Inverted scope and equipped with a Nikon CFI Apochromat Lambda D 10x/0.45 objective (Nikon Instruments), fluorescence spectral detector, and multiple laser lines (Nikon LU-NV laser unit; 405, 440, 488, 514, 561, 640nm). Bound dye was excited with the 405nm laser and the spectral detector's variable filter was set to 620-690nm. The free dye was excited with the 488nm laser and the variable filter collected from 640-690nm. Images were collected at 1 frame/sec at 6 second intervals. Each islet was considered a region of interest for further analysis. ROI intensity was collected by NIS Elements and exported for further analysis. All microscopy was

performed at the University of Wisconsin-Madison Biochemistry Optical Core, which was established with support from the University of Wisconsin-Madison Department of Biochemistry Endowment.

Islet perifusion:

Isolated islets were kept in RPMI-based medium (see above) overnight prior to perifusion, which was performed as previously described, with minor modifications (38, 73). Islets were equilibrated in 2 mM glucose for 55 minutes, after which 100 µL fractions were collected every minute with the perifusion solutions set at a flow rate of 100 µL/min. All solutions and islet chambers were kept at 37°C. After the final fraction was collected, islet chambers were disconnected, inverted, and flushed with 2 mL of NP-40 Alternative lysis buffer containing protease inhibitors for islet insulin extraction.

Secreted insulin assay:

Insulin in each perifusion fraction and islet insulin content were determined using a custom assay, as previously described (14).

Imaging data analysis:

Trace segments for each solution condition were analyzed using Matlab and R. Traces were detrended using custom R scripts and Graphpad PRISM. Custom Matlab scripts (https://github.com/hrfoster/Merrins-Lab-Matlab-Scripts, also stored on Dryad https://doi.org/10.5281/zenodo.6540721) determined oscillation peak amplitude, pulse duration, active duration (the time when Ca^{2+} is above 50% peak amplitude), silent duration (the difference between period and active duration). , plateau fraction (the fraction of overall time per pulse spent in the active duration), pulse period and other parameters. Spectral density deconvolution for the trace segments to determine principal frequencies was done using R. Animal averages for the different parameters defined by Matlab and R were computed and graphed using custom R scripts. Figures were created using CorelDraw and Biorender.com. All R scripts and the citations for the relevant packages used to generate them are available via Dryad (https://doi.org/10.5061/dryad.j0zpc86jc).

Correlation and Z-score calculations:

Correlation analysis was performed using the imaging data measurements and our published islet protein abundance data, *ex vivo* static insulin secretion measurements, and *in vivo* measurements made in a separate cohort of mice on the WD from the same strains and sexes used in these studies (14). For each imaging parameter or previously published measurement, the Z-score was calculated using the formula $z = (x-\mu) / \sigma$ where z is the Z-score, x is the animal average for that trait given the strain and sex, μ is the average of all animals' values for that trait, and σ is the standard deviation for all animals' values for that trait. Z-scores were computed in R and excel for the imaging parameters and the previously published (14) islet proteomic, *ex vivo* secretion, and *in vivo* measurements.

Correlation coefficients between the Z-score values of the imaging parameters and Z-scores of the previously published protein abundance, islet secretion, and *in vivo* traits were computed in Excel using the CORREL function. The equation used for this function is:

$$Correl(X,Y) = \frac{\sum(x-\dot{x})(y-\dot{y})}{\sum(x-\dot{x})^2 * \sum(y-\dot{y})^2}$$

Where X and Y are the Z-scores for the correlated traits/parameters, $\dot{x}$ is the population average for trait X and $\dot{y}$ is the population average for trait Y. Traits were considered highly correlated if absolute value for their Z-score correlation coefficients was ≥ 0.5.

Gene enrichment and human GWAS analysis:

Proteins highly correlated or anticorrelated to imaging parameters were further analyzed using pathway enrichment and presence of human GWAS SNPs. Briefly, for a given parameter, pathway analysis for the highly correlated or anti-correlated proteins to that parameter was done using Enrichr (74, 75).

For GWAS analysis, human orthologues for genes encoding the previously measured islet proteins were identified using BioMart (76). For highly correlated proteins, the protein was deemed of human interest if its orthologue had SNPs for glycemia-related traits (see table 2) either along the gene body,

within +/- 100 kbp of the gene start or end, or if any region in the gene body was connected to regions with SNPs by chromatin looping. SNPs were queried using Lunaris tool of the Common Metabolic Diseases Knowledge Portal (cmdkp.org). Chromatin loop anchor points for the relevant gene orthologues were identified using previously published human islet promoter-capture HiC data (35) and the alignment between these anchor loops and orthologues of interest was done using R scripts.

For those proteins having ortholgoues with SNPs via this analysis, we conducted further literature searches using Pubmed, Google Scholar, ChEMBL (59, 60, 77), canSAR (58), Uniprot (61), Tabula Muris (78), and the Human Protein Atlas (62, 63), and other resources (64, 79, 80) to determine tissue expression and identify any prior roles in islet biology. Figures for the relevant protein examples were created using Prism, CorelDraw, and the WashU Epigenome Browser (81).

Statistics:

For the islet perifusion insulin measurements, statistics were determined in GraphPad Prism. Fractional secretion area-under-the-curve (AUC) was determined using Prism and differences in AUCs analyzed using post-tests following 2-way ANOVA for the indicated trace segments. Islet total insulins between strains were compared using a two-tailed Student's t-test with Welch's correction.

Data Availability:

All R scripts and raw data are available via Dryad (https://doi.org/10.5061/dryad.j0zpc86jc). Image files are available upon request.

Study approval:

All protocols were approved by the University of Wisconsin-Madison IACUC (Protocol A005821-R01)

Author contributions. C. Emfinger, L. Clark, M. Merrins, M. Keller, and A. Attie designed experiments. C. Emfinger, L. Clark, K. Schueler, S. Simonett, D. Stapleton, and K. Mitok performed experiments. C. Emfinger and L. Clark wrote the paper. C. Emfinger, L. Clark, M. Keller performed data analysis. C. Emfinger, L. Clark, M. Merrins, M. Keller, and A. Attie edited the paper.

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FIGURES

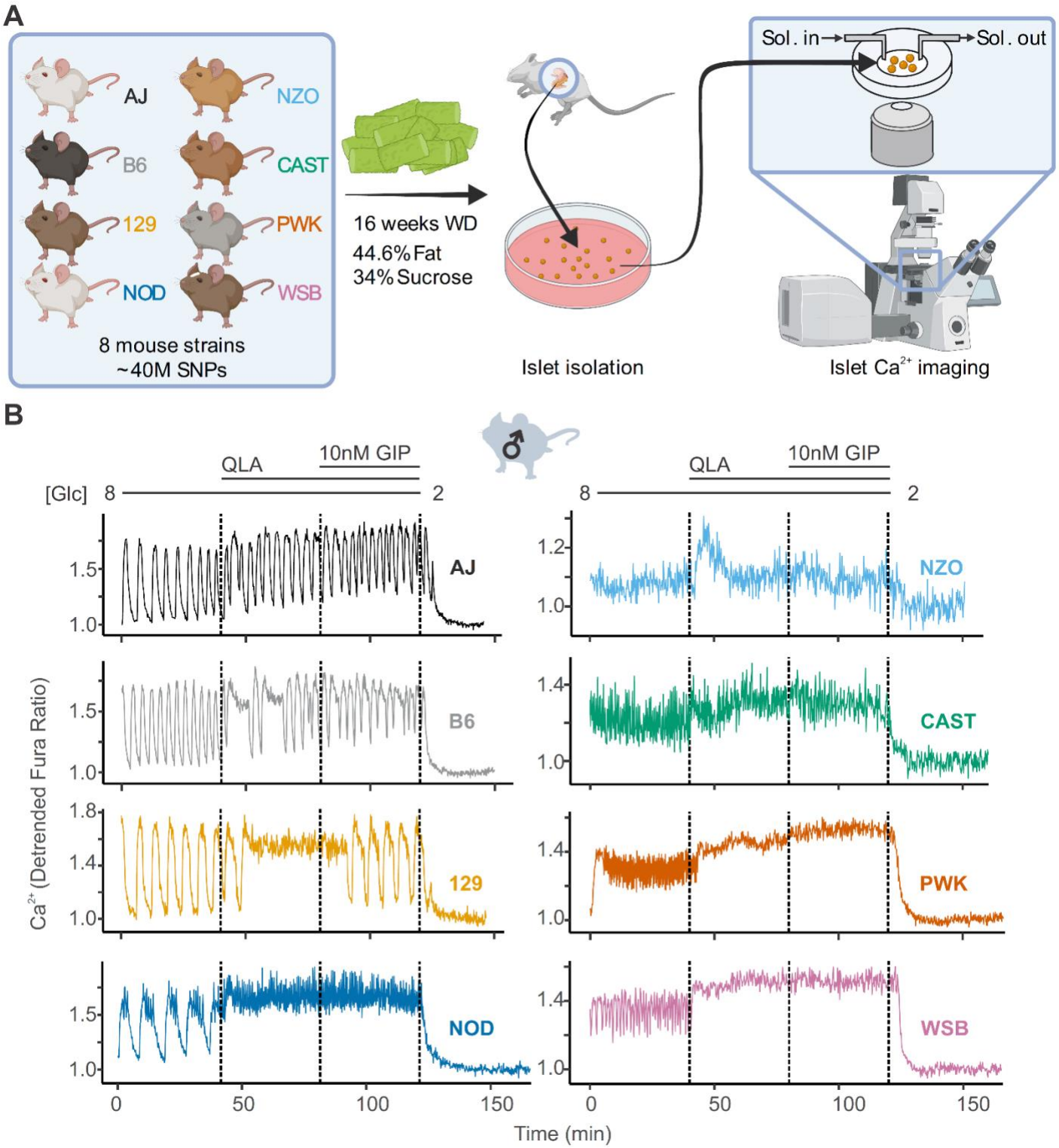

Figure 1. High diversity in Ca^{2+} oscillation across eight genetically distinct mouse strains.

(A) Male and female mice from eight strains (A/J; C57BL/6J (B6); 129S1/SvImJ (129); NOD/ShiLtJ

(NOD); NZO/HILtJ (NZO); CAST/EiJ (CAST); PWK/PhJ (PWK); and WSB/EiJ (WSB)) were placed on a Western Diet (WD) for 16 weeks, before their islets were isolated. The islets were then imaged on a confocal microscope using Fura Red dye under conditions of 8 mM glucose; 8 mM glucose + 2 mM L-glutamine, 0.5 mM L-leucine, and 1.25 nM L-alanine (QLA); 8 mM glucose + QLA + 10 nM GIP; and 2 mM glucose. **(B)** Representative Ca^{2+} traces for male mice (n = 3-8 mice per strain, and 15-83 islets per mouse), with the transitions between solution conditions indicated by dashed lines. Abbreviations: '[Glu]' = 'concentration of glucose in mM' ; 'Sol.' = 'solution'; 'SNPs'= 'single-nucleotide polymorphisms'

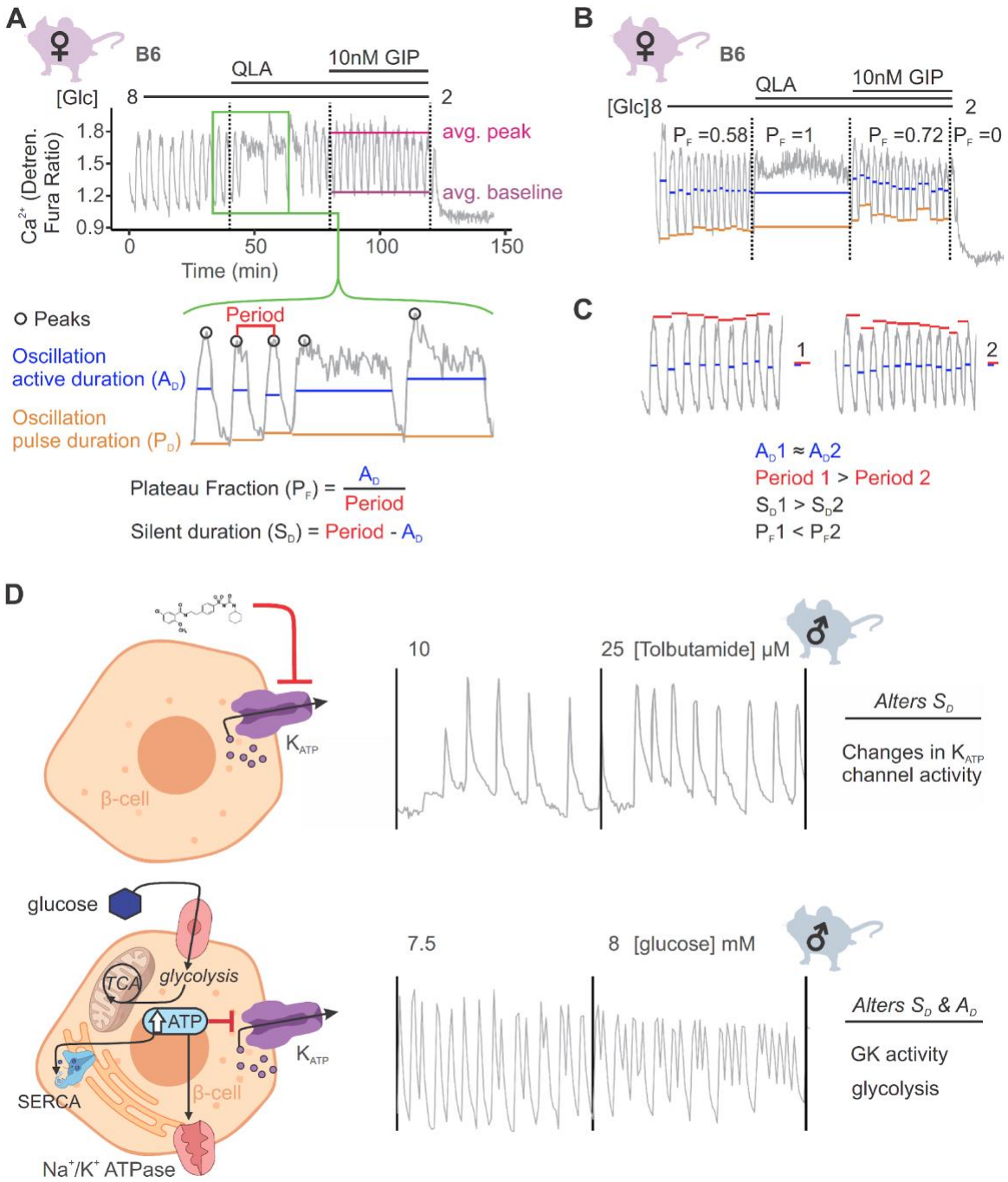

Figure 2. Ca^{2+} wave breakdown reveals mechanisms underlying Ca^{2+} responses. (A) In the example B6 female Ca^{2+} wave, the islet oscillations can change in their average peak and average baseline in response to different nutrients. Additionally, shifts in wave shape (green box) can be broken down into changes in time between peaks (period), the time in the active phase (active duration, A_D),

and the length of the oscillation (pulse duration, P_D). From these, the relative time in active phase, or plateau-fraction (P_F), and the time the islet is inactive between oscillations (silent duration, S_D) can be calculated. Each parameter can be changed by different underlying mechanisms. **(B)** For islets that plateaued, as in the example islet in 8/QLA, they were assigned a plateau-fraction of one and a period of zero. For islets that ceased to oscillate, such as the example islet in 2 mM glucose, they were assigned a plateau-fraction of zero and a period of the time of measurement (40 minutes). **(C)** For trace 1 (left), which has a longer period (red bars) than trace 2 (right), but the same active duration (blue bars), the silent duration is greater and consequently the P_F is shorter, in contrast to the trace in (**A**) where the P_F increases between 8mM and 8/QLA are largely due to increases in A_D. **(D)** Changes in specific Ca^{2+} wave parameters can reflect different mechanisms in β-cells. For example, changing K_{ATP} activity pharmacologically (upper panels) predominantly increases P_F by altering S_D, whereas increasing glucose concentrations by elevating glucose or activating GK cause significant alterations in both A_D and S_D to increase P_F. Abbreviations: '[Glc]' = 'concentration of glucose in mM' ; 'GK' = 'glucokinase'

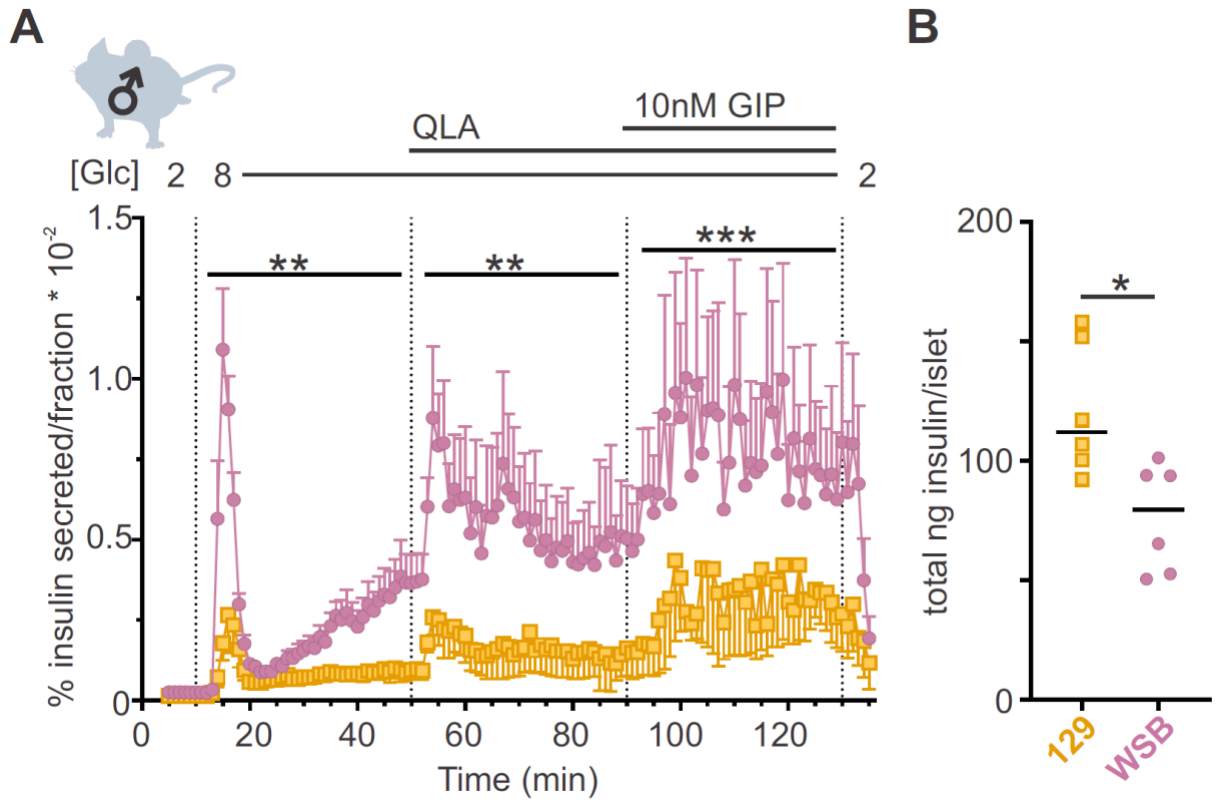

Figure 3. WSB mice secrete significantly more insulin than 129 mice. (**A**) Insulin secretion was measured for perifused islets from WSB (n=6, magenta circles) and 129 (n=5, yellow squares) male mice in 2 mM glucose, 8 mM glucose, 8 mM glucose + QLA, and 8 mM glucose + QLA + GIP. Transitions between solutions are indicated by dotted lines and the conditions for each are indicated above the graph. "[Glc]" denotes the concentration of glucose in mM. Data are shown as a percentage of total islet insulin (mean ± SEM). (**B**) Average total insulin per islet for the WSB and 129 males used in (**A**) with one exception: islets from one of the 129 mice were excluded from perifusion analysis due to technical issues with perifusion system on the day those animals' islets were perifused. Dots represent individual values, and the mean is denoted by the black line. For (**A**), asterisks denote strain effect for the area-und-the-curve of the section determined by 2-way ANOVA, mixed effects model; ** $p < 0.01$, *** $p < 0.001$. For (**B**), asterisk denotes $p < 0.05$ from Student's T-test with Welch's correction.

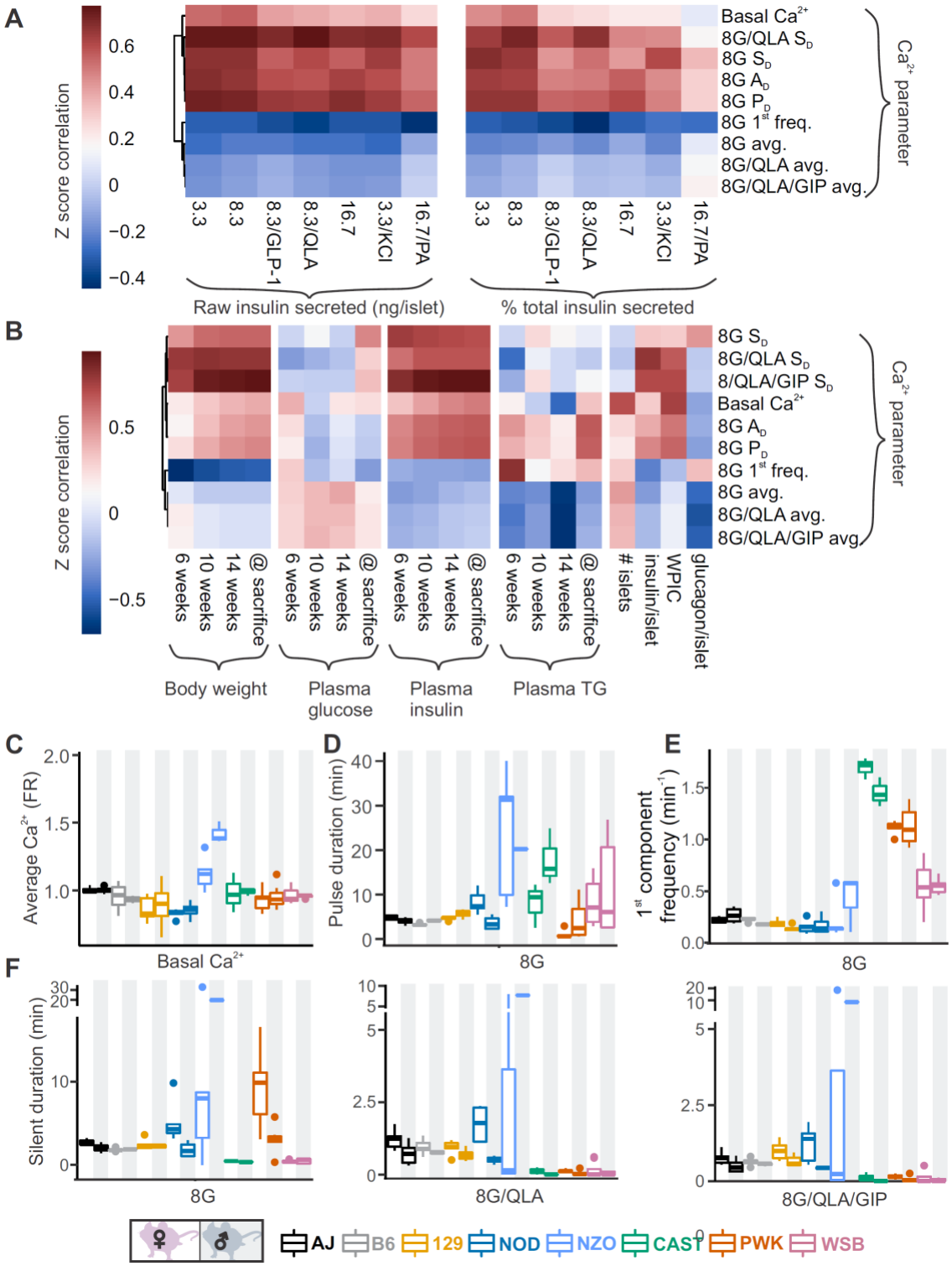

Figure 4. Comparing sex and strain patterns for Ca^{2+} metrics, insulin secretion, and clinical traits nominates Ca^{2+} metrics of interest. (A) The z-score correlation coefficient was calculated for

Ca^{2+} parameters and raw insulin secreted and % total insulin secreted. Insulin measurements were previously collected for seven different secretagogues (16.7 mM glucose + 0.5 mM palmitic acid (16.7G/PA); 3.3 mM glucose + 50 mM KCl (3.3G/KCl); 16.7 mM glucose (16.7G); 8.3 mM glucose + 1.25 mM L-alanine, 2 mM L-glutamine, and 0.5 mM L-leucine (8.3G/QLA); 8.3 mM glucose + 100 nM GLP-1 (8.3G/GLP-1); 8.3 mM glucose (8.3G); and 3.3 mM glucose (3.3G)) (32). (**B**) Correlation of the Ca^{2+} parameters to the clinical measurements in the founder mice which include 1) plasma insulin, triglycerides, and glucose at 6, 10, and 14 weeks as well as at time of sacrifice; 2) number of islets; 3) whole-pancreas insulin content (WPIC); and 5) islet content for insulin and glucagon. For (**A**) and (**B**), the Ca^{2+} parameters shown here include average Ca^{2+} in 2 mM glucose (basal Ca^{2+}); average Ca^{2+} in 8 mM glucose (8G avg.); average Ca^{2+} in 8 mM glucose + 1.25 mM L-alanine, 2 mM L-glutamine, and 0.5 mM L-leucine (8G/QLA avg); average Ca^{2+} in 8 mM glucose + QLA + 10 nM GIP (8G/QLA/GIP avg.); pulse duration in 8 mM glucose (8G P_D); active duration in 8G (8G A_D); silent duration in 8G (8G S_D), 8G/QLA (8G/QLA/S_D), and 8G/QLA/GIP (8G/QLA/GIP S_D); and 1st component frequency in 8 mM glucose (8G 1st freq.). Other parameters analyzed are indicated in supplemental figure 4. (**B-E**) Sex and strain variability for **(C)** average Ca^{2+} determined by the fura-ratio (FR) in 2 mM glucose, **(D)** pulse duration of oscillations in 8G, **(E)** 1st component frequency in 8G and **(F)** silent duration of oscillations in 8G, 8G/QLA, and 8G/QLA/GIP.

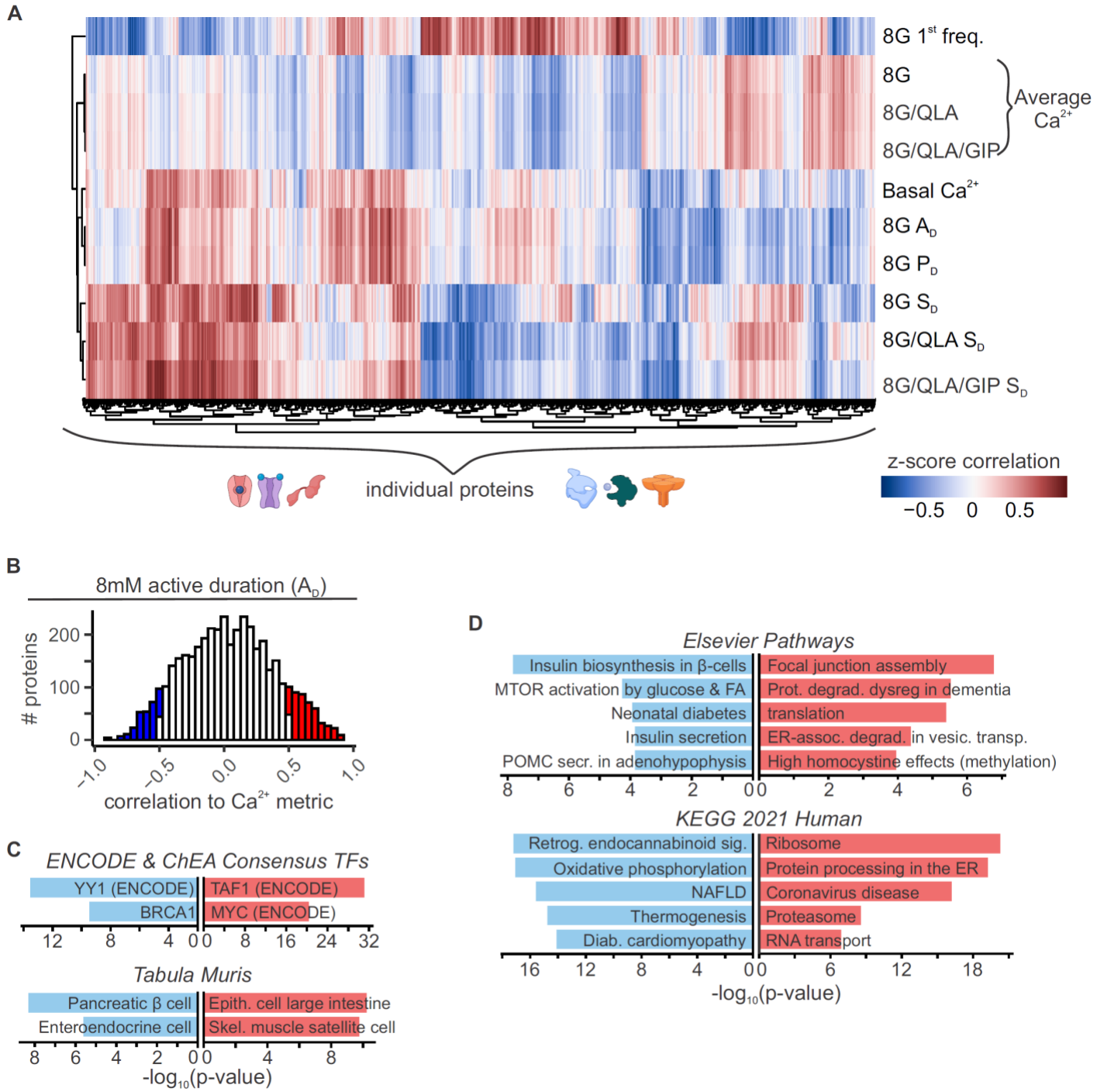

Figure 5. Islet proteins show correlation architecture to specific Ca^{2+} parameters. (**A**) Unsupervised clustering of correlation coefficients between protein abundance z-scores and z-scores for the Ca^{2+} parameters indicated. Islet proteins show differential correlation values to basal Ca^{2+}, excitatory Ca^{2+} (detrended average values for 8mM, 8/QLA, and 8/QLA/GIP), active duration and pulse

duration in 8mM glucose (8G P_D & A_D), and silent durations (S_D) in 8G, 8G/QLA, and 8G/QLA/GIP. Correlation coefficients for other parameters are indicated in Supplemental Figure 5. **(B)** Histograms representing the number of proteins that are correlated (red) and anti-correlated (blue) to 8G A_D. TRRUST transcription factor motif database and ARCHS4 Tissue signature database (C) as well as pathway enrichments for the Elsevier Pathway database and KEGG 2021 Human pathway database (D) (-$\log_{10}$(p-values)), for the highly correlated (red) and anticorrelated (blue) proteins to 8 A_D metric. Databases were queried using Enrichr (39, 40).

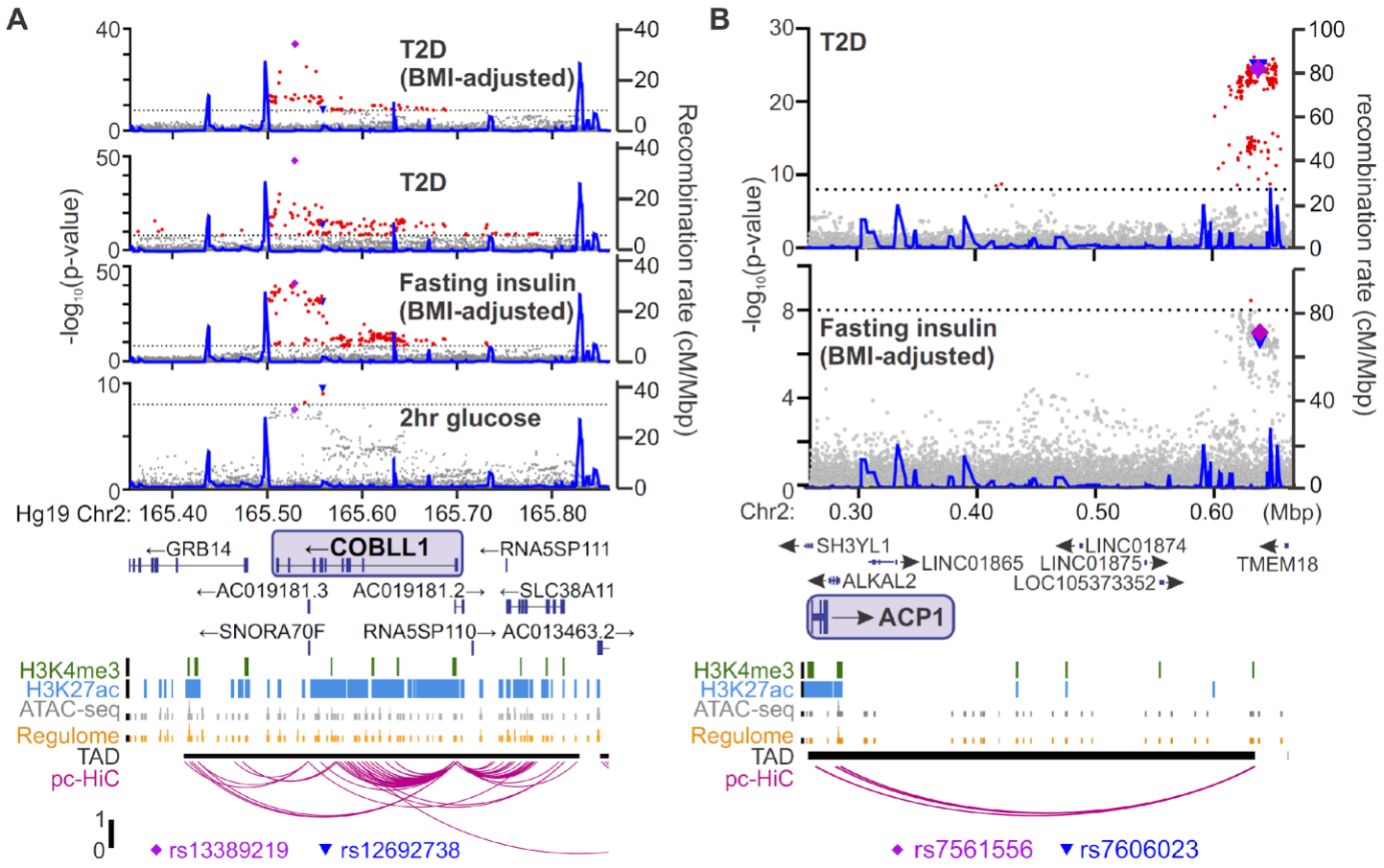

Figure 6. Identifying candidate protein targets by integrating human GWAS. (**A**) An example gene, *COBLL1*, orthologous to a gene coding for a protein identified as highly correlated to Ca^{2+} wave

parameters in the founder mice. The recombination rate is indicated by the solid blue line. Significant SNPs (8 < $-\log_{10}(p)$, red) decorate the gene body for multiple glycemia-related parameters (in bold). Human islet chromatin data (34) for histone methylation, histone acetylation, ATAC-sequencing, and regulome score suggest active transcription of the gene. Human islet promoter-capture HiC data (34) show contacts between the SNP-containing regions decorating the gene and its promoter. The highest SNP for 2hr glucose (▾) and the other parameters (♦) are indicated. (**B**) Some orthologues did not show SNPs decorating the gene itself but did show looping to regions with SNPs for glycemic traits. The promoter of *ACP1*, for example, loops to a region within its topologically associated domain (black bar) with strong SNPs for type 2 diabetes risk and near-threshold SNPs for fasting insulin adjusted for BMI. Some SNPs (▾, ♦) lie directly on the contact regions identified by HiC, whereas others lie immediately proximal to these contacts. For both panels, the significance of association ($-\log_{10}$ of the p-value) for the individual SNPs is on the left y axis and the recombination rate per megabasepair is on the right y axis. Chromosomal position in Mbp is aligned to Hg19. SNP data were provided by the Common Metabolic Diseases Knowledge Portal (cmdkp.org).

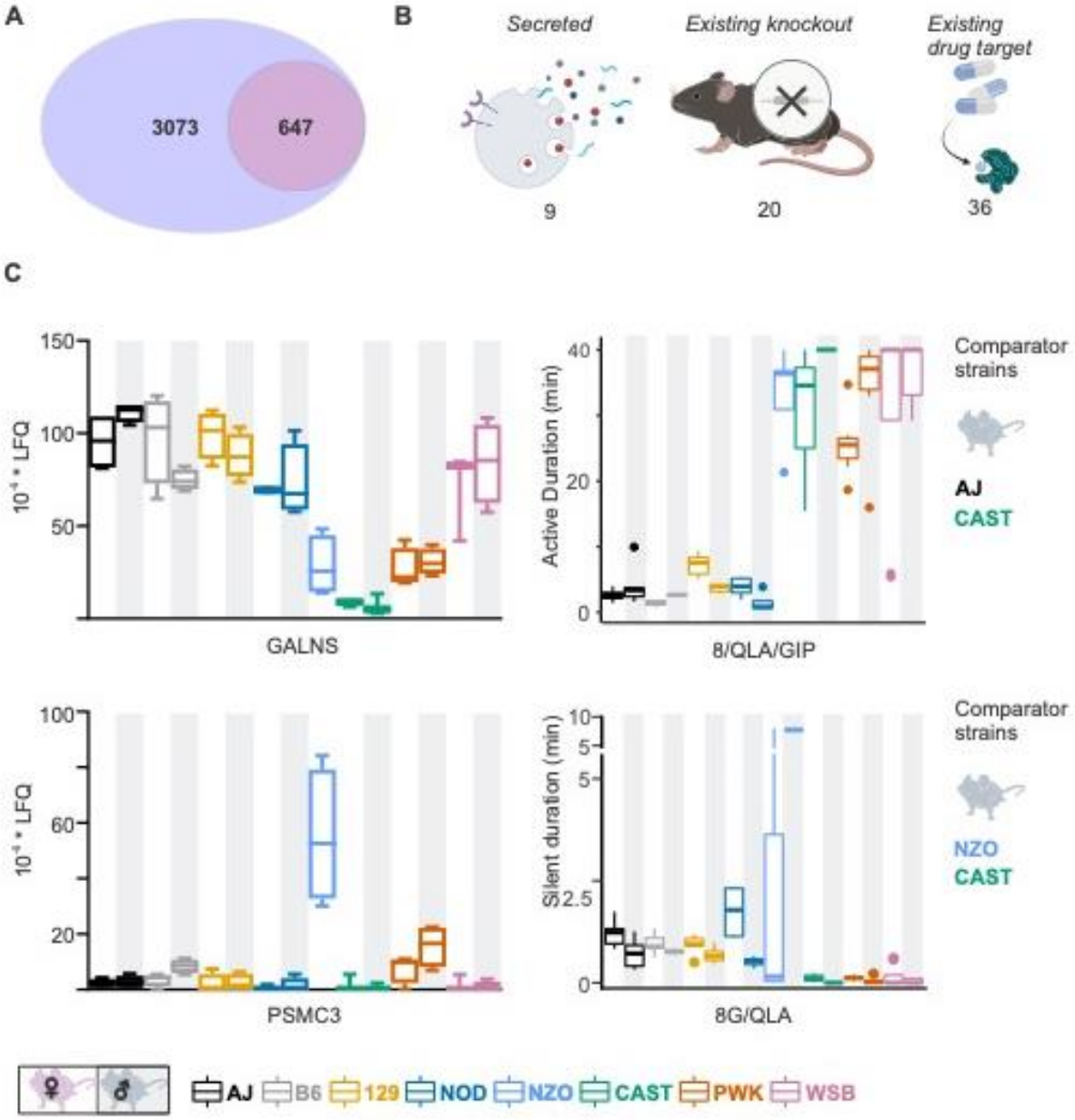

Figure 7. Strain variance alters model selections for protein/parameter testing. (**A**) Venn diagram illustrating that of 3073 proteins with significant correlation to at least 1 Ca^{2+} wave parameter of interest, 647 had orthologues with glycemic SNPs. (**B**) Of the 647 candidates, 9 were previously suggested to be secreted (61-64), 20 had existing KO mice with at least one metabolic phenotype (65), and 36 had existing compounds targeting them (57-60). (**C**) Example comparisons of strain variance

for proteins (left column, (4)) and Ca^{2+} traits (right column). GALNS (upper) is highly anticorrelated to several traits including active duration (A_D) in 8mM glucose + amino acids (8/QLA). Extreme strains to test the effect of gain or loss of this protein include B6 (high protein abundance and low A_D) and CAST (low protein abundance and high A_D), PSMC3 (lower) highly correlated to silent duration (S_D) for several conditions including 8mM glucose and QLA. The protein is largely absent in most strains (including AJ, which has low S_D) except the NZO, which has high S_D.

TABLES:

Component	Concentration (mM)
NaCl	137
KCl	5.6
$MgCl_2$	1.2
$NaH_2PO_4.H_2O$	0.5
$NaHCO_3$	4.2
HEPES	10
$CaCl_2$	2.6

Table 1: Imaging medium formula. Components are indicated by chemical abbreviation on the left and final concentration in mM is indicated in the right column.

Fasting hormones	Glucose-related	Tolerance test	Diabetes risk
insulin	fasting glucose	2hr glucose	T1D
proinsulin	random glucose	2hr insulin	T2D
c-peptide	Hba1c	2hr c-peptide	
fasting glc-BMI interaction		2hr insulin	
fasting ins-BMI interaction		Acute insulin response	
Gestational diabetes/altered fast glucose in pregnancy		SI-adjusted acute ins. Resp.	
		AUC insulin	
		AUC insulin/AUC glucose	
		Corrected insulin response	
		HOMA-B	
		HOMA-IR	
		Ins. Secretion rate	
		Ins. Sensitivity	
		Incremental ins. @ 30 min OGTT	
		Insulin @ 30min OGTT	
		Peak ins. response	
		Peak ins. Response adj SI	

Table 2 (on previous page): Categories included in SNP queries. These terms were considered as glycemia-related and are categorized as such on the Common Metabolic Diseases Knowledge portal, which was queried for the relevant SNPs. Also included but not listed here were variations of these terms that were adjusted for BMI.

Table 3 (on following pages): Proteins correlated with Ca^{2+} parameters that have glycemic-related SNPs. This includes protein IDs, gene names, gene IDs, and human orthologues for each of the proteins that correlate to one of the following metrics and have a glycemic-related SNP (see **Table 2**): basal Ca^{2+}, 8G S_D, 8G/QLA S_D, 8G/QLA/GIP S_D, 8G A_D, 8G P_D, and 8G 1st freq.

Protein ID	Gene name	Gene ID or gene number	Human orthologue
Q9CQA1	Trappc5	66682	TRAPPC5
Q8CC86	Naprt	223646	NAPRT
Q5H8C4-2;Q5H8C4;Q8CDS8;Q6P6M9	Vps13a	271564	VPS13A
P10639	Txn	22166	TXN
I1E4X5;Q8BWQ6;D3YW20;D3YW19;Q8BWQ6-3	9030624J02Rik	71517	VPS35L
E0CXW2;E9PUK2;Q80V03-2;Q80V03	Adck5	268822	ADCK5
A2A6P4;Q8BKU4;Q9CQP1;Q3TYF6;Q3TY58	Fam104a	28081	FAM104A
Q91ZE0	Tmlhe	MGI:2180203	TMLHE
P70280	Vamp7	MGI:1096399	VAMP7
Q8VE95	C030006K11Rik	ENSMUSG00000116138	C8orf82
P42208;E9Q3V6;F6WYM0;D3YYB1;D3Z3C0	Septin2	ENSMUSG00000116048	SEPTIN2
Q543K9;P23492	Pnp	ENSMUSG00000115338	PNP
Q9CRC0	Vkorc1	ENSMUSG00000096145	VKORC1
Q6ZWR6-4;Q6ZWR6	Syne1	ENSMUSG00000096054	SYNE1
Q14A47;Q8K003	Tma7	ENSMUSG00000091537	TMA7
Q5BLJ7;P62301;Q921R2	Rps13	ENSMUSG00000090862	RPS13
Q9WV96;D6RG99;D3YVK5;D3YVK4	Timm10b	ENSMUSG00000089847	TIMM10B
Q9CPW2	Fdx2	ENSMUSG00000079677	FDX2
A0A087WQE6;A0A087WNT1;P83940;A0A087WPE4	Eloc	ENSMUSG00000079658	ELOC
Q8R2U0-2;Q8R2U0	Seh1l	ENSMUSG00000079614	SEH1L
Q9D002;Q9CZE1;Q545N1;P56873	Znrd2	ENSMUSG00000079478	ZNRD2
Q99JR8-2;Q99JR8;Q3TXH6;Q3TM59	Smarcd2	ENSMUSG00000078619	SMARCD2
S4R191;S4R1P3;S4R2T3;P0C8K7	Smim1	ENSMUSG00000078350	SMIM1
Q9JJQ6;Q3TLS9;Q8CCG9;Q00558	F8a	ENSMUSG00000078317	F8A1
Q80TA1;Q9D4D0	Selenoi	ENSMUSG00000075703	SELENOI
Q8VCQ3;E0CZ57	Nrbf2	ENSMUSG00000075000	NRBF2
Q3ULL5;Q99L45	Eif2s2	ENSMUSG00000074656	EIF2S2
G5E8V9;E9Q3G5	Arfip1	ENSMUSG00000074513	ARFIP1
Q9D9Z5	Dda1	ENSMUSG00000074247	DDA1
Q62084	Ppp1r14bl	ENSMUSG00000073730	PPP1R14B
O78207;W5XQG0;Q792Z7;P01899;Q31168;Q31167;O78206;O19467;Q569W0	H2-D1	ENSMUSG00000073411	HLA-E
B1AVZ0	Uprt	ENSMUSG00000073016	UPRT
P68369	Tuba1a	ENSMUSG00000072235	TUBA1A
Q505N7;Q3UW66;Q99J99	Mpst	ENSMUSG00000071711	MPST
Q3U781;Q9D6W4;P84104-2;P84104;A2A4X6	Srsf3	ENSMUSG00000071172	SRSF3
A2AP32;A2AP31;Q3UIU2	Ndufb6	ENSMUSG00000071014	NDUFB6
Q80X95	Rraga	ENSMUSG00000070934	RRAGA
Q9JJL8	Sars2	ENSMUSG00000070699	SARS2
Q04750	Top1	ENSMUSG00000070544	TOP1
Q544H0;Q9Z1D1;Q3THA0	Eif3g	ENSMUSG00000070319	EIF3G
Q8BTZ7	Gmppb	ENSMUSG00000070284	GMPPB
Q8BXR1;D3YY38	Slc7a14	ENSMUSG00000069072	SLC7A14
G3X9M0;Q9ER88;Q9ER88-2	Dap3	ENSMUSG00000068921	DAP3
Q3U7U8;C5H0E8;P62835;Q3V3W9;C5H0E9	Rap1a	ENSMUSG00000068798	RAP1A
Q9CQU1	Mfap1	ENSMUSG00000068479	MFAP1
D3YX27;Q3TXN0;Q3UJR3;Q9JIY5;S4R1B3;Q80V84;F6XUR8;F6TCV0;D3YX28	Htra2	ENSMUSG00000068329	HTRA2
Q8R0J7	Vps37b	ENSMUSG00000066278	VPS37B
Q9EPL8	Ipo7	ENSMUSG00000066232	IPO7
P11352	Gpx1	ENSMUSG00000063856	GPX1
Q6PAL3;Q8BNE3;Q8BSZ2	Ap3s2	ENSMUSG00000063801	AP3S2
Q9CQ65	Mtap	ENSMUSG00000062937	MTAP
Q4KL81;P63260;Q3TSB7;Q3UD81	Actg1	ENSMUSG00000062825	ACTG1
Q6P1A9;Q5EBG5;Q58ET1;Q80UT7;P12970	Rpl7a	ENSMUSG00000062647	RPL7A
Q9JME5	Ap3b2	ENSMUSG00000062444	AP3B2
Q3UIZ0;Q99KY4-2;Q99KY4;Q3UDE5	Gak	ENSMUSG00000062234	GAK
Q9DB29	Iah1	ENSMUSG00000062054	IAH1
Q3THU8;Q8VEM8;G5E902;Q3UB63;Q3U995	Slc25a3	ENSMUSG00000061904	SLC25A3
E9PVD1	Ccdc62	ENSMUSG00000061882	CCDC62
Q5M9L7;Q8BT90;P63276;Q3TK12	Rps17	ENSMUSG00000061787	RPS17
Q9CRY7	Gdpd1	ENSMUSG00000061666	GDPD1
A0MNP4;Q9ERF3;Q8BVQ0;D6RDC7	Wdr61	ENSMUSG00000061559	WDR61
Q6RJ37;Q5KTQ2;O35641;P01902;Q31634;Q31191;Q31148;Q31614;Q31290	H2-K1	ENSMUSG00000061232	HLA-E
Q9ER38	Tor3a	ENSMUSG00000060519	TOR3A
Q99L69;Q3U3J1;P50136	Bckdha	ENSMUSG00000060376	BCKDHA
G3UYD0;Q3UHU8;Q9ESZ8-5;Q9ESZ8-4;Q9ESZ8-3;Q9ESZ8-6;Q9ESZ8-2;Q9ESZ8	Gtf2i	ENSMUSG00000060261	GFT2I
Q9DCD8;Q58EV4;O70435;Q3TEL1;E0CX62	Psma3	ENSMUSG00000060073	PSMA3
P17156;B7U582	Hspa2	ENSMUSG00000059970	HSPA2
I6L960;G3X9Y5;Q6A0C5;E9Q735	Ube4a	ENSMUSG00000059890	UBE4A
Q4FZL1;Q5F2A7;P60843;Q3UXC2;Q3TGK7;Q3TFG3;Q3TLL6;Q3U8I0;Q78WR5	Eif4a1	ENSMUSG00000059796	EIF4A1
Q540I4;Q3TJS0;O08917;G3UYU4	Flot1	ENSMUSG00000059714	FLOT1
Q5NCJ9;Q8R1I1	Uqcr10	ENSMUSG00000059534	UQCR10
A2RSB1;B7ZNL2;Q8C1W9;Q78ZA7	Nap1l4	ENSMUSG00000059119	NAP1L4
Q642K1;Q58EW0;P35980;Q0QEW9;G3UZJ6;G3UZK4	Rpl18	ENSMUSG00000059070	RPL18
Q1WWK3;P43276	H1f5	ENSMUSG00000058773	H1-5
Q4PZA2-3;Q4PZA2-4;Q4PZA2;Q4PZA2-2	Ece1	ENSMUSG00000057530	ECE1
Q3UHJ0;Q3UHJ0-2	Aak1	ENSMUSG00000057230	AAK1
F6RPJ9;Q8CGB9;Q9JHR7	Ide	ENSMUSG00000056999	IDE
P42128	Foxk1	ENSMUSG00000056493	FOXK1
Q544Y7;P18760;F8WGL3;Q9CX22	Cfl1	ENSMUSG00000056201	CFL1
E9Q5W5;Q5SSH7-2;Q5SSH7	Zzef1	ENSMUSG00000055670	ZZEF1
A0AUN0;Q4G0C0;G3X928	Sec23ip	ENSMUSG00000055319	SEC23IP
Q8R395	Commd5	ENSMUSG00000055041	COMMD5
Q4W4C9;Q3TVC0;B2L107;P62761	Vsnl1	ENSMUSG00000054459	VSNL1
B0FTY3;Q8R1N4;Q8R1N4-2;Q8R1N4-3	Nudcd3	ENSMUSG00000053838	NUDCD3
Q61292;Q3USI2	Lamb2	ENSMUSG00000052911	LAMB2
Q9R1T2;Q9R1T2-2	Sae1	ENSMUSG00000052833	SAE1
Q7TMK6;Q3UWV9;Q3TKK8	Hook2	ENSMUSG00000052566	HOOK2
Q505D7	Opa3	ENSMUSG00000052214	OPA3
Q8K3W0;D3Z7P0;Q8K3W0-1;Q8K3W0-5;Q8K3W0-6;E9Q0U3;Q8K3W0-4	Babam2	ENSMUSG00000052139	BABAM2
Q9QY96;Q9QY96-2;Q8CDP3	Casr	ENSMUSG00000051980	CASR
A2ASS6;E9Q8N1;E9Q8K5;A2ASS6-2	Ttn	ENSMUSG00000051747	TTN
P43274	H1f4	ENSMUSG00000051627	H1-4
Q9CZP0	Ufsp1	ENSMUSG00000051502	UFSP1
Q91WK1	Spryd4	ENSMUSG00000051346	SPRYD4
Q9Z0W3;Q9Z0W3-2	Nup160	ENSMUSG00000051329	NUP160
Q2M4J2;Q9Z1B3-2;Q9Z1B3-3;Q9Z1B3;Q6ZQ92;Q3UPW0	Plcb1	ENSMUSG00000051177	PLCB1
A2AIL4	Ndufaf6	ENSMUSG00000050323	NDUFAF6
P27661	H2ax	ENSMUSG00000049932	H2AX
Q8R086	Suox	ENSMUSG00000049858	SUOX
P43275	H1f1	ENSMUSG00000049539	H1-1

Q3U3H9;P61963;Q80ZU1	Dcaf7	ENSMUSG00000049354	DCAF7
A2ASW4;Q9EQZ6-3;Q9EQZ6;A2ASW8;Q571A8;Q9EQZ6-2	Rapgef4	ENSMUSG00000049044	RAPGEF4
P59266	Fitm2	ENSMUSG00000048486	FITM2
O88845;Q3TR91;O88845-3	Akap10	ENSMUSG00000047804	AKAP10
Q3U487	Hectd3	ENSMUSG00000046861	HECTD3
Q566K0;P17095;Q3TE85	Hmga1	ENSMUSG00000046711	HMGA1
Q8C4B4;Q8C4B4-2	Unc119b	ENSMUSG00000046562	UNC119B
Q3UK83;Q3U7F3;Q3TIK8;Q5EBP8;P49312;Q3TFB1;P49312-2	Hnrnpa1	ENSMUSG00000046434	HNRNPA1
Q3UAP1;Q9WUQ2;D3Z3S1	Preb	ENSMUSG00000045302	PREB
Q4VAI2;Q9D358	Acp1	ENSMUSG00000044573	ACP1
Q8C298;E9Q179;Q8C5Q4	Grsf1	ENSMUSG00000044221	GRSF1
B2RX64;Q571E5;B7ZWH8	Prss53	ENSMUSG00000044139	PRSS53
Q8R3Y8-2;Q8R3Y8	Irf2bp1	ENSMUSG00000044030	IRF2BP1
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Q52L87;P68373;Q3TIZ0	Tuba1c	ENSMUSG00000043091	TUBA1C
Q561M4;Q3UDC3;O88746	Tom1	ENSMUSG00000042870	TOM1
Q9JHC0	Gpx2	ENSMUSG00000042808	GPX2
D3Z7X0;D3Z2B3	Acad12	ENSMUSG00000042647	ACAD10
P70227	Itpr3	ENSMUSG00000042644	ITPR3
O70305-2;E9QM77;O70305;O70305-3;F6U2C2;Q3UX07;F7B6X4;Q3UX51	Atxn2	ENSMUSG00000042605	ATXN2
Q60520;Q60520-1	Sin3a	ENSMUSG00000042557	SIN3A
Q3TK27;Q8CI11;Q8CI11-2	Gnl3	ENSMUSG00000042354	GNL3
E9Q7L3;D3Z1W6;E9Q7L2;D3Z1N4;E9Q4Y5;F8VQD1;Q8BSQ9-2;Q8BSQ9;D3YYF2;D6RIL0;D6RI94;D3Z3R4;F6THL5	Pbrm1	ENSMUSG00000042323	PBRM1
Q3V3R4;Q3V391;Q05DI0	Itga1	ENSMUSG00000042284	ITGA1
Q3THL5;Q80X73	Pelo	ENSMUSG00000042275	PELO
B2RQR5;Q3TDT4;Q8BPQ7;D3Z7V4;D3YUT7	Sgsm1	ENSMUSG00000042216	SGSM1
E9Q481;Q6P2K6	Ppp4r3a	ENSMUSG00000041846	PPP4R3A
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P12968	Iapp	ENSMUSG00000041681	IAPP
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Q8QZS1;E0CX19	Hibch	ENSMUSG00000041426	HIBCH
B2RVP5;Q3THW5;P0C0S6;Q8R029;Q3TFU6;Q3UA95	H2az2	ENSMUSG00000041126	H2AZ2
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E9Q9J4;Q6ZQB6-3;Q6ZQB6;Q6ZQB6-2;Q80V47	Ppip5k2	ENSMUSG00000040648	PPIP5K2
K3W4R5;A2AGT5-3;A2AGT5;Z4YL78;A2AGT5-2;Q80U79	Ckap5	ENSMUSG00000040549	CKAP5
Q8K4R4-2;X1WI19;Q8BTD8;Q8K4R4-3;Q8K4R4;Q8K4R4-4	Pitpnc1	ENSMUSG00000040430	PITPNC1
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Q543N6;P58389;Q8C0E1;A2AWE9;A2AWF0	Ptpa	ENSMUSG00000039515	PTPA
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G3X972;Q80U83;Q3V222;Q8R2V9	Sec24c	ENSMUSG00000039367	SEC24C
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Q9ER72;Q3UXN3	Cars	ENSMUSG00000010755	CARS1
P54731	Faf1	ENSMUSG00000010517	FAF1
Q9CW46	Raver1	ENSMUSG00000010205	RAVER1
Q61686	Cbx5	ENSMUSG00000009575	CBX5
Q8BFY9-2;Q8BFY9;Q3TKD0	Tnpo1	ENSMUSG00000009470	TNPO1
Q64332	Syn2	ENSMUSG00000009394	SYN2
Q5SVG5;Q5SVG4;O35643;Q8CC13;Q3TVN4;Q3U1K9	Ap1b1	ENSMUSG00000009090	AP1B1
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Q3TMH2	Scrn3	ENSMUSG00000008226	SCRN3
Q564F4;Q3TII0;P80315;Q3UJZ8;G5E839	Cct4	ENSMUSG00000007739	CCT4
B2RRS4;E9PWV7;Q923K4;D6RDC6;Q923K4-2	Gtpbp3	ENSMUSG00000007610	GTPBP3
Q3UKQ5;Q3UF03;P24668	M6pr	ENSMUSG00000007458	M6PR
Q3U9X2;Q9ES84;O35901;O35900;Q9EP83	Lsm2	ENSMUSG00000007050	LSM2
Q542F1;Q9Z1Q5;Q3TIP8	Clic1	ENSMUSG00000007041	CLIC1
Q99LD8;O08972	Ddah2	ENSMUSG00000007039	DDAH2
Q3UL64;O35657	Neu1	ENSMUSG00000007038	NEU1
Q790I0;Q9Z1Q9;Q7TPT7;Q3U3D3;G3UY93;Q3TII4	Vars	ENSMUSG00000007029	VARS1
E9Q9M5;J3KMM1;Q3UJD6-2;Q3UJD6	Usp19	ENSMUSG00000006676	USP19
P08030	Aprt	ENSMUSG00000006589	APRT
Q9CVB6;Q3UA52;Q4FZG5;D3YXG6	Arpc2	ENSMUSG00000006304	ARPC2
P62814	Atp6v1b2	ENSMUSG00000006273	ATP6V1B2
Q922Z3;Q3UPJ8;Q3TK29;Q9CQN1;Q922R9;Q3TSG8	Trap1	ENSMUSG00000005981	TRAP1
P99026	Psmb4	ENSMUSG00000005779	PSMB4
Q3U8E7;P18155	Mthfd2	ENSMUSG00000005667	MTHFD2
M4TKR7;P15208	Insr	ENSMUSG00000005534	INSR
P37040;Q05DV1	Por	ENSMUSG00000005514	POR
Q9DCT2	Ndufs3	ENSMUSG00000005510	NDUFS3
P28659-4;P28659-2;P28659-3;P28659	Celf1	ENSMUSG00000005506	CELF1
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Q99MZ3;Q99MZ3-4;Q99MZ3-3;H9U1Q1;Q99MZ3-5;Q99MZ3-2	Mlxipl	ENSMUSG00000005373	MLXIPL
Q8C2D2;P70362;Q9CWQ7;Q9CZJ3	Ufd1	ENSMUSG00000005262	UFD1
Q9Z186	G6pc2	ENSMUSG00000005232	G6PC2
O08847;P08775	Polr2a	ENSMUSG00000005198	POLR2A
Q61171;Q5M9N9;D3Z4A4	Prdx2	ENSMUSG00000005161	PRDX2
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Q9R0N5	Syt5	ENSMUSG00000004961	SYT5
Q3U9G9	Lbr	ENSMUSG00000004880	LBR
Q8R1V4;Q5SVW9	Tmed4	ENSMUSG00000004394	TMED4
Q6ZQ84;Q9JLV5;E9Q4T8	Cul3	ENSMUSG00000004364	CUL3
Q91V01	Lpcat3	ENSMUSG00000004270	LPCAT3
Q542P8;O35130	Emg1	ENSMUSG00000004268	EMG1
Q545V3;Q3UJ20;P17183;D3Z6E4;Q922A0	Eno2	ENSMUSG00000004267	ENO2
Q3V235;O35129;F6QPR1	Phb2	ENSMUSG00000004264	PHB2
Q544R7;Q3U6W4;O70252;D3YX62	Hmox2	ENSMUSG00000004070	HMOX2

Q3TY95;Q60823;F8WHG5;Q8CE74;D3YXM7;D3Z3N2	Akt2	ENSMUSG00000004056	AKT2
Q3ULI4;Q3U5Q4;P42227;Q6GU23;P42227-2;B7ZC18;Q3U6S9	Stat3	ENSMUSG00000004040	STAT3
P62918;Q3UJS0;Q3THC7;Q9Z237	Rpl8	ENSMUSG00000003970	RPL8
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B2MWM9;P14211;Q3UWP8	Calr	ENSMUSG00000003814	CALR
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Q99K86;Q9R069;Q8BGB4	Bcam	ENSMUSG00000002980	BCAM
Q3UMU9;Q3UMU9-3;Q3UMU9-4;Q3UMU9-2	Hdgfl2	ENSMUSG00000002833	HDGFL2
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Q9D0K8;Q5RL57;Q3TLG2;Q9R0L7	Akap8l	ENSMUSG00000002625	AKAP8L
P28028	Braf	ENSMUSG00000002413	BRAF
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P99024	Tubb5	ENSMUSG00000001525	TUBB
Q11011;E9Q039;F6QYF8;E9Q6F4	Npepps	ENSMUSG00000001441	NPEPPS
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B2RPS1;Q0PD56;P61021;Q8C458	Rab5b	ENSMUSG00000000711	RAB5B
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D3Z596;D3YWU5;D3Z595	Ins2	ENSMUSG00000000215	INS
P24529;Q3UTB3;E9Q9G5	Th	ENSMUSG00000000214	TH