Title

Proteomics Analysis of the Regenerating Proximal Nerve After Injury and Repair: Autograft versus Nerve Lengthening

Author

Chhugani, Neha

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Proteomics Analysis of the Regenerating Proximal Nerve After Injury and Repair: Autograft versus Nerve Lengthening

A thesis submitted in partial satisfaction of the requirements
for the degree Master of Science

in

Bioengineering

by

Neha Chhugani

Committee in charge:

Professor Sameer Bhrugu Shah, Chair
Professor Geert W Schmid-Schönbein, Co-Chair
Professor Adam J Engler

2020

The thesis of Neha Chhugani is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2020

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ABSTRACT OF THE THESIS

Proteomics Analysis of the Regenerating Proximal Nerve After Injury and Repair: Autograft versus Nerve Lengthening

by

Neha Chhugani

Master of Science in Bioengineering

University of California San Diego, 2020

Professor Sameer Bhrugu Shah, Chair
Professor Geert W Schmid-Schönbein, Co-Chair

Peripheral nerve injuries are damaging nerve conditions that can result in pain and motor and sensory deficits. A number of biological processes, including structural, transcriptional, translational and growth-related pathways within nerve cells are affected by injury. In this study, we examine a peripheral nerve injury to compare protein expression level changes among control uninjured nerves and two different injury repair strategies at an early regenerative time point; such changes may be useful in predicting the eventual success of a particular repair strategy. UPLC-ESI mass spectrometry and MaxQuant LFQ and PEAKS v8.5 bioinformatic algorithms were performed on samples from the proximal stump of peripheral nerves injured and acutely repaired by autograft or a new nerve lengthening strategy, as well as uninjured contralateral control nerves. The proteins overexpressed in the lengthened sample by two-fold or greater were analyzed in DAVID, and the output data was manually clustered into 15 pathways relevant to nerve injury and regenerative processes. We present evidence of upregulated structural, immune response, bioenergetic, and protein synthesis pathways in the lengthened condition to support the stretch-activated growth hypothesis for nerves. We also highlight candidate proteins for future diagnostic or manipulation studies to characterize the nerve regeneration environment. These findings are important in advancing our understanding of the peripheral nerve regeneration process post-injury.

1. INTRODUCTION

1.1 Peripheral Nervous System

The nervous system is responsible for autonomic, sensory and motor control in the human body. The two main components are the central nervous system (CNS), composed of the brain and spinal cord, and the peripheral nervous system (PNS), which encompasses all other nerves and ganglia. Unlike the CNS, the PNS isn't protected by bone structures and are located superficially throughout the body, leaving the peripheral nerves more susceptible to mechanical injury (Schmidt and Leach 2003).

Glial cells are the non-neuronal cells that provide structural and metabolic support to the peripheral nerves (Hall 2005). The main glial cells of the peripheral nervous system are called Schwann cells, which wrap around the axons of motor and sensory neurons to form the myelin sheath (Siddiqui, Khazaei and Fehlings 2015).

1.2 Nerve Injury/Molecular Biology of Repair Process

Peripheral nerve injuries are often the result of bodily injuries that cause deformation to the nerve. Common types include complete nerve transections, stretch-injuries, lacerations, and compression injuries. Nerve transections are the most severe, characterized by a complete discontinuation of the nerve. Peripheral nerve injuries can undermine a patient's motor and sensory abilities. Unlike nerves in the central nervous system, peripheral nerves are capable of regeneration on a small scale, with axons regenerating at a rate of around 2-5 mm/day. However, this growth is undirected, so surgical intervention is often necessary.

In these injuries, the nerve is severed, and the distal portion separated from the cell body degenerates. Wallerian degeneration leads to the removal of axonal and myelin-derived material and prepares the environment in which the axons will regenerate. Regeneration then begins in the severed end after phagocytic cells clear the debris (Hall 2005). Schwann cells play a key role in promoting axonal regeneration, as they are the main source of neurotrophic factors. These factors interact with tyrosine kinase receptors to alter the gene expression profile of the neuron to promote regeneration.

Autografts are the standard of care for peripheral nerve injuries because they have minimized risk of immune rejection (Rinker and Vyas 2014). This technique involves harvesting a nerve from a less critical area of the same patient, often the sural nerve from the upper leg. This process has several drawbacks including the inability to repair longer nerve gaps, and possible size mismatches between donor graft and the injured nerve (Schmidt and Leach 2003). In larger nerve gaps, grafts are used because they offer tension-free repair.

End-to-end repair is the recommended therapeutic strategy for short transected nerve gaps. End to end repair is promising because axons can grow directly into the distal nerve stump rather than into and out of the graft. End-to-end repair of a larger nerve gap can also be achieved by redistribution of tension away from the nerve site via a nerve-interfacing device (Howarth et al. 2019a).

1.3 Mass Spectrometry for Protein Quantification/Proteomics

Proteomics is the large-scale analysis of gene and cellular functions at the protein level. The identification, quantitation, and characterization of all proteins in a sample offers insight into the underlying cellular physiology and molecular processes (Aebersold and Mann 2003). Mass spectrometry can be used to analyze protein samples systematically by identifying peptides and their respective concentrations within a sample. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) uses laser light pulses to vaporize the matrix via desorption. Electrospray ionization (ESI) is a mass spectrometry to produce ions using an electrospray.

MALDI-TOF introduces sample in solution to the ion source while ESI uses the solid state. ESI has advantages when identifying a large number of new peptides, including resolving larger particles.

Researchers can generate testable hypotheses based on biological information and pre-existing knowledge. The output of a proteome analysis is a list of identified factors, with a quantitative value associated. Lists are classified and filtered to understand and interpret the protein data.

1.4 Specific Background

For my project, I will be examining early-stage responses of nerve environments to injury. In particular, I will be evaluating three groups, autograft implanted, lengthening device, and non-injury (control). The comparison between the non-injury and lengthening device groups provides insight into the pathways activated by injury processes. The second comparison, autograft vs. lengthening, demonstrates how different intervention methods differ.

There are multiple previous papers that discuss proteomics analysis after nerve injury at an early time point. We present a proteomics investigation of the proximal stump nerve injury environment five days post-operation with comparisons between two intervention options.

The genetic changes in rat proximal nerve stumps after sciatic nerve transection have been previously investigated (Gong et al. 2019). Differentially expressed genes in the proximal nerve stumps at 0.5-hour, 1 hour, 3-hour, 6-hour, 9-hour, 1 day, 4-day, 7 day, and 14 day after rat sciatic nerve transection were subjected to Ingenuity pathway analysis (IPA) bioinformatic analysis. Cytokine signaling, cellular immune response, nuclear receptor signaling, disease-specific pathways, and organismal growth and development pathways were significantly activated in the proximal stump. Gene expression profiling has demonstrated gene categories, but proteomic investigations can offer additional insight into translational shifts.

The proteomics of the injured rat sciatic nerve and protein expression dynamics during regeneration have been previously examined at multiple time points (Jiménez et al. 2005). Extracts of sciatic nerves were collected at 5, 10, and 35 days after a forceps crush injury and were analyzed via mass spectrometry. 82 proteins were identified pertaining to several functional classes, including acute-phase proteins, antioxidant proteins, and proteins involved in protein synthesis/maturation/degradation, cytoskeletal (re)organization, and in lipid metabolism. Neuronal proteins were moderately downregulated after crush and recovered expression at 35 days after nerve injury, which is consistent with what is known regarding Wallerian degeneration and subsequent axon regeneration.

Tissue samples were extracted from the proximal stump of a rat sciatic nerve 5-days post-injury and intervention. The three experimental conditions offer insight into the differences in protein expression in two post-injury environments compared to a non-injured group. These changes can indicate protein expression dynamics and regenerative potential at the 5-day post-injury time point. Sampling at the proximal stump allows us to examine cellular processes that support regrowth and regeneration. Based on success of lengthening procedures, we are interested in activated growth pathways between the lengthened and graft groups.

We hypothesize that protein synthesis, growth-related, cytoskeletal, and axonal transport pathways will be upregulated in stretch. Tension can lead to either growth or damage and based on previous findings, we hypothesize that growth will be activated. We also hypothesize other pathways upregulated in growth that may be affected, such as the coagulation and degradation pathways.

2. METHODS

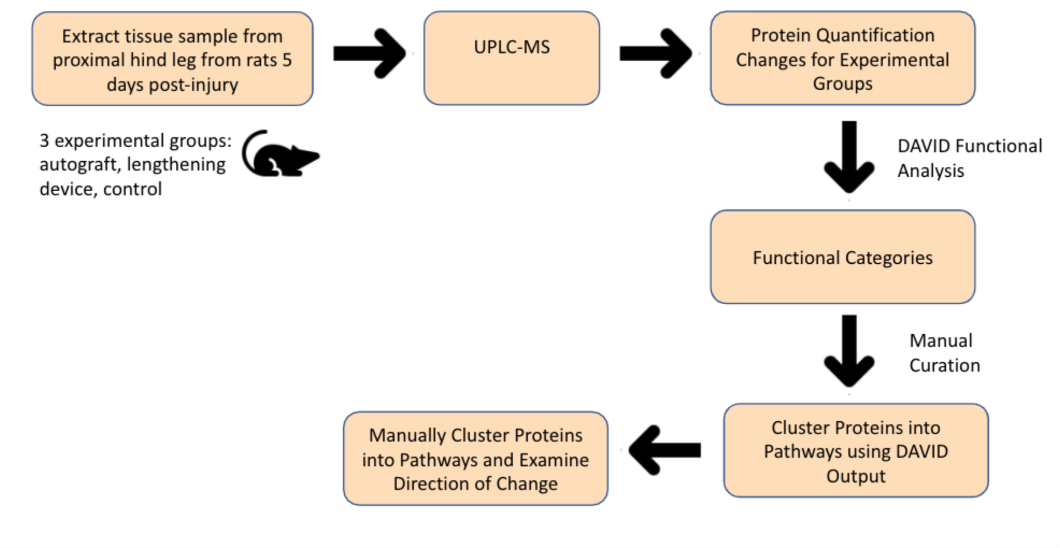

Figure 1: Workflow diagram demonstrates our method in progressing from tissue sample to clusters of proteins with directional fold changes between experimental groups.

2.1 Surgical Repair

Three experimental samples were autograft, lengthening/end-to-end repair, and control nerve. The methods of the autograft and lengthening/end-to-end repair rats are detailed in Howarth et al., 2019 (Howarth et al. 2019b).

“A dorsal incision was made in the hindlimb, and the femoral biceps was split to expose the sciatic nerve. The sciatic nerve was then decompressed. For the autograft group, 10 mm of the sciatic nerve was cut cleanly using a no. 11 blade, between the hip and knee and above the bifurcation. This nerve piece was then flipped and resutured to the proximal and distal ends using three epineurial sutures (8-0 Ethilon, Ethicon, Guaynabo, Puerto Rico; Grinsell & Keating, 2014). Muscle was then sutured together using 4-0 polyglycolic acid suture (Oasis, Ottawa, IL), and the skin was stapled using AutoClip staples (MikRon Precision, Gardena, CA). The rats were then allowed to recover on a heating pad prior to rehousing.

For lengthening surgeries, the proximal stumps of transected nerves were lengthened by 12 mm to span a final gap of 10 mm at the time of repair. Either a 10- or 3-mm segment of the nerve was removed prior to lengthening. For the former, an additional 2 mm of nerve stumps was trimmed prior to end-to-end anastomosis, and so, the repair was under slight tension (as is also typical for flipped auto-grafts). For the latter, additional nerve was trimmed back at the time of surgery, such that 10-mm total nerve was excised before a tension free repair."

Five days after the injury, approximately 30 minutes after stretching, about 1 cm of nerve was harvested proximal to the injury site, above any visible swelling of the nerve. For the control samples, tissue was harvested from the healthy leg. Tubes containing the nerve samples were frozen in isopentane cooled liquid nitrogen, and stored at -80 ^{O}C. Four tissue samples at each experimental condition were tested in mass spectrometry.

2.2 Mass Spectrometry

Mass spectrometry-based proteomics allowed us to assess the nerve injury proteome on a quantitative scale. The twelve individual tissue samples were digested with protease solution (Meyer et al. 2014). The protease solution included trypsin, endoproteinase LysC, wild type α-lytic protease (WaLP), and M190A α-lytic protease (MaLP), which aid in digestion to improve proteome coverage. Samples were separated using ultra performance liquid chromatography and analyzed via electrospray ionization. The Thermo Scientific Orbitrap Fusion Lumos Tribrid MS with electron-transfer dissociation was the instrumentation and method used. Label free quantification was then performed using the MaxQuant LFQ algorithm as described in Cox et al. 2014 (Cox et al. 2014). This was performed at the UC San Diego Biomolecular and Proteomics Mass Spectrometry Facility.

2.3 Statistics

PEAKS Studio v8.5 is a peptide/protein identification and software used for the protein quantification in complex biological samples. Zhang et al. 2012 details the scoring algorithm used to classify the peptide spectrum matches reported by PEAKS DB (Zhang et al. 2012). This software was used to map the raw mass spectrometry data to peptides and proteins. A protein filter was applied to the protein group significance calculation, which determined which protein groups were listed. The significance threshold was set to 20 and the fold change threshold was set to 20 for both experimental comparisons. The software outputs included Accession IDs, fold changes, and p-values.

2.4 Analysis Strategy

The Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.7 was used to generate pathways based on the Uniprot Accession IDs. A number of ontological classification schemes based on keyword-, pathway-, sequence-, and classification schemes were used to group proteins. Key protein clusters were identified based on a combination of DAVID-generated and manual classification. DAVID-generated pathway analyses did not capture all of the cellular processes occurring at the injury site (Huang da, Sherman and Lempicki 2009). We elected to cluster the protein list by genes.

803 Accession IDs from Control vs. Lengthening comparison were uploaded into the version 6.7 software, and corresponded to 794 DAVID Uniprot Accession IDS in the Rattus norvegicus species. Using the Functional Annotation feature, all Functional Chart terms of p-value $< 10^{-4}$ were selected, as shown in **Table S1**. These 180 terms were sorted into 14 clusters by function. These clusters and the number of unique accession IDs in each cluster are given in **Table S2.** 35 DAVID-generated pathways (Kegg) were enriched in our protein dataset with significant regulatory changes between the two experimental conditions (p-value < 0.05). This

includes Complement and Coagulation Cascades (33 proteins, p-value = 1.5E-20),Proteasome (22 proteins, p-value = 6.3E-14), Regulation of actin cytoskeleton (26 proteins, p-value = 1.6E-3), Focal adhesion (25 proteins, p-value = 2.2E-3). DAVID was used to gather all of the genes associated with each Functional Chart term. These genes were screened for relevance to the overall cluster category via Gene Ontology definition, and associated gene lists were created for each cluster, as shown in **Table S3**.

Using the Database for Annotation, Visualization and Integrated Discovery (DAVID), 7 pathways were enriched in our protein dataset with significant regulatory changes between the two experimental conditions ($p\text{-value} < 0.05$). 160 Accession IDs from Graft vs. Lengthening comparison were uploaded into the DAVID software, and corresponded to 158 DAVID Uniprot Accession IDs in the Rattus norvegicus species. Using the Functional Annotation feature on DAVID 6.7, all Functional Chart terms of $p\text{-value} < 10^{-4}$ were selected, as shown in **Table S4**. These 46 resultant terms were sorted into the clusters by Gene Ontology definition. These clusters and the number of unique accession IDs in each cluster are given in **Table S5**. The genes belonging to each Functional Chart term on DAVID's catalog were manually screened using Gene Ontology definitions and the relevant genes in each process are shown in **Table S6**. A breakdown of the number of hits in each cluster by intervention method is summarized in **Table 1**.

Table 1: Summary of clusters for both Control versus Lengthening and Graft versus Lengthening experimental conditions with corresponding # of hits

Cluster	Control versus Lengthening	Graft versus Lengthening
Cytoskeleton/Motility	89	11
Peripheral Nervous System/ Myelin/ Proliferation Regulator	15	2
ECM/ Focal Adhesion	68	24
Bioenergetics	152	60
Enzymatic Activity/ Serpin	45	13
Post-Translational Modifications	65	33
Calcium	49	20
mRNA Processing/ Transcription	100	39
Ribosome/ Translation	116	23
Protein Folding, Processing and Sorting (Intracellular Transport)	238	22
Coagulation	42	28
Complement Cascade/ Immune	41	28
Acute Phase Immunity	21	0
Protein Degradation/ Clearance (Ubiquitin-Proteasome)	0	7
Apoptosis	8	0

3. RESULTS/DISCUSSION

3.1 Summary of Analysis Strategy

We hypothesized that structural, damage/injury, transcriptional, translational and growth-related pathways are affected by injury. We additionally hypothesized that stretch enhances the regenerative response compared to graft-based approaches to nerve repair. Using a proteomics-based approach, we tested these hypotheses. Mass spectrometry was used to identify significant differences across experimental groups. DAVID-based analysis and manual curation were performed to identify clusters of proteins and pathway responses that differed between the experimental groups.

3.2 Injured Versus Non-Injured Nerves

We compared outcomes between uninjured control nerves and injured lengthened nerves. Based on raw mass spectrometry data and Peaks and David analysis, the 159 proteins were identified in 39 DAVID-generated clusters (Table S1, Table S2). Given the considerable overlap among DAVID-derived clusters, we consolidated these data manually into 15 clusters (Table S3). Our general findings of amplified processes were consistent with previous proteomics literature in the nerve injury site. These processes at the five-day post-injury time point were also consistent with what is currently known about early injury response.

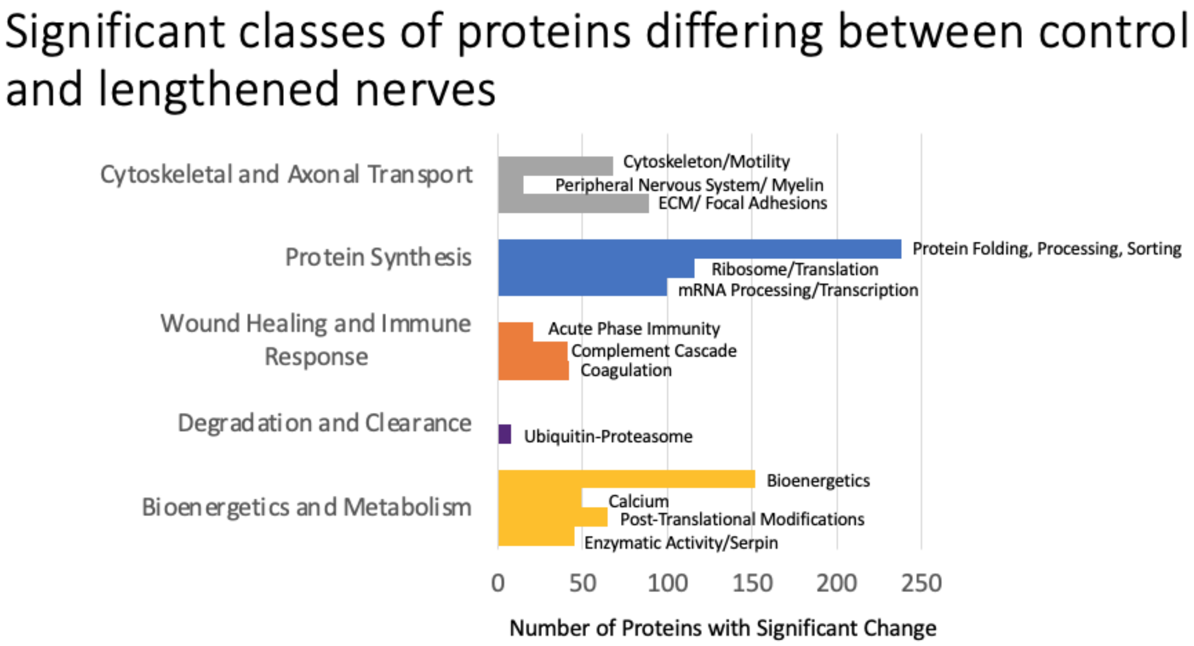

Figure 2: Significant classes of proteins differing between control and lengthened nerves in each of five overarching clusters.

For all clusters, most proteins were upregulated in lengthened nerves compared to the control sample. There are eight proteins that have a ratio of less than 1.00, indicating that they were downregulated in the lengthened sample. The Uniprot IDs are D4ACE7, D3ZK72, M0RC38, A7M777, F1LZR0, A7M746, F1MAF7, D4A3G7, which are all keratin-associated proteins involved in intermediate filaments.

3.2.1 Cytoskeletal and Axonal Transport

Within the cytoskeletal and axonal transport cluster, extracellular matrices, cytoskeletal reorganization, and microtubule stabilization related proteins were largely upregulated. We categorized these into the Cytoskeleton/Motility, Peripheral Nervous System/Myelin/Proliferation Regulator, and Extracellular Matrix/Focal Adhesion subclusters. This is relevant conceptually in our model because an increase in extracellular matrix provides growing cell structure. Cytoskeletal remodeling and neuronal transport upregulation support a regenerating neuron (Schmidt and Leach 2003). Specific indicator proteins of cytoskeletal reorganization and microtubule stabilization were upregulated, including Tnnt1, Palld, Ckap4, and Tnc. These changes suggest growth cone formation, allowing for anterograde transport of growth elements to support axonal regrowth and elongation.

3.2.2 Protein Synthesis

The three Protein Synthesis pathways include mRNA Processing/Transcription, Ribosome/Translation, and Protein Folding, Processing and Sorting (Intracellular Transport) These were the three highest clusters in terms of number of proteins significantly upregulated between the control and lengthening groups. This indicates that regenerative processes are initiating in the lengthened nerve compared to the control sample. These processes require significantly more material to fuel rebuilding compared to the nerve at homeostasis. Cellular outgrowth consisting of small axon bundles and Schwann cells has been shown to emerge from the proximal stump within several days after injury (Hall 2005). Our data showed a 10-fold upregulation in calcium-binding protein calumenin (CALU) under stretch conditions. This protein was also found to be upregulated in 5-10 days post crush in literature, and has also been implicated in protein synthesis, cell adhesion and immunological defense (Jiménez et al. 2005). DNAJC3, DnaJ heat shock protein family member C3, was not present in control samples that was highly present in lengthened nerves. This protein is an endoplasmic reticulum localized chaperone protein that promotes normal protein folding functions. EIF3G, eukaryotic translation initiation factor 3 subunit G, was also highly increased expression in stretch nerves. EIF3G is part of the eIF-3 complex required for protein synthesis initiation.

3.2.3 Wound Healing and Immune Response

The Wound Healing and Immune Response cluster includes Coagulation, Complement Cascade, and Acute Phase Immunity pathways. The complement and coagulation systems are majorly activated early after injury (Amara et al. 2008). The upregulation of many factors in the intrinsic and extrinsic pathways demonstrates that that these pathways are activated (Figure 6). A previous study has shown that cellular immune response and cytokine signaling pathways were activated in the peripheral nerve stumps after transection (Gong et al. 2019).

3.2.4 Degradation and Clearance

Wallerian degeneration has been carefully studied as a distal stump processes, but we do believe there is evidence of a clearance process in the proximal stump as well. The protein degradation pathway was highlighted, and may be attributed to proximal stump degeneration and clearance at the injury site. Following nerve injury, the axonal skeleton disintegrates and the axonal membrane breaks apart. The activation of ubiquitin-proteasome pathway and m-calpain leads to cytoskeletal and myelin sheath disintegration. Macrophages and Schwann cells infiltrate, allowing for debris clearance.

3.2.5 Bioenergetics and Metabolism

Bioenergetics and Metabolism encompass Bioenergetics, Enzymatic Activity/Serpin, Post-Translational Modifications, and Calcium. Based on the entropy phenomena, this follows as a nerve in stretch conditions is in more disorder and higher energy compared to the control nerve. Additionally, increased calcium is required to induce axonal degeneration and to activate the proteolytic enzymes that are involved in cytoskeletal breakdown (Hall 2005).

3.3 Graft versus Lengthening

We next compared outcomes between injured nerves repaired with gold standard autograft and nerve lengthening device (Howarth et al. 2019b). Based on raw mass spectrometry data and Peaks and David analysis, the 794 proteins were identified in over 60 David-generated clusters (Table S4, Table S5). As we did for analysis of control vs injured nerves, we consolidated these data manually into 16 clusters (Table S6). Our findings revealed interesting insights into the possible cellular pathways that underly and enhanced regenerative response in lengthened nerves.

In rats, with the implanted nerve lengthening device, we expect to find the hallmarks of stretch-activated growth. Our subsequent analysis was to summarize pathways between graft and nerve lengthened implants. We hypothesized that clustering of proteins would demonstrate upregulated expression of injury and growth-related pathways, including the complement and coagulation cascade, protein synthesis, and cytoskeletal/axonal transport. Each category is shown with its numerical quantification of genes for each experimental condition in **Table 1.** These high-level analyses demonstrated a number of pathways activated by injury, including the coagulation and complement cascades, cytoskeletal restructuring, protein degradation, and ER processes.

Relative to the first comparison, several pathways were no longer calculated as significantly different, indicating that these were specific to injury. Calculated protein expression changes between graft and lengthening samples represent differences based on the method of intervention. Therefore, we wanted to perform a more in-depth analysis of these differential pathways, to understand how lengthening may alter the early regenerative response.

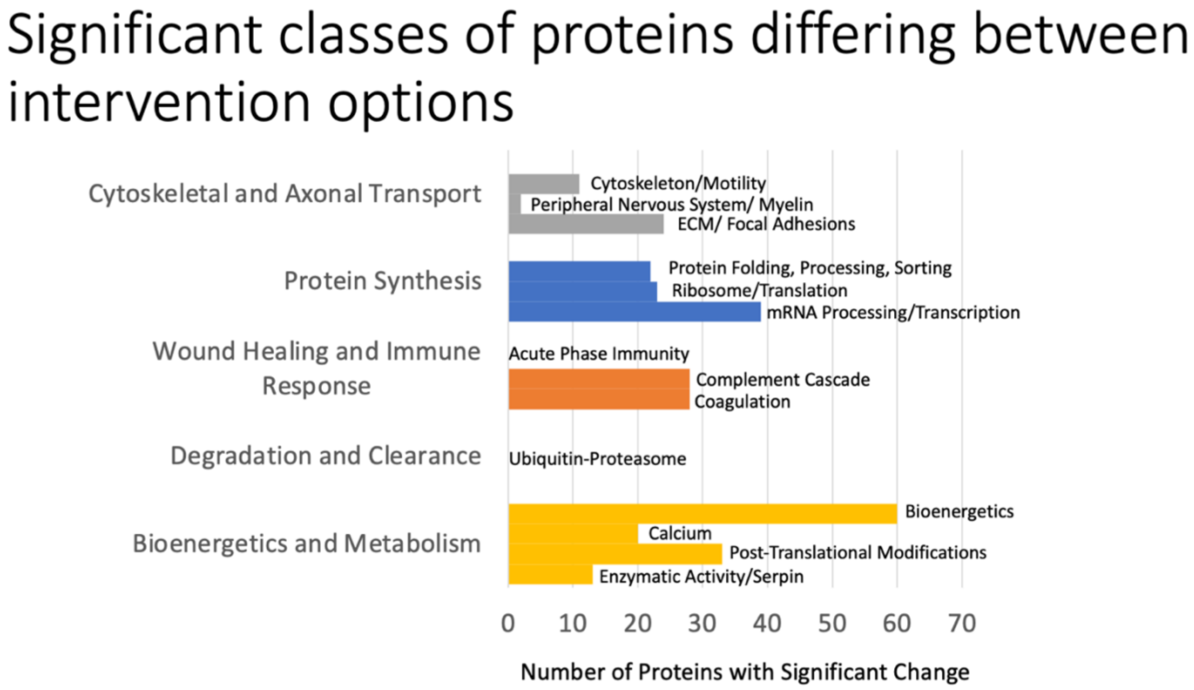

Figure 3: Significant classes of proteins differing between intervention options (graft versus lengthening) in each of five overarching clusters.

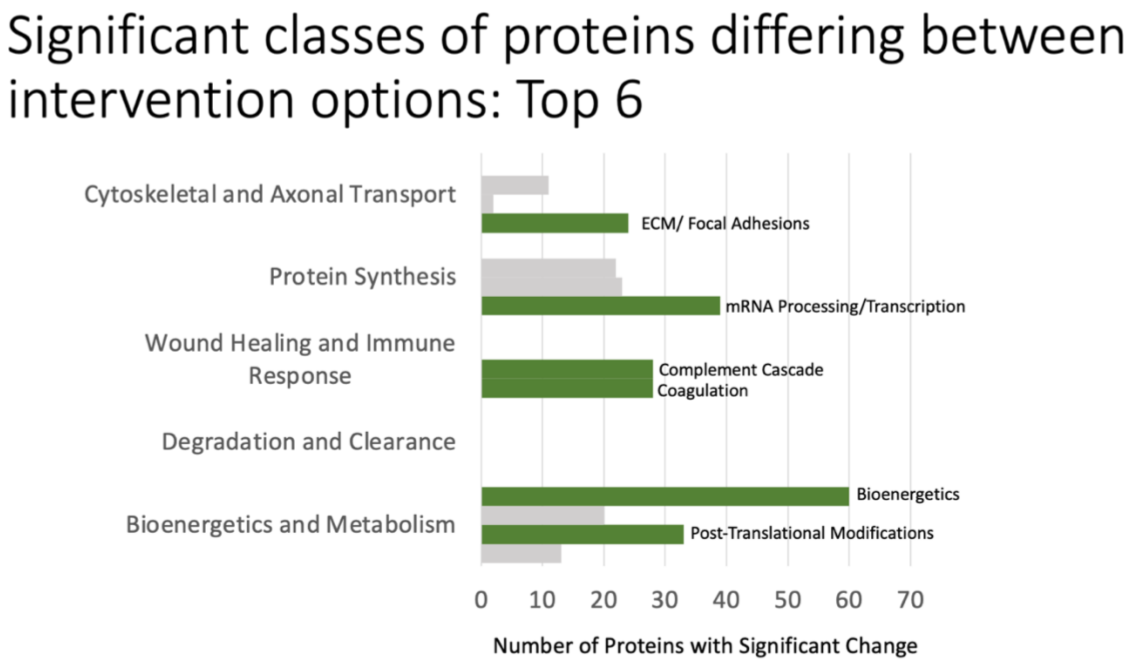

Figure 4: Top six significant classes of proteins differing between intervention options (graft versus lengthening).

For all clusters, most proteins were upregulated in lengthened nerves compared to the autograft sample. There are twelve proteins that have a ratio of less than 1.00, indicating that they were downregulated in the lengthened sample. The Uniprot IDs are A0A0G2JXR0, P09605, B4F789, A0A0G2JSQ1, P27768, G3V6F1, G3V7S2, Q304F3, P04466, P02600, A0A0G2K7F7, and A0A0G2JSP8. These mostly involve cytoskeletal and structural elements, including creatine kinases, myosin chains, neurofilaments, tropomyosin, and troponin.

3.3.1 Cytoskeletal and Axonal Transport

Pathways implicated in Cytoskeletal and Axonal Transport cluster included focal adhesions and collagen fibrillogenesis. Though these pathways would be increased in any regenerating nerve, we might expect increased enhancement if growth pathways are accelerated with stretch, because the material demands are higher for a growing nerve. A number of ribosomal proteins were categorized under focal adhesions, and literature demonstrates that mechanical tension induces movement of ribosomes to focal adhesions (Chicurel et al. 1998). Thus the focal adhesions may be involved not only in regulatory signaling and force transmission but also in protein synthesis. Mechanical tension present from the lengthening device may induce movement of ribosomes to focal adhesions.

3.3.2 Protein Synthesis

Protein Synthesis processes include Transcription, Translation, and Protein Processing. As growth requires structural changes in both the ECM and nerve environments, protein synthesis and folding are necessary to support these functions. Consistent with enhanced protein synthesis required to sustain stretch-activated growth, a number of pathways related to ribosomal and endoplasmic reticulum function were identified. Broadly, ER functions could be classified as related to routing (to or from the ER), structure, and chaperone/protein folding functions.

Intriguingly, several proteins also demonstrated linkage to specific protein classes. While we do not have insight into the broader set of synthesized proteins, there was an upregulation of proteins specifically implicated in collagen protofibril folding (e.g., P4ha1, P4ha2, P4hb, Ppib, and Plod1). Thus, enhanced protein synthesis appears not only to supply expanding neurons and Schwann cells, but also surrounding extracellular matrix.

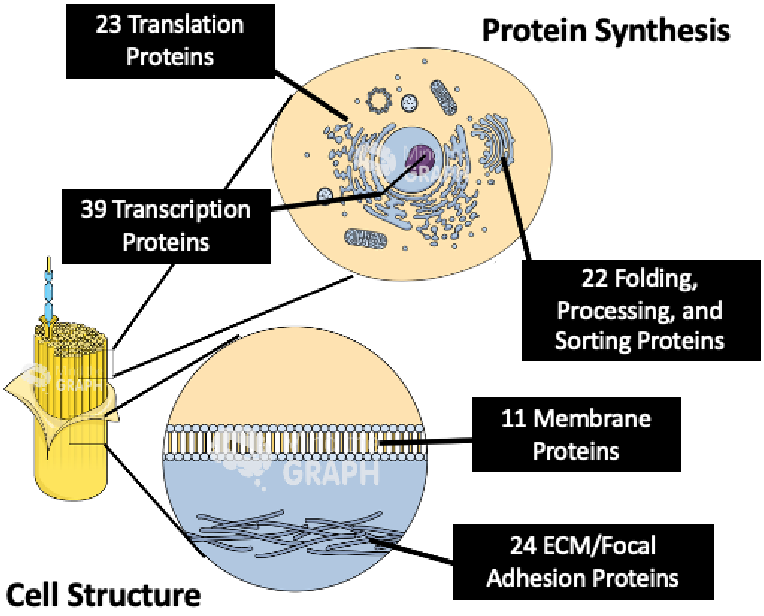

Figure 5: Quantified proteins for the Protein Synthesis and Cell Structure pathways that are upregulated in lengthening condition.

3.3.3 Wound Healing and Immune Response

Many of the proteins in the intrinsic and extrinsic pathway that were upregulated in stretch versus control, are also upregulated in stretch compared to the graft condition. This suggests the immune response is activated in stretch at the 5-day time point, which may be related to the additional tension applied on the nerve.

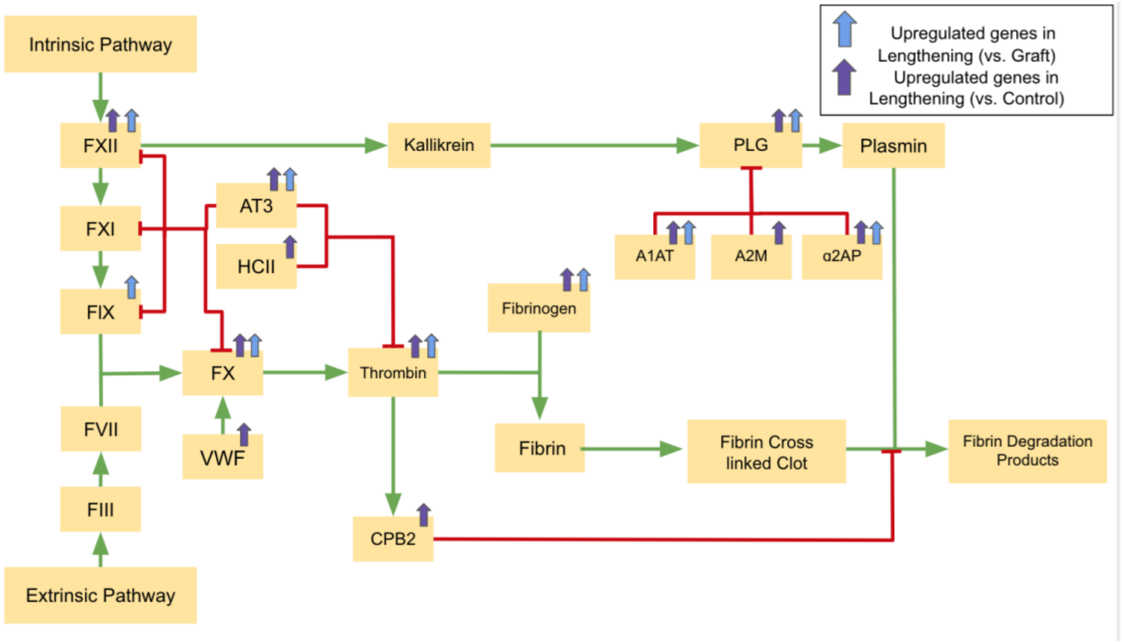

Figure 6: Workflow diagram demonstrates the overlap between the intrinsic and extrinsic pathways and indicates upregulation for each comparison. Green and red lines indicate positive and negative feedback loops, respectively.

3.3.4 Degradation and Clearance

There are no significant pathways in the degradation and clearance pathways that are upregulated in lengthened nerves versus autograft implanted. This indicates that these two experimental conditions may have similar levels of clearance and degradation pathways by the 5-day timepoint.

3.3.5 Bioenergetics and Metabolism

Many bioenergetic proteins relating to calcium, metabolism, post-translational modifications, and enzymatic activity were also upregulated in stretch. This category is the most ambiguous and does contain a wide variety of proteins. Our interpretation of this cluster is an assessment of the overall activity level within the cell.

Overall our findings support literature on stretch, which show that it can enhance key wound healing and regenerative growth pathways.

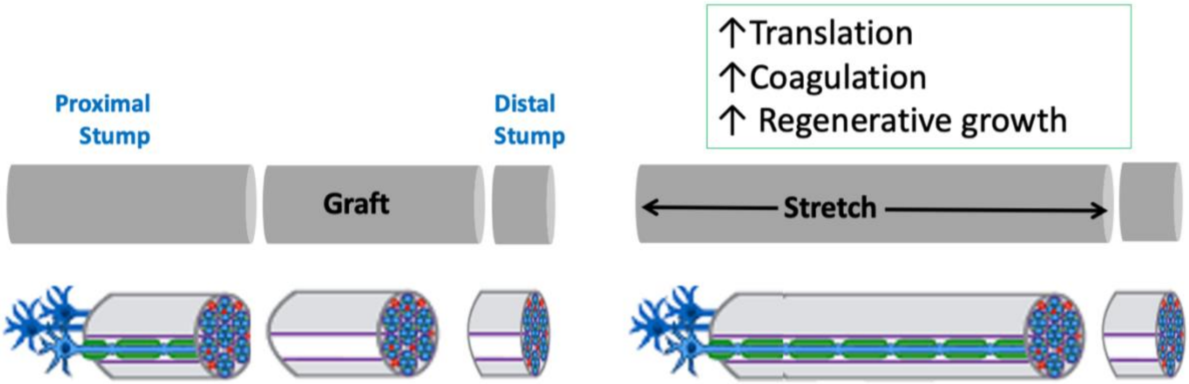

Figure 7: Cartoon of two intervention strategies, implanted graft and lengthened proximal stump. Key shows processes upregulated in stretch (lengthened) conditions.

Our data support a model in which wound healing must resolve before protein synthetic pathways required to supply a regenerating nerve are increased. We did see upregulation in degradation, coagulation cascades, transcription and protein synthesis and axonal regrowth related pathways in the lengthening condition. Although we show simultaneous processes, and are only sampling one time point, we do present literature evidence for late state coagulation and a link with start of protein synthesis and beginning wave of regenerative processes.

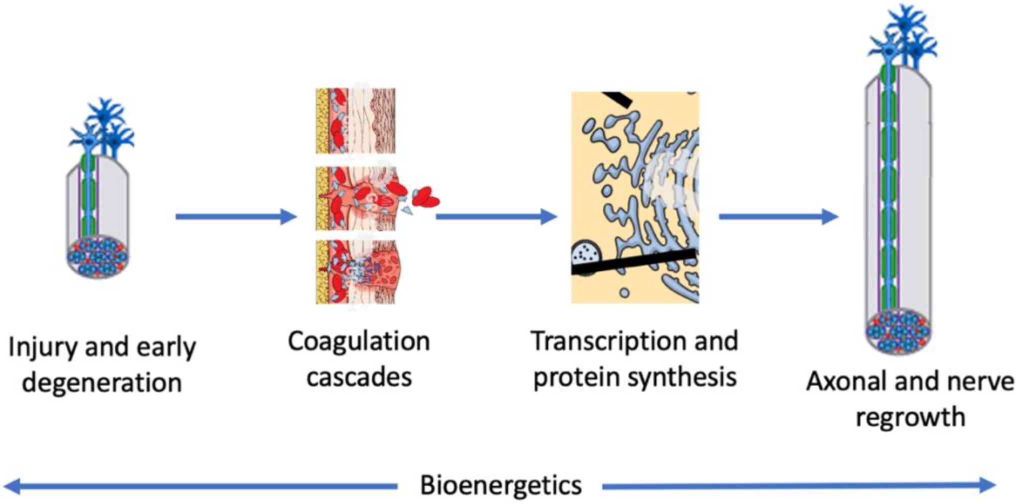

Figure 8: Workflow diagram demonstrates the progression of processes involved in nerve injury and repair.

3.4 Limitations

The p-value cutoff for statistical significance for the DAVID Functional Chart terms that was used (10^{-4}) is stricter than the classically accepted p-value cutoff (0.05). The Benjamini-Hochberg adjusted p-value controls the false discovery rate.

Graft versus control nerves were not formally compared as we did for the previous two comparisons. Based on our numerical findings and examination of this comparison (data not shown) it is apparent that similar pathways are upregulated in control versus graft as we saw in control versus lengthening based on the similarities in repair strategies.

Samples were taken at one time point so our protein expression profile is not a temporal analysis of the nerve injury environment. The tissue sample was extracted on Day 5 after the stretch was performed. Between the time of stretch and freezing, there was approximately half an hour. Though this is not significant enough time to affect translation, some of these processes can depend on the relative timing of stretch in the day. Processes like post-translational modifications could have been affected. In order to account for this stretch-activated response, we will compare our findings to literature on proteomics of normal nerve regeneration processes.

4. CONCLUSION

In this study, we demonstrated the proteomic expression profiles at a single time point in the peripheral nerve injury model of the rat sciatic limb. We also presented new evidence to support an interaction between coagulation and protein synthesis. We also demonstrate data to support to theory that upregulated translational pathways are paired with stretch. These insights are novel and advance our understanding of nerve injury pathways. However, a key limitation to our study is that the samples were solely derived from the proximal stump at an early time point, which only addresses one phrase of the nerve degeneration and regeneration process.

Overall, we established a method to analyze nerve injury and regeneration related samples. We anticipate making comparisons between early and later stage injury expression to offer additional insight in the temporal changes throughout the nerve injury and repair processes. Another comparison includes the distal versus proximal nerve injury location to identify spatially relevant expression changes. We also plan to validate our findings by making comparisons to literature on typical neuronal growth protein expression levels.

Future aims for this project would be to capture a more inclusive dataset to track these spatial and temporal changes in the peripheral nerve, and apply these findings toward nerve injury repair strategies. Experimental aims also include manipulating key pathways in structural stability and intracellular transport. Confirming the expression of these primary structural components, including collagen, neurofilaments, actin, and microtubules, will provide evidence for structural manipulation during growth processes. This will also provide context for the cytoskeletal proteins that are downregulated in the lengthened samples. Validation of specific proteins can be performed via Western blot and Immunohistochemistry.

This thesis, in part is currently being prepared for submission for publication of the material. Chhugani, Neha; Azar, Carmelina; Patel, Nevil; Howarth, Holly; Ghassemian, Majid; Shah, Sameer. “Proteomics Analysis of the Regenerating Proximal Nerve After Injury and Repair: Autograft versus Nerve Lengthening.” The thesis author was the primary investigator and author of this material.

APPENDIX

Table S1: DAVID-generated Functional Chart terms for Control versus Lengthening condition with corresponding p-values and Benjamini-Hochberg adjusted p-values

Functional Chart Term	P-Value	Benjamini
extracellular exosome	5.90E-194	3.60E-191
Acetylation	2.10E-164	7.20E-162
Phosphoprotein	1.70E-84	3.00E-82
poly(A) RNA binding	4.80E-75	4.40E-72
Cytoplasm	3.10E-60	3.60E-58
focal adhesion	1.00E-48	3.00E-46
membrane	6.30E-48	1.30E-45
blood microparticle	5.00E-47	7.60E-45
cytoplasm	2.10E-44	2.50E-42
Isopeptide bond	1.10E-39	9.60E-38
extracellular space	1.70E-35	1.70E-33
Ribonucleoprotein	1.80E-34	1.20E-32
extracellular matrix	2.20E-33	1.90E-31
Ubl conjugation	1.40E-32	7.90E-31
myelin sheath	2.90E-32	2.20E-30
intracellular ribonucleoprotein complex	4.50E-29	3.00E-27
Actin-binding	6.80E-27	3.40E-25
Methylation	2.20E-26	9.70E-25
Ribosomal protein	2.60E-25	9.90E-24
cytosol	1.30E-21	8.10E-20
Secreted	7.80E-21	2.70E-19
Complement and coagulation cascades	1.50E-20	3.80E-18
Chaperone	5.60E-20	1.80E-18
Ribosome	5.70E-20	7.10E-18
actin filament binding	7.70E-20	3.60E-17
cadherin binding involved in cell-cell adhesion	1.20E-18	3.80E-16
translation	3.60E-18	1.00E-14
protein binding	6.30E-18	1.50E-15
cell-cell adherens junction	7.40E-18	4.10E-16
melanosome	1.60E-17	8.10E-16
Muscle protein	2.20E-17	6.40E-16
nucleus	2.50E-17	1.20E-15
Proteasome	2.60E-17	6.90E-16
endoplasmic reticulum lumen	3.70E-17	1.60E-15
RNA-binding	6.50E-17	1.60E-15
cell-cell adhesion	2.30E-16	3.40E-13
proteasome complex	6.00E-16	2.40E-14
Protein biosynthesis	1.00E-15	2.30E-14
ribosome	1.80E-15	6.60E-14
protein folding	2.60E-15	2.50E-12
structural constituent of ribosome	8.00E-15	1.50E-12
Nucleotide-binding	1.30E-14	2.90E-13
negative regulation of endopeptidase activity	2.40E-14	1.70E-11
Proteasome	6.30E-14	5.20E-12
endoplasmic reticulum	3.40E-13	1.20E-11
Hemostasis	2.90E-12	5.60E-11
Blood coagulation	2.90E-12	5.60E-11
Isomerase	4.00E-12	7.30E-11
mRNA binding	4.20E-12	6.50E-10
cytosolic large ribosomal subunit	4.40E-12	1.50E-10
cytosolic small ribosomal subunit	9.50E-12	3.00E-10
ATP-binding	1.10E-11	1.90E-10
Biosynthesis of antibiotics	1.80E-11	1.00E-09
hydrogen peroxide catabolic process	2.10E-11	1.20E-08
Carbon metabolism	2.10E-11	1.00E-09
short sequence motif:Prevents secretion from ER	4.30E-11	6.50E-08
Redox-active center	4.80E-11	8.00E-10
Complement pathway	5.50E-11	8.70E-10
RNA recognition motif domain	6.40E-11	9.00E-08
unfolded protein binding	1.00E-10	1.40E-08
small ribosomal subunit	1.00E-10	3.10E-09

Table S1: DAVID-generated Functional Chart terms for Control versus Lengthening condition with corresponding p-values and Benjamini-Hochberg adjusted p-values (continued)

Functional Chart Term	P-Value	Benjamini
Nucleotide-binding, alpha-beta plait	1.20E-10	9.00E-08
complement activation, classical pathway	1.60E-10	7.60E-08
serine-type endopeptidase inhibitor activity	2.30E-10	2.70E-08
acute-phase response	2.40E-10	9.90E-08
mitochondrion	2.40E-10	6.90E-09
Cytoskeleton	3.50E-10	5.20E-09
Serpin family	3.60E-10	1.90E-07
Protein processing in endoplasmic reticulum	3.70E-10	1.50E-08
RRM	3.70E-10	1.00E-07
nucleoplasm	3.80E-10	1.00E-08
Serpin domain	5.00E-10	1.90E-07
perinuclear region of cytoplasm	5.80E-10	1.50E-08
cell redox homeostasis	1.00E-09	3.60E-07
protein complex binding	1.40E-09	1.50E-07
Threonine protease	1.40E-09	2.10E-08
muscle contraction	1.50E-09	4.80E-07
fibrinolysis	1.90E-09	5.50E-07
Thioredoxin-like fold	2.00E-09	4.90E-07
Thioredoxin domain	2.20E-09	4.90E-07
Protease inhibitor I4, serpin, conserved site	2.20E-09	4.90E-07
Prion diseases	2.40E-09	8.70E-08
Z disc	2.50E-09	6.30E-08
Serine protease inhibitor	2.90E-09	4.00E-08
SERPIN	3.40E-09	4.70E-07
proteasome core complex	3.40E-09	8.10E-08
cellular oxidant detoxification	3.50E-09	9.30E-07
endoplasmic reticulum chaperone complex	3.70E-09	8.50E-08
Proteasome, subunit alpha/beta	4.70E-09	9.10E-07
actin filament	5.50E-09	1.20E-07

Functional Chart Term	P-Value	Benjamini
liver regeneration	6.50E-09	1.50E-06
protein stabilization	6.80E-09	1.50E-06
nucleotide binding	6.90E-09	6.40E-07
aging	9.10E-09	1.90E-06
Antioxidant	1.00E-08	1.40E-07
smooth endoplasmic reticulum	1.00E-08	2.20E-07
Protease	1.30E-08	1.70E-07
Endoplasmic reticulum	1.40E-08	1.70E-07
cortical cytoskeleton	1.60E-08	3.30E-07
Protease inhibitor	1.70E-08	2.00E-07
Initiation factor	1.80E-08	2.00E-07
nucleolus	2.00E-08	4.00E-07
enzyme binding	2.20E-08	1.80E-06
RNA binding	3.30E-08	2.60E-06
Hydrolase	3.60E-08	4.00E-07
threonine-type endopeptidase activity	3.80E-08	2.70E-06
Acute phase	4.10E-08	4.50E-07
identical protein binding	4.50E-08	3.00E-06
mRNA splicing	4.90E-08	5.10E-07
Nucleus	5.40E-08	5.50E-07
response to endoplasmic reticulum stress	5.70E-08	1.10E-05
RNA splicing	6.00E-08	1.10E-05
Peroxidase	8.00E-08	7.90E-07
peroxidase activity	8.20E-08	5.10E-06
protein complex	1.50E-07	2.80E-06
proteasome accessory complex	1.50E-07	2.80E-06
positive regulation of protein localization to Cajal body	1.60E-07	2.50E-05
proteolysis involved in cellular protein catabolic process	1.60E-07	2.50E-05
Oxidoreductase	1.60E-07	1.50E-06
response to hydrogen peroxide	1.60E-07	2.50E-05
Innate immunity	1.70E-07	1.60E-06

Table S1: DAVID-generated Functional Chart terms for Control versus Lengthening condition with corresponding p-values and Benjamini-Hochberg adjusted p-values (continued)

Functional Chart Term	P-Value	Benjamini
glutathione metabolic process	2.00E-07	3.00E-05
translation initiation factor activity	2.10E-07	1.30E-05
Transport	2.30E-07	2.10E-06
Signal	2.70E-07	2.40E-06
actin binding	3.30E-07	1.80E-05
chaperonin-containing T-complex	3.80E-07	7.00E-06
Glycolysis	4.60E-07	4.00E-06
GroEL-like apical domain	4.70E-07	7.30E-05
GroEL-like equatorial domain	4.70E-07	7.30E-05
mRNA processing	5.50E-07	4.70E-06
zona pellucida receptor complex	5.60E-07	9.80E-06
Actinin-type, actin-binding, conserved site	5.80E-07	8.10E-05
blood coagulation	6.20E-07	8.60E-05
Calcium	6.50E-07	5.30E-06
S-nitrosylation	6.90E-07	5.60E-06
osteoblast differentiation	7.30E-07	9.60E-05
stress fiber	7.60E-07	1.30E-05
Chaperone tailless complex polypeptide 1 (TCP-1)	8.00E-07	8.80E-05
Chaperonin TCP-1, conserved site	8.00E-07	8.80E-05
TCP-1-like chaperonin intermediate domain	8.00E-07	8.80E-05
platelet aggregation	8.30E-07	1.00E-04
Chaperonin Cpn60/TCP-1	8.50E-07	8.80E-05
Immunity	1.10E-06	8.60E-06
response to oxidative stress	1.10E-06	1.40E-04
Glycoprotein	1.20E-06	8.90E-06
positive regulation of telomerase RNA localization to Cajal body	1.20E-06	1.40E-04
complement activation	1.20E-06	1.40E-04
intracellular membrane-bounded organelle	1.30E-06	2.10E-05
rRNA processing	1.30E-06	1.40E-04
Thioredoxin, conserved site	1.50E-06	1.40E-04
Mitochondrion	1.50E-06	1.10E-05
translational initiation	1.50E-06	1.60E-04
catalytic step 2 spliceosome	1.70E-06	2.80E-05
protein homodimerization activity	2.10E-06	1.10E-04
mRNA processing	2.30E-06	2.30E-04
cell body	2.30E-06	3.60E-05
fibrinogen complex	2.40E-06	3.60E-05
A band	2.40E-06	3.60E-05
Elongation factor	2.50E-06	1.80E-05
chaperone-mediated protein folding	3.00E-06	2.90E-04
spliceosomal complex	3.50E-06	5.20E-05
repeat:1-1	3.60E-06	2.70E-03
proteasome regulatory particle, base subcomplex	3.80E-06	5.30E-05
COPI vesicle coat	3.80E-06	5.30E-05
glycolytic process	4.10E-06	3.80E-04
Systemic lupus erythematosus	4.30E-06	1.30E-04
formation of translation preinitiation complex	4.40E-06	3.90E-04
substantia nigra development	4.50E-06	3.90E-04
peripheral nervous system axon regeneration	4.50E-06	3.90E-04
ER-Golgi transport	4.80E-06	3.40E-05
Protein transport	4.90E-06	3.40E-05
cytoplasmic ribonucleoprotein granule	5.00E-06	6.80E-05
polysome	5.10E-06	6.80E-05
toxin transport	5.30E-06	4.40E-04

Table S1: DAVID-generated Functional Chart terms for Control versus Lengthening condition with corresponding p-values and Benjamini-Hochberg adjusted p-values (continued)

Functional Chart Term	P-Value	Benjamini
Spliceosome	5.80E-06	4.00E-05
Biosynthesis of amino acids	6.00E-06	1.70E-04
repeat:1-2	7.30E-06	3.70E-03
glycoprotein binding	8.00E-06	3.90E-04
response to ethanol	9.50E-06	7.60E-04

Table S2: DAVID-generated Functional Chart terms for Control versus Lengthening experimental condition sorted into clusters

Cluster/Process	Functional Chart Terms
Ribosome/ Translation	ribosome
	structural constituent of ribosome
	Ribosomal protein
	Ribonucleoprotein
	Ribosome
	intracellular ribonucleoprotein complex
	cytosolic large ribosomal subunit
	cytosolic small ribosomal subunit
	small ribosomal subunit
	positive regulation of protein localization to Cajal body
	translation initiation factor activity
	translational initiation
	formation of translation preinitiation complex
	translation
	cytoplasmic ribonucleoprotein granule
Protein Synthesis/ Transport	Protein biosynthesis
	Biosynthesis of antibiotics
	protein complex binding
	protein stabilization
	protein complex
	enzyme binding
	ER-Golgi transport
	Protein transport
	Biosynthesis of amino acids
	Glycoprotein
	protein homodimerization activity
	Elongation factor
	COPI vesicle coat
	polysome
	glycoprotein binding

Cluster/Process	Functional Chart Terms
Protein Degradation/ Clearance	Proteasome
	Ubl conjugation
	proteasome core complex
	Proteasome, subunit alpha/beta
	Proteasome
	Chaperone
	proteasome complex
	Threonine protease
	cellular oxidant detoxification
	Protease
	Protease inhibitor
	proteasome accessory complex
	Innate immunity
	identical protein binding
	proteolysis involved in cellular protein catabolic process
	proteasome regulatory particle, base subcomplex
	Systemic lupus erythematosus
Extracellular Matrix	extracellular matrix
	focal adhesion
	extracellular space
	extracellular exosome
Coagulation	Blood coagulation
	Complement and coagulation cascades
	Hemostasis
	blood microparticle
	Complement pathway
	complement activation, classical pathway
	acute-phase response
	fibrinolysis
	Acute phase
	complement activation

Table S2: DAVID-generated Functional Chart terms for Control versus Lengthening experimental condition sorted into clusters (continued)

Cluster/Process	Functional Chart Terms
Coagulation (cont.)	blood coagulation
	platelet aggregation
	Immunity
	fibrinogen complex
Endoplasmic Reticulum	endoplasmic reticulum lumen
	Protein processing in endoplasmic reticulum
	endoplasmic reticulum
	Secretion
	protein folding
	short sequence motif:Prevents secretion from ER
	unfolded protein binding
	endoplasmic reticulum chaperone complex
	smooth endoplasmic reticulum
	Endoplasmic reticulum
	Prion diseases
	response to endoplasmic reticulum stress
	Transport
Nerve Structure/ Muscle Contraction	myelin sheath
	Actin-binding
	actin filament binding
	Muscle protein
	Cytoskeleton
	muscle contraction
	actin filament
	Z disc
	cortical cytoskeleton
	actin binding
	stress fiber
	Actinin-type, actin-binding, conserved site
	Calcium
	cell body

Cluster/Process	Functional Chart Terms
Nerve Structure/ Muscle Contraction (cont.)	A band
Post Translational Modifications	Acetylation
	Phosphoprotein
	Isopeptide bond
	Methylation
	Redox-active center
	Hydrolase
	S-nitrosylation
Nucleic Acid Processing	poly(A) RNA binding
	nucleus
	RNA-binding
	Nucleotide-binding
	mRNA binding
	RNA recognition motif domain
	Nucleotide-binding, alpha-beta plait
	RRM
	nucleotide binding
	RNA binding
	RNA splicing
	mRNA splicing
	Initiation factor
	mRNA processing
	positive regulation of telomerase RNA localization to Cajal body
	rRNA processing
	catalytic step 2 spliceosome
	mRNA processing
	spliceosomal complex
	Spliceosome
Cell Structure	Cytoplasm
	membrane
	cytosol

Table S2: DAVID-generated Functional Chart terms for Control versus Lengthening experimental condition sorted into clusters (continued)

Cluster/Process	Functional Chart Terms
Cell Structure (cont.)	melanosome
	mitochondrion
	nucleoplasm
	perinuclear region of cytoplasm
	nucleolus
	Nucleus
	Mitochondrion
	intracellular membrane-bounded organelle
Cell-Cell Interaction	cadherin binding involved in cell-cell adhesion
	cell-cell adherens junction
	cell-cell adhesion
Endopeptidase/Serpin	negative regulation of endopeptidase activity
	Serpin family
	serine-type endopeptidase inhibitor activity
	Serpin domain
	Serine protease inhibitor
	SERPIN
	Protease inhibitor I4, serpin, conserved site
	threonine-type endopeptidase activity
Regulatory/Energy	ATP-binding
	liver regeneration
	aging
	Signal
	GroEL-like equatorial domain
	GroEL-like apical domain

Cluster/Process	Functional Chart Terms
Regulatory/ Energy (cont.)	zona pellucida receptor complex
Processes	Glycolysis
	Carbon metabolism
	glutathione metabolic process
	glycolytic process
Oxidize	Antioxidant
	Peroxidase
	peroxidase activity
	response to hydrogen peroxide
	hydrogen peroxide catabolic process
	Oxidoreductase
Stress	Chaperonin TCP-1, conserved site
	TCP-1-like chaperonin intermediate domain
	Chaperone tailless complex polypeptide 1 (TCP-1)
	chaperonin-containing T-complex
	Chaperonin Cpn60/TCP-1
	response to oxidative stress
	chaperone-mediated protein folding
	toxin transport
	response to ethanol
Growth	osteoblast differentiation
	peripheral nervous system axon regeneration
	substantia nigra development

Table S3: Control versus Lengthening genes sorted into designated cluster

Cluster	Accession ID	Gene Name
Cytoskeleton/Motility	Q5M7U6	ARP2 actin related protein 2 homolog(Actr2)
	Q4V7C7	ARP3 actin related protein 3 homolog(Actr3)
	Q99MZ8	LIM and SH3 protein 1(Lasp1)
	Q5RKI0	WD repeat domain 1(Wdr1)
	A0A0G2K9A2	actin related protein 2/3 complex, subunit 2(Arpc2)
	B2GV73	actin related protein 2/3 complex, subunit 3(Arpc3)
	Q4KLF8	actin related protein 2/3 complex, subunit 5(Arpc5)
	D3ZCV0	actinin alpha 2(Actn2)
	Q8R4I6	actinin alpha 3(Actn3)
	Q9QXQ0	actinin alpha 4(Actn4)
	Q9Z1P2	actinin, alpha 1(Actn1)
	Q05764	adducin 2(Add2)
	Q08163	adenylate cyclase associated protein 1(Cap1)
	A0A0G2JTV2	caldesmon 1(Cald1)
	B2GUZ5	capping actin protein of muscle Z-line alpha subunit 1(Capza1)
	Q5XI32	capping actin protein of muscle Z-line beta subunit(Capzb)
	Q6AYC4	capping actin protein, gelsolin like(Capg)
	B0BNA5	coactosin-like F-actin binding protein 1(Cotl1)
	P45592	cofilin 1(Cfl1)
	M0RC65	cofilin 2(Cfl2)
	Q91ZN1	coronin 1A(Coro1a)
	G3V940	coronin 1B(Coro1b)
	O35828	coronin 7(Coro7)
	Q7M0E3	destrin, actin depolymerizing factor(Dstn)
	C0JPT7	filamin A(Flna)
	A0A0H2UHR7	filamin C(Flnc)
	Q68FY4	group specific component(Gc)
	Q5XI38	lymphocyte cytosolic protein 1(Lcp1)
	A0A0G2K9E8	myosin IE(Myo1e)
	A0A0G2JUE5	myosin binding protein C, slow type(Mybpc1)
	A0A0G2K484	myosin heavy chain 1(Myh1)
	G3V6E1	myosin heavy chain 2(Myh2)
	G3V6D8	myosin heavy chain 3(Myh3)
	G3V8B0	myosin heavy chain 7(Myh7)
	G3V6P7	myosin, heavy chain 9, non-muscle-like 1(Myh9l1)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Cytoskeleton/ Motility (cont.)	F1LMW7	myristoylated alanine rich protein kinase C substrate(Marcks)
	Q63598	plastin 3(Pls3)
	P62963	profilin 1(Pfn1)
	A0A140UHX6	spectrin, beta, erythrocytic(Sptb)
	P62329	thymosin beta 4, X-linked(Tmsb4x)
	F1LR10	LIM domain and actin binding 1(Lima1)
	Q07936	annexin A2(Anxa2)
	O08839	bridging integrator 1(Bin1)
	G3V852	talin 1(Tln1)
	P31232	transgelin(Tagln)
	A0A0G2K7F7	tropomyosin 1, alpha(Tpm1)
	P58775	tropomyosin 2, beta(Tpm2)
	Q63610, A0A140TAF0	tropomyosin 3(Tpm3)
	P09495	tropomyosin 4(Tpm4)
	Q304F3	troponin C2, fast skeletal type(Tnnc2)
	F1M265	palladin, cytoskeletal associated protein(Palld)
	A0A0G2JZ11	myozenin 1(Myoz1)
	D3Z9Z0	ankyrin 1(Ank1)
	Q6P725	desmin(Des)
	P68136	actin, alpha 1, skeletal muscle(Acta1)
	P19633	calsequestrin 1(Casq1)
	Q9QZ76	myoglobin(Mb)
	P08733	myosin light chain 2(Myl2)
	P16409	myosin light chain 3(Myl3)
	P04466	myosin light chain, phosphorylatable, fast skeletal muscle(Mylpf)
	P02600	myosin, light chain 1(Myl1)
	P27768	troponin I2, fast skeletal type(Tnni2)
	Q7TNB2	troponin T1, slow skeletal type(Tnnt1)
	P60711	actin, beta(Actb)
	A0A1W2Q6E9	moesin(Msn)
	A0A0G2JUL7	septin 11(Sept11)
	A0A0G2JZT5	septin 7(Sept7)
	Q4QQV0	tubulin, beta 6 class V(Tubb6)
	Q5RJR2	twinfilin actin-binding protein 1(Twf1)
	P62329	thymosin beta 4, X-linked(Tmsb4x)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Cytoskeleton/ Motility (cont.)	P28480	t-complex 1(Tcp1)
	A0A1W2Q6E9	moesin(Msn)
	Q6P502	chaperonin containing TCP1 subunit 3(Cct3)
	Q7TPB1	chaperonin containing TCP1 subunit 4(Cct4)
	Q68FQ0	chaperonin containing TCP1 subunit 5(Cct5)
	Q3MHS9	chaperonin containing TCP1 subunit 6A(Cct6a)
	D4AC23	chaperonin containing TCP1 subunit 7(Cct7)
	D4ACB8	chaperonin containing TCP1 subunit 8(Cct8)
	P47819	glial fibrillary acidic protein(Gfap)
Peripheral Nervous System/ Myelin/ Proliferation Regulator	Q8R4I6	actinin alpha 3(Actn3)
	P04762	catalase(Cat)
	Q6IMY8	heterogeneous nuclear ribonucleoprotein U(Hnrnpu)
	P67779	prohibitin(Phb)
	A0A0G2K1L0	tenascin C(Tnc)
	P62329	thymosin beta 4, X-linked(Tmsb4x)
	P09495	tropomyosin 4(Tpm4)
	P60711	actin, beta(Actb)
	Q5RKI0	WD repeat domain 1(Wdr1)
	P31000	vimentin(Vim)
	P47819	glial fibrillary acidic protein(Gfap)
	Q63716	peroxiredoxin 1(Prdx1)
	Q9Z0V6	peroxiredoxin 3(Prdx3)
	Q9JK11	reticulon 4(Rtn4)
	P68136	actin, alpha 1, skeletal muscle(Acta1)
Bioenergetics and Metabolism	G3V8D5	6-phosphogluconolactonase(Pgls)
	P05065	aldolase, fructose-bisphosphate A(Aldoa)
	P04762	catalase(Cat)
	G3V936	citrate synthase(Cs)
	G3V6P2	dihydrolipoamide S-succinyltransferase(Dlst)
	Q6P6R2	dihydrolipoamide dehydrogenase(Dld)
	P15429	enolase 3(Eno3)
	B0BNE5	esterase D(Esd)
	Q5M964	fumarate hydratase(Fh)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Bioenergetics and Metabolism (cont.)	P05370	glucose-6-phosphate dehydrogenase(G6pd)
	Q6P6V0	glucose-6-phosphate isomerase(Gpi)
	P10860	glutamate dehydrogenase 1(Glud1)
	P00507	glutamic-oxaloacetic transaminase 2(Got2)
	P04797	glyceraldehyde-3-phosphate dehydrogenase(Gapdh)
	Q64428	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit(Hadha)
	P56574	isocitrate dehydrogenase (NADP(+)) 2, mitochondrial(Idh2)
	P04636	malate dehydrogenase 2(Mdh2)
	D3ZJH9	malic enzyme 2(Me2)
	P30835	phosphofructokinase, liver type(Pfkl)
	P85968	phosphogluconate dehydrogenase(Pgd)
	P16617	phosphoglycerate kinase 1(Pgk1)
	P25113	phosphoglycerate mutase 1(Pgam1)
	P16290	phosphoglycerate mutase 2(Pgam2)
	A0A0G2JVG3, P11980	pyruvate kinase, muscle(Pkm)
	D4A7L6	ribose 5-phosphate isomerase A(Rpia)
	Q5U3Z7	serine hydroxymethyltransferase 2(Shmt2)
	P21913	succinate dehydrogenase complex iron sulfur subunit B(Sdhb)
	F1LM47	succinate-CoA ligase ADP-forming beta subunit(Sucla2)
	F1LPV8	succinate-CoA ligase, GDP-forming, beta subunit(Suclg2)
	Q9EQS0	transaldolase 1(Taldo1)
	P48500	triosephosphate isomerase 1(Tpi1)
	Q6P6G4	bisphosphoglycerate mutase(Bpgm)
	P97608	5-oxoprolinase (ATP-hydrolysing)(Oplah)
	B0BNJ4	ETHE1, persulfide dioxygenase(Ethe1)
	Q6MG61	chloride intracellular channel 1(Clic1)
	G3V8C4	chloride intracellular channel 4(Clic4)
	Q68FR6	eukaryotic translation elongation factor 1 gamma(Eef1g)
	A0A096MJ04	glutathione S-transferase omega 1(Gsto1)
	M0RAM5	glutathione peroxidase 1(Gpx1)
	A0A0G2K531	glutathione peroxidase 3(Gpx3)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Bioenergetics and Metabolism (cont.)	Q6P7Q4	glyoxalase 1(Glo1)
	P02091	hemoglobin subunit beta(Hbb)
	P07632	superoxide dismutase 1, soluble(Sod1)
	P07895	superoxide dismutase 2, mitochondrial(Sod2)
	O89049	thioredoxin reductase 1(Txnrd1)
	A0JN30	canopy FGF signaling regulator 2(Cnpy2)
	G3V734	2,4-dienoyl CoA reductase 1, mitochondrial(Decr1)
	P15999	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle(Atp5a1)
	G3V6D3	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide(Atp5b)
	P19511	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1(Atp5f1)
	P29419	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit E(Atp5i)
	B0K020	CDGSH iron sulfur domain 1(Cisd1)
	P63036	DnaJ heat shock protein family (Hsp40) member A1(Dnaja1)
	Q66HF1	NADH dehydrogenase (ubiquinone) Fe-S protein 1(Ndufs1)
	Q5XIF3	NADH:ubiquinone oxidoreductase subunit S4(Ndufs4)
	G3V644	TNF receptor-associated protein 1(Trap1)
	G3V644	Tu translation elongation factor, mitochondrial(Tufm)
	P85834	acyl-CoA binding domain containing 3(Acbd3)
	A0A0G2K756	acyl-CoA dehydrogenase, very long chain(Acadvl)
	Q64057	aldehyde dehydrogenase 7 family, member A1(Aldh7a1)
	P43138	apurinic/apyrimidinic endodeoxyribonuclease 1(Apex1)
	P19633	calsequestrin 1(Casq1)
	P05371	clusterin(Clu)
	O35796	complement C1q binding protein(C1qbp)
	P12075	cytochrome c oxidase subunit 5B(Cox5b)
	G3V6P2	cytochrome c, somatic(Cycs)
	P62898	dihydrolipoamide S-succinyltransferase(Dlst)
	G3V6P2	dihydrolipoamide dehydrogenase(Dld)
	Q6P6R2	electron transfer flavoprotein alpha subunit(Etfa)
	P13803	electron transfer flavoprotein beta subunit(Etfb)
	P09606	glutamate-ammonia ligase(Glul)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Bioenergetics and Metabolism (cont.)	B0BMW2	hydroxysteroid (17-beta) dehydrogenase 10(Hsd17b10)
	P04182	ornithine aminotransferase(Oat)
	Q9Z0V6	peroxiredoxin 3(Prdx3)
	A0A0G2JSS8	peroxiredoxin 5(Prdx5)
	A0A0G2KB63	prohibitin 2(Phb2)
	P67779	prohibitin(Phb)
	P62909	ribosomal protein S3(Rps3)
	Q6P9Y4	solute carrier family 25 member 4(Slc25a4)
	Q09073	solute carrier family 25 member 5(Slc25a5)
	F1LQ55	sterol carrier protein 2(Scp2)
	Q68FY0	ubiquinol-cytochrome c reductase core protein I(Uqcrc1)
	Q5U300	ubiquitin-like modifier activating enzyme 1(Uba1)
	Q3MIE4	vesicle amine transport 1(Vat1)
	P81155	voltage-dependent anion channel 2(Vdac2)
	Q9R1Z0	voltage-dependent anion channel 3(Vdac3)
	G3V644	NADH:ubiquinone oxidoreductase subunit V3(Ndufv3)
	Q5XHZ0	TNF receptor-associated protein 1(Trap1)
	P85834	Tu translation elongation factor, mitochondrial(Tufm)
	A0A0G2K756	acyl-CoA binding domain containing 3(Acbd3)
	Q5M9H2	acyl-CoA dehydrogenase, very long chain(Acadvl)
	P62898	cytochrome c, somatic(Cycs)
	P13803	electron transfer flavoprotein alpha subunit(Etfa)
	Q68FU3	electron transfer flavoprotein beta subunit(Etfb)
	P63039	heat shock protein family D member 1(Hspd1)
	P26772	heat shock protein family E member 1(Hspe1)
	O35567	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase(Atic)
	D3ZD23	ATP binding cassette subfamily E member 1(Abce1)
	D4A746	GDP-mannose pyrophosphorylase B(Gmppb)
	Q6IN37	GM2 ganglioside activator(Gm2a)
	D3ZG43	NADH dehydrogenase (ubiquinone) Fe-S protein 3(Ndufs3)
	B2RZD6	NADH:ubiquinone oxidoreductase subunit A4(Ndufa4)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Bioenergetics and Metabolism (cont.)	Q05982	NME/NM23 nucleoside diphosphate kinase 1(Nme1)
	P19804	NME/NM23 nucleoside diphosphate kinase 2(Nme2)
	P50475	alanyl-tRNA synthetase(Aars)
	D3ZTP0	aldehyde dehydrogenase 1 family, member L2(Aldh1l2)
	P01015	angiotensinogen(Agt)
	F1LPV0	asparaginyl-tRNA synthetase(Nars)
	Q6AYS3	cathepsin A(Ctsa)
	Q6IN22	cathepsin B(Ctsb)
	P24268	cathepsin D(Ctsd)
	D4AC23	chaperonin containing TCP1 subunit 7(Cct7)
	P23928	crystallin, alpha B(Cryab)
	Q3B8P4	decapping enzyme, scavenger(Dcps)
	P07483	fatty acid binding protein 3(Fabp3)
	Q66HI5	ferritin heavy chain 1(Fth1)
	P34058	heat shock protein 90 alpha family class B member 1(Hsp90ab1)
	P06761	heat shock protein family A member 5(Hspa5)
	B4F7C7	heme binding protein 1(Hebp1)
	P61980	heterogeneous nuclear ribonucleoprotein K(Hnrnpk)
	P97852	hydroxysteroid (17-beta) dehydrogenase 4(Hsd17b4)
	P04642	lactate dehydrogenase A(Ldha)
	Q68FS4	leucine aminopeptidase 3(Lap3)
	P33436	matrix metallopeptidase 2(Mmp2)
	A0A0G2JT30	methionine adenosyltransferase 2B(Mat2b)
	P63086	mitogen activated protein kinase 1(Mapk1)
	Q01986	mitogen activated protein kinase kinase 1(Map2k1)
	P36506	mitogen activated protein kinase kinase 2(Map2k2)
	A0A0G2K1A2	myeloperoxidase(Mpo)
	Q497B0	nitrilase family, member 2(Nit2)
	F1M265	palladin, cytoskeletal associated protein(Palld)
	Q6DGG0	peptidylprolyl isomerase D(Ppid)
	Q63716	peroxiredoxin 1(Prdx1)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Bioenergetics and Metabolism (cont.)	Q9Z0V5	peroxiredoxin 4(Prdx4)
	O35244	peroxiredoxin 6(Prdx6)
	P54001	prolyl 4-hydroxylase subunit alpha 1(P4ha1)
	P10960	prosaposin(Psap)
	P11598	protein disulfide isomerase family A, member 3(Pdia3)
	P63329	protein phosphatase 3 catalytic subunit alpha(Ppp3ca)
	P63245	receptor for activated C kinase 1(Rack1)
	P62907	ribosomal protein L10A(Rpl10a)
	F1LQ14	ribosomal protein L34(Rpl34)
	P13471	ribosomal protein S14(Rps14)
	P16975	secreted protein acidic and cysteine rich(Sparc)
	A0A0G2JZG7	seryl-tRNA synthetase(Sars)
	P52631	signal transducer and activator of transcription 3(Stat3)
	Q66X93	staphylococcal nuclease and tudor domain containing 1(Snd1)
	R4GNK3	thioredoxin 1(Txn1)
	Q642E6	tripeptidyl peptidase 1(Tpp1)
	P62260	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon(Ywhae)
	P63102	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta(Ywhaz)
	Q04462	valyl-tRNA synthetase(Vars)
mRNA Processing/ Transcription	Q641Y8	DEAD-box helicase 1(Ddx1)
	Q3B8Q1	DExD-box helicase 21(Ddx21)
	Q63413	DExD-box helicase 39B(Ddx39b)
	B5DF91	ELAV like RNA binding protein 1(Elavl1)
	Q99PF5	KH-type splicing regulatory protein(Khsrp)
	G3V6P6	RNA binding motif (RNP1, RRM) protein 3(Rbm3)
	Q498U4	SAP domain containing ribonucleoprotein(Sarnp)
	Q66HM7	Sjogren syndrome antigen B(Ssb)
	P62961	Y box binding protein 1(Ybx1)
	P50475	alanyl-tRNA synthetase(Aars)
	P43138	apurinic/apyrimidinic endodeoxyribonuclease 1(Apex1)
	P18395	cold shock domain containing E1, RNA binding(Csde1)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
mRNA Processing/ Transcription (cont.)	Q920D2	dihydrofolate reductase(Dhfr)
	P22509	fibrillarin(Fbl)
	Q6P6G9	heterogeneous nuclear ribonucleoprotein A1(Hnrnpa1)
	F1LNF1	heterogeneous nuclear ribonucleoprotein A2/B1(Hnrnpa2b1)
	Q6URK4	heterogeneous nuclear ribonucleoprotein A3(Hnrnpa3)
	Q9JJ54	heterogeneous nuclear ribonucleoprotein D(Hnrnpd)
	Q794E4	heterogeneous nuclear ribonucleoprotein F(Hnrnpf)
	A0A0G2JTG7	heterogeneous nuclear ribonucleoprotein H1(Hnrnph1)
	Q6AY09	heterogeneous nuclear ribonucleoprotein H2 (H')(Hnrnph2)
	P61980	heterogeneous nuclear ribonucleoprotein K(Hnrnpk)
	F1LQ48	heterogeneous nuclear ribonucleoprotein L(Hnrnpl)
	F2Z3T4	muscleblind-like splicing regulator 2(Mbnl2)
	Q5FVM4	non-POU domain containing, octamer-binding(Nono)
	P13084	nucleophosmin 1(Npm1)
	A0A140TAD1	nudix hydrolase 5(Nudt5)
	Q9EPH8	poly(A) binding protein, cytoplasmic 1(Pabpc1)
	G3V9N0	poly(A) binding protein, cytoplasmic 4(Pabpc4)
	Q6AYD3	proliferation-associated 2G4(Pa2g4)
	Q4V8I6	ribosomal protein L11(Rpl11)
	P23358	ribosomal protein L12(Rpl12)
	P09895	ribosomal protein L5(Rpl5)
	P05426	ribosomal protein L7(Rpl7)
	P62919	ribosomal protein L8(Rpl8)
	P62282	ribosomal protein S11(Rps11)
	A0A0H2UHT6	ribosomal protein S18(Rps18)
	P62909	ribosomal protein S3(Rps3)
	A0A0H2UHX3	ribosomal protein S4, X-linked(Rps4x)
	P29314	ribosomal protein S9(Rps9)
	M0R735	synaptotagmin binding, cytoplasmic RNA interacting protein(Syncrip)
	D3ZYS7	G3BP stress granule assembly factor 1(G3bp1)
	Q6AY21	G3BP stress granule assembly factor 2(G3bp2)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
mRNA Processing/ Transcription (cont.)	B2RYP6	LUC7-like 2 pre-mRNA splicing factor(Luc7l2)
	P18418	calreticulin(Calr)
	D3ZPL1	cleavage and polyadenylation specific factor 6(Cpsf6)
	O35796	complement C1q binding protein(C1qbp)
	P62630	eukaryotic translation elongation factor 1 alpha 1(Eef1a1)
	P82995	heat shock protein 90, alpha (cytosolic), class A member 1(Hsp90aa1)
	D4A3E1	heterogeneous nuclear ribonucleoprotein L-like(Hnrnpll)
	Q5RK10	ribosomal protein L13A(Rpl13a)
	P17078	ribosomal protein L35(Rpl35)
	P62278	ribosomal protein S13(Rps13)
	P49242	ribosomal protein S3a(Rps3a)
	B0BN81	ribosomal protein S5(Rps5)
	P62755	ribosomal protein S6(Rps6)
	D4A9L2	serine and arginine rich splicing factor 1(Srsf1)
	B2RZ74	small nuclear ribonucleoprotein U1 subunit 70(Snrnp70)
	Q4KLZ3	DAZ associated protein 1(Dazap1)
	E9PTI6	RALY heterogeneous nuclear ribonucleoprotein(Raly)
	A0A0G2K850	RNA-binding protein EWS-like(LOC100912481)
	I6L9G6	TAR DNA binding protein(Tardbp)
	F2Z3T9	U2 small nuclear RNA auxiliary factor 2(U2af2)
	Q5RKG9	eukaryotic translation initiation factor 4B(Eif4b)
	Q5PQK2	fused in sarcoma RNA binding protein(Fus)
	Q9QX80	heterogeneous nuclear ribonucleoprotein A/B(Hnrnpab)
	G3V7Z8	poly(A) binding protein, nuclear 1(Pabpn1)
	D4A720	serine and arginine rich splicing factor 7(Srsf7)
	A0A0G2K8K0	splicing factor proline and glutamine rich(Sfpq)
	A0A0G2K719	DEAD-box helicase 3, X-linked(Ddx3x)
	Q71UF4	RB binding protein 7, chromatin remodeling factor(Rbbp7)
	Q68FS8	RNA terminal phosphate cyclase domain 1(Rtcd1)
	P05197	eukaryotic translation elongation factor 2(Eef2)
	Q6AYK8	eukaryotic translation initiation factor 3, subunit D(Eif3d)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
mRNA Processing/ Transcription (cont.)	Q3T1J1	eukaryotic translation initiation factor 5A(Eif5a)
	A0A140TAJ3	far upstream element binding protein 1(Fubp1)
	A0A0A0MY09	heat shock protein 90 beta family member 1(Hsp90b1)
	B2RZC6	interleukin enhancer binding factor 2(Ilf2)
	Q68FT7	phenylalanyl-tRNA synthetase, beta subunit(Farsb)
	Q6AYU5	poly(rC) binding protein 2(Pcbp2)
	B1WC34	protein kinase C substrate 80K-H(Prkcsh)
	P62907	ribosomal protein L10A(Rpl10a)
	P12001	ribosomal protein L18(Rpl18)
	F1LQ14	ribosomal protein L34(Rpl34)
	F1M013	ribosomal protein L7a(Rpl7a)
	P13471	ribosomal protein S14(Rps14)
	P62845	ribosomal protein S15(Rps15)
	P62250	ribosomal protein S16(Rps16)
	A0A0H2UHG7	ribosomal protein S20(Rps20)
	D4AD70	similar to 60S ribosomal protein L38(RGD1561636)
	M0R907	small nuclear ribonucleoprotein D3 polypeptide(Snrpd3)
	D3ZQM0	splicing factor 3a, subunit 1(Sf3a1)
	A0A0G2K9V6	threonyl-tRNA synthetase(Tars)
	A0A0G2JXN6	galectin 3(Lgals3)
	Q5M7V8	thyroid hormone receptor associated protein 3(Thrap3)
	Q3B8P4	decapping enzyme, scavenger(Dcps)
	Q9JMJ4	pre-mRNA processing factor 19(Prpf19)
	Q5XIG8	serine/threonine kinase receptor associated protein(Strap)
	D3ZD97	DEAH-box helicase 15(Dhx15)
	D3ZMS1	splicing factor 3b, subunit 2(Sf3b2)
Coagulation	Q66HH8	annexin A5(Anxa5)
	Q9EQV9	carboxypeptidase B2(Cpb2)
	P18292	coagulation factor II (F2)
	Q63207	coagulation factor X(F10)
	D3ZTE0	coagulation factor XII(F12)
	Q7TQ70	fibrinogen alpha chain(Fga)
	P14480	fibrinogen beta chain(Fgb)
	P02680	fibrinogen gamma chain(Fgg)
	A0A0G2K9Y5	histidine-rich glycoprotein(Hrg)
	P08934	kininogen 2(Kng2)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Coagulation (cont.)	Q01177	plasminogen(Plg)
	Q64268	serpin family D member 1(Serpind1)
	Q6P734	serpin family G member 1(Serping1)
	Q62975	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 10(Serpina10)
	F1M957	von Willebrand factor(Vwf)
	P06238	alpha-2-macroglobulin(A2m)
	P01048	kininogen 1(Kng1)
	A0A0G2JY31	serpin family A member 1(Serpina1)
	Q5M7T5	serpin family C member 1(Serpinc1)
	F7FHF3	serpin family F member 2(Serpinf2)
	A0A0G2K9Y5	histidine-rich glycoprotein(Hrg)
	Q5I0M1	apolipoprotein H(Apoh)
	P02680	hemoglobin subunit beta(Hbb)
	G3V852	talin 1(Tln1)
	F1LST1, A0A096P6L8	fibronectin 1(Fn1)
	D3ZQ25	fibulin 1(Fbln1)
	P20760	Ig gamma chain segment(LOC679045)
	P06238	alpha-2-macroglobulin(A2m)
	P01015	angiotensinogen(Agt)
	P02651	apolipoprotein A4(Apoa4)
	P11517	beta-globin(LOC689064)
	F1LQT4	carboxypeptidase N subunit 2(Cpn2)
	A0A0G2K9I6	ceruloplasmin(Cp)
	O70513	galectin 3 binding protein(Lgals3bp)
	Q68FY4	group specific component(Gc)
	A0A0H2UHM3	haptoglobin(Hp)
	P01946	hemoglobin, alpha 1(Hba1)
	D3ZFH5	inter-alpha-trypsin inhibitor heavy chain 2(Itih2)
	Q5EBC0	inter-alpha-trypsin inhibitor heavy chain family, member 4(Itih4)
	P55159	paraoxonase 1(Pon1)
	P12346	transferrin(Tf)
	Q3KR94	vitronectin(Vtn)
Ribosome/Translation	F1M2E9	60S ribosomal protein L13-like(LOC100361259)
	Q5BJN7	FAU, ubiquitin like and ribosomal protein S30 fusion(Fau)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Ribosome/ Translation (cont.)	P35565	calnexin(Canx)
	P68101	eukaryotic translation initiation factor 2 subunit 1 alpha(Eif2s1)
	Q4V8I6	ribosomal protein L11(Rpl11)
	P23358	ribosomal protein L12(Rpl12)
	Q5RK10	ribosomal protein L13A(Rpl13a)
	F1LSW7	ribosomal protein L14(Rpl14)
	P12001	ribosomal protein L18(Rpl18)
	P62718	ribosomal protein L18A(Rpl18a)
	P62832	ribosomal protein L23(Rpl23)
	P61354	ribosomal protein L27(Rpl27)
	P21531	ribosomal protein L3(Rpl3)
	P62890	ribosomal protein L30(Rpl30)
	F1LQ14	ribosomal protein L34(Rpl34)
	A0A140TAI6	ribosomal protein L36(Rpl36)
	P05426	ribosomal protein L7(Rpl7)
	F1M013	ribosomal protein L7a(Rpl7a)
	A0A0G2JXD0	ribosomal protein L9-like(LOC103692829)
	P62282	ribosomal protein S11(Rps11)
	P62250	ribosomal protein S16(Rps16)
	A0A0H2UHQ8	ribosomal protein S17(Rps17)
	A0A0H2UHT6	ribosomal protein S18(Rps18)
	A0A0H2UHH9	ribosomal protein S24(Rps24)
	P62982	ribosomal protein S27a(Rps27a)
	P62909	ribosomal protein S3(Rps3)
	A0A0H2UHX3	ribosomal protein S4, X-linked(Rps4x)
	P62755	ribosomal protein S6(Rps6)
	P62083	ribosomal protein S7(Rps7)
	P62243	ribosomal protein S8(Rps8)
	F1M853	ribosome binding protein 1(Rrbp1)
	A0A0G2K743	similar to 40S ribosomal protein S26(RGD1562415)
	D4A4D5	similar to 60S acidic ribosomal protein P2(LOC498555)
	A0A0G2K6I0	similar to ribosomal protein S15a(LOC691716)
	Q6PDV7	ribosomal protein L10(Rpl10)
	P62907	ribosomal protein L10A(Rpl10a)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Ribosome/ Translation (cont.)	P61314	ribosomal protein L15(Rpl15)
	F1LZX7	ribosomal protein L17(Rpl17)
	P84100	ribosomal protein L19(Rpl19)
	Q6PDV8	ribosomal protein L22-like(LOC100360057)
	P83732	ribosomal protein L24(Rpl24)
	G3V6I9	ribosomal protein L26(Rpl26)
	P62902	ribosomal protein L31(Rpl31)
	D4A412	ribosomal protein L32-like(LOC688684)
	P17078	ribosomal protein L35(Rpl35)
	Q6P3V9	ribosomal protein L4(Rpl4)
	P09895	ribosomal protein L5(Rpl5)
	P62919	ribosomal protein L8(Rpl8)
	Q6PDW1	ribosomal protein S12(Rps12)
	P62278	ribosomal protein S13(Rps13)
	P13471	ribosomal protein S14(Rps14)
	P62845	ribosomal protein S15(Rps15)
	D4A6G6	ribosomal protein S19-like(LOC100362339)
	A0A0H2UHG7	ribosomal protein S20(Rps20)
	Q71TY3	ribosomal protein S27(Rps27)
	P49242	ribosomal protein S3a(Rps3a)
	B0BN81	ribosomal protein S5(Rps5)
	P29314	ribosomal protein S9(Rps9)
	P38983	ribosomal protein SA(Rpsa)
	P19945	ribosomal protein lateral stalk subunit P0(Rplp0)
	A0A0G2K7W6	similar to 60S ribosomal protein L27a(RGD1562402)
	D4AD70	similar to 60S ribosomal protein L38(RGD1561636)
	Q9QZ86	NOP58 ribonucleoprotein(Nop58)
	P22509	fibrillarin(Fbl)
	Q9QX80	heterogeneous nuclear ribonucleoprotein A/B(Hnrnpab)
	Q6P6G9	heterogeneous nuclear ribonucleoprotein A1(Hnrnpa1)
	F1LNF1	heterogeneous nuclear ribonucleoprotein A2/B1(Hnrnpa2b1)
	Q6URK4	heterogeneous nuclear ribonucleoprotein A3(Hnrnpa3)
	Q9JJ54	heterogeneous nuclear ribonucleoprotein D(Hnrnpd)
	Q794E4	heterogeneous nuclear ribonucleoprotein F(Hnrnpf)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Ribosome/ Translation (cont.)	A0A0G2JTG7	heterogeneous nuclear ribonucleoprotein H1(Hnrnph1)
	Q6AY09	heterogeneous nuclear ribonucleoprotein H2 (H')(Hnrnph2)
	P61980	heterogeneous nuclear ribonucleoprotein K(Hnrnpk)
	F1LQ48	heterogeneous nuclear ribonucleoprotein L(Hnrnpl)
	Q6IMY8	heterogeneous nuclear ribonucleoprotein U(Hnrnpu)
	Q62667	major vault protein(Mvp)
	Q6AYD3	proliferation-associated 2G4(Pa2g4)
	B2RZ74	small nuclear ribonucleoprotein U1 subunit 70(Snrnp70)
	M0R735	synaptotagmin binding, cytoplasmic RNA interacting protein(Syncrip)
	Q641Y8	DEAD-box helicase 1(Ddx1)
	Q6AYI1	DEAD-box helicase 5(Ddx5)
	D3ZYS7	G3BP stress granule assembly factor 1(G3bp1)
	Q6AY21	G3BP stress granule assembly factor 2(G3bp2)
	G3V7Q7	IQ motif containing GTPase activating protein 1(Iqgap1)
	P60123	RuvB-like AAA ATPase 1(Ruvbl1)
	Q66HM7	Sjogren syndrome antigen B(Ssb)
	P62961	Y box binding protein 1(Ybx1)
	D3ZPL1	cleavage and polyadenylation specific factor 6(Cpsf6)
	P05197	eukaryotic translation elongation factor 2(Eef2)
	Q3B8Q2	eukaryotic translation initiation factor 4A3(Eif4a3)
	P04797	glyceraldehyde-3-phosphate dehydrogenase(Gapdh)
	B2RZC6	interleukin enhancer binding factor 2(Ilf2)
	P13084	nucleophosmin 1(Npm1)
	Q9EPH8	poly(A) binding protein, cytoplasmic 1(Pabpc1)
	G3V9N0	poly(A) binding protein, cytoplasmic 4(Pabpc4)
	G3V7Z8	poly(A) binding protein, nuclear 1(Pabpn1)
	A0A0G2K719	DEAD-box helicase 3, X-linked(Ddx3x)
	P01946	hemoglobin, alpha 1(Hba1)
	P63245	receptor for activated C kinase 1(Rack1)
	Q6VV72	eukaryotic translation initiation factor 1A(Eif1a)
	Q6P685	eukaryotic translation initiation factor 2 subunit beta(Eif2s2)
	P81795	eukaryotic translation initiation factor 2 subunit gamma(Eif2s3)
	Q1JU68	eukaryotic translation initiation factor 3, subunit A(Eif3a)
	B5DFC8	eukaryotic translation initiation factor 3, subunit C(Eif3c)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Ribosome/ Translation (cont.)	Q6AYK8	eukaryotic translation initiation factor 3, subunit D(Eif3d)
	D4AC36	eukaryotic translation initiation factor 3, subunit F(Eif3f)
	Q5RK09	eukaryotic translation initiation factor 3, subunit G(Eif3g)
	Q6P3V8	eukaryotic translation initiation factor 4A1(Eif4a1)
	Q5RKG9	eukaryotic translation initiation factor 4B(Eif4b)
	A0A1W2Q627	eukaryotic translation initiation factor 4E(Eif4e)
	A0A0G2KAW7	eukaryotic translation initiation factor 4H(Eif4h)
	Q07205	eukaryotic translation initiation factor 5(Eif5)
	G3V6P6	RNA binding motif (RNP1, RRM) protein 3(Rbm3)
	P62630	eukaryotic translation elongation factor 1 alpha 1(Eef1a1)
	Q6P9Y4	solute carrier family 25 member 4(Slc25a4)
	Q09073	solute carrier family 25 member 5(Slc25a5)
Complement Cascade/Immune	P31720	complement C1q A chain(C1qa)
	G3V7N9	complement C1q B chain(C1qb)
	O35796	complement C1q binding protein(C1qbp)
	G3V7L3	complement C1s(C1s)
	M0RBF1	complement C3(C3)
	A0A096P6L9	complement C5(C5)
	P55314	complement C8 beta chain(C8b)
	Q62930	complement C9(C9)
	Q63514	complement component 4 binding protein, alpha(C4bpa)
	P08649	complement component 4A (Rodgers blood group)(C4a)
	Q9WUW3	complement factor I(Cfi)
	Q6P734	serpin family G member 1(Serping1)
	P48199	C-reactive protein(Crp)
	P20760	Ig gamma chain segment(LOC679045)
	P20761	immunoglobulin heavy chain 6(Igh-6)
	P24090	alpha-2-HS-glycoprotein(Ahsg)
	P06238	alpha-2-macroglobulin(A2m)
	P18292	coagulation factor II(F2)
	Q7TQ70	fibrinogen alpha chain(Fga)
	F1LST1, A0A096P6L8	fibronectin 1(Fn1)
	A0A0H2UHM3	haptoglobin(Hp)
	P61980	heterogeneous nuclear ribonucleoprotein K(Hnrnpk)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Complement Cascade/ Immune (cont.)	Q5EBC0	inter-alpha-trypsin inhibitor heavy chain family, member 4(Itih4)
	P01048	kininogen 1(Kng1)
	P02764	orosomucoid 1(Orm1)
	A0A0G2JY31	serpin family A member 1(Serpina1)
	Q7TMC3	serum amyloid A4(Saa4)
	P52631	signal transducer and activator of transcription 3(Stat3)
	P12346	transferrin(Tf)
	Q6AYD3	proliferation-associated 2G4(Pa2g4)
	P08649	complement component 4 binding protein, alpha(C4bpa)
	P31720	complement C1q A chain(C1qa)
	G3V7N9	complement C1q B chain(C1qb)
	B5DEH7	complement C1r(C1r)
	A0A0G2K7X7	complement C7(C7)
	D3ZWD6	complement C8 alpha chain(C8a)
	P55314	complement C8 beta chain(C8b)
	D3ZPI8	complement C8 gamma chain(C8g)
	G3V615	complement factor B(Cfb)
	F1M983	complement factor H(Cfh)
	Q5I0M3	complement factor H-related 1(Cfhr1)
Enzymatic Activity/Serpin	P05544	Serine protease inhibitor(LOC299282)
	G3V9J1	alpha-1-inhibitor III(LOC297568)
	P24090	alpha-2-HS-glycoprotein(Ahsg)
	P06238	alpha-2-macroglobulin(A2m)
	A0A0H2UHI5	serine (or cysteine) peptidase inhibitor, clade A, member 3N(Serpina3n)
	A0A0G2JSK1	serine (or cysteine) proteinase inhibitor, clade A, member 3C(Serpina3c)
	F1LR92	serine (or cysteine) proteinase inhibitor, clade A, member 3M(Serpina3m)
	A0A0G2JY31	serpin family A member 1(Serpina1)
	Q5M8C3	serpin family A member 4(Serpina4)
	P31211	serpin family A member 6(Serpina6)
	Q4G075	serpin family B member 1A(Serpinb1a)
	Q5M7T5	serpin family C member 1(Serpinc1)
	Q64268	serpin family D member 1(Serpind1)
	Q80ZA3	serpin family F member 1(Serpinf1)
	F7FHF3	serpin family F member 2(Serpinf2)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Enzymatic Activity/ Serpin (cont.)	Q6P734	serpin family G member 1(Serping1)
	Q5RJR9	serpin family H member 1(Serpinh1)
	Q62975	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 10(Serpina10)
	P01015	angiotensinogen(Agt)
	Q64240	alpha-1-microglobulin/bikunin precursor(Ambp)
	D3ZBS2	inter-alpha trypsin inhibitor, heavy chain 3(Itih3)
	P18420	proteasome subunit alpha 1(Psma1)
	P17220	proteasome subunit alpha 2(Psma2)
	P18422	proteasome subunit alpha 3(Psma3)
	P21670	proteasome subunit alpha 4(Psma4)
	Q6P9V6	proteasome subunit alpha 5(Psma5)
	A0A0G2K0W9	proteasome subunit alpha 7(Psma7)
	P18421	proteasome subunit beta 1(Psmb1)
	Q4KM35	proteasome subunit beta 10(Psmb10)
	G3V7Q6	proteasome subunit beta 5(Psmb5)
	Q9JHW0	proteasome subunit beta 7(Psmb7)
	A0A0G2JSL0	proteasome subunit beta type 6-like(LOC100360846)
	Q66H94	FK506 binding protein 9(Fkbp9)
	Q4QRB0	UDP-galactose-4-epimerase(Gale)
	Q6P6G4	bisphosphoglycerate mutase(Bpgm)
	P97852	hydroxysteroid (17-beta) dehydrogenase 4(Hsd17b4)
	P24368	peptidylprolyl isomerase B(Ppib)
	Q6AYQ9	peptidylprolyl isomerase C(Ppic)
	P04785	prolyl 4-hydroxylase subunit beta(P4hb)
	P11598	protein disulfide isomerase family A, member 3(Pdia3)
	G3V6T7	protein disulfide isomerase family A, member 4(Pdia4)
	Q5I0H9	protein disulfide isomerase family A, member 5(Pdia5)
	Q63081	protein disulfide isomerase family A, member 6(Pdia6)
	D4A7L6	ribose 5-phosphate isomerase A(Rpia)
	P48500	triosephosphate isomerase 1(Tpi1)
Post-Translational Modifications	Q02874	H2A histone family, member Y(H2afy)
	A0A0A0MXW3	H2A histone family, member Z(H2afz)
	Q99PF5	KH-type splicing regulatory protein(Khsrp)
	Q71UF4	RB binding protein 7, chromatin remodeling factor(Rbbp7)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Post-Translational Modifications (cont.)	P62961	Y box binding protein 1(Ybx1)
	P18395	cold shock domain containing E1, RNA binding(Csde1)
	Q68FR6	eukaryotic translation elongation factor 1 gamma(Eef1g)
	P05197	eukaryotic translation elongation factor 2(Eef2)
	Q3B8Q2	eukaryotic translation initiation factor 4A3(Eif4a3)
	Q6P6G9	heterogeneous nuclear ribonucleoprotein A1(Hnrnpa1)
	F1LNF1	heterogeneous nuclear ribonucleoprotein A2/B1(Hnrnpa2b1)
	Q6URK4	heterogeneous nuclear ribonucleoprotein A3(Hnrnpa3)
	Q9JJ54	heterogeneous nuclear ribonucleoprotein D(Hnrnpd)
	Q794E4	heterogeneous nuclear ribonucleoprotein F(Hnrnpf)
	P61980	heterogeneous nuclear ribonucleoprotein K(Hnrnpk)
	F1LQ48	heterogeneous nuclear ribonucleoprotein L(Hnrnpl)
	D3ZBN0	histone cluster 1, H1b(Hist1h1b)
	P62804	histone cluster 1, H4b(Hist1h4b)
	Q6P7A7	ribophorin I(Rpn1)
	A0A0G2K757	ribophorin II(Rpn2)
	Q6PDV7	ribosomal protein L10(Rpl10)
	P62907	ribosomal protein L10A(Rpl10a)
	F1LSW7	ribosomal protein L14(Rpl14)
	P62718	ribosomal protein L18A(Rpl18a)
	P84100	ribosomal protein L19(Rpl19)
	G3V6I9	ribosomal protein L26(Rpl26)
	P21531	ribosomal protein L3(Rpl3)
	Q6P3V9	ribosomal protein L4(Rpl4)
	P09895	ribosomal protein L5(Rpl5)
	A0A0H2UHQ8	ribosomal protein S17(Rps17)
	A0A0H2UHG7	ribosomal protein S20(Rps20)
	P62982	ribosomal protein S27a(Rps27a)
	P62909	ribosomal protein S3(Rps3)
	P49242	ribosomal protein S3a(Rps3a)
	P19945	ribosomal protein lateral stalk subunit P0(Rplp0)
	B5DF91	ELAV like RNA binding protein 1(Elavl1)
	P62630	eukaryotic translation elongation factor 1 alpha 1(Eef1a1)
	P62632	eukaryotic translation elongation factor 1 alpha 2(Eef1a2)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Post-Translational Modifications (cont.)	A0A0G2KAW7	eukaryotic translation initiation factor 4H(Eif4h)
	A0A140TAJ3	far upstream element binding protein 1(Fubp1)
	A0A0G2JTG7	heterogeneous nuclear ribonucleoprotein H1(Hnrnph1)
	Q6AY09	heterogeneous nuclear ribonucleoprotein H2 (H')(Hnrnph2)
	B2RZC6	interleukin enhancer binding factor 2(Ilf2)
	Q9EPH8	poly(A) binding protein, cytoplasmic 1(Pabpc1)
	P62282	ribosomal protein S11(Rps11)
	Q6P6R2	dihydrolipoamide dehydrogenase(Dld)
	Q63716	peroxiredoxin 1(Prdx1)
	Q9Z0V6	peroxiredoxin 3(Prdx3)
	Q9Z0V5	peroxiredoxin 4(Prdx4)
	A0A0G2JSS8	peroxiredoxin 5(Prdx5)
	O35244	peroxiredoxin 6(Prdx6)
	P04785	prolyl 4-hydroxylase subunit beta(P4hb)
	P11598	protein disulfide isomerase family A, member 3(Pdia3)
	G3V6T7	protein disulfide isomerase family A, member 4(Pdia4)
	Q5I0H9	protein disulfide isomerase family A, member 5(Pdia5)
	Q63081	protein disulfide isomerase family A, member 6(Pdia6)
	R4GNK3	thioredoxin 1(Txn1)
	Q498E0	thioredoxin domain containing 12(Txndc12)
	D3ZZC1	thioredoxin domain containing 5(Txndc5)
	O89049	thioredoxin reductase 1(Txnrd1)
	Q5M9H2	acyl-CoA dehydrogenase, very long chain(Acadvl)
	P43138	apurinic/apyrimidinic endodeoxyribonuclease 1(Apex1)
	A0A1W2Q6E9	moesin(Msn)
	Q6P9Y4	solute carrier family 25 member 4(Slc25a4)
	P31000	vimentin(Vim)
Protein Folding, Processing and Sorting (Intracellular Transport)	A0A096MK61	cartilage associated protein(Crtap)
	A0A0A0MY09	heat shock protein 90 beta family member 1(Hsp90b1)
	A0A0A0MY48	dynamin 2(Dnm2)
	A0A0G2JT30	methionine adenosyltransferase 2B(Mat2b)
	A0A0G2JTG7	heterogeneous nuclear ribonucleoprotein H1(Hnrnph1)
	A0A0G2JVG3, P11980	pyruvate kinase, muscle(Pkm)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	A0A0G2JX79	signal sequence receptor subunit 1(Ssr1)
	A0A0G2JY31	serpin family A member 1(Serpina1)
	A0A0G2JZG7	seryl-tRNA synthetase(Sars)
	A0A0G2JZM2	Sec23 homolog A, coat complex II component(Sec23a)
	A0A0G2JZT5	septin 7(Sept7)
	A0A0G2K0L0	3'-phosphoadenosine 5'-phosphosulfate synthase 1(Papss1)
	A0A0G2K199	prolyl 3-hydroxylase 1(P3h1)
	A0A0G2K2Y3	endoplasmic reticulum aminopeptidase 1(Erap1)
	A0A0G2K542	UDP-glucose pyrophosphorylase 2(Ugp2)
	A0A0G2K757	ribophorin II(Rpn2)
	A0A0G2K7F7	tropomyosin 1, alpha(Tpm1)
	A0A0G2K845	adiponectin, C1Q and collagen domain containing(Adipoq)
	A0A0G2K9A2	actin related protein 2/3 complex, subunit 2(Arpc2)
	A0A0G2K9E8	myosin IE(Myo1e)
	A0A0G2K9V6	threonyl-tRNA synthetase(Tars)
	A0A0G2KAW7	eukaryotic translation initiation factor 4H(Eif4h)
	A0A0G2KB63	prohibitin 2(Phb2)
	A0A0H2UHL6	cathepsin H(Ctsh)
	A0A140TAA4	programmed cell death 6 interacting protein(Pdcd6ip)
	A0A140UHX6	spectrin, beta, erythrocytic(Sptb)
	A0A1W2Q627	eukaryotic translation initiation factor 4E(Eif4e)
	B0BMW2	hydroxysteroid (17-beta) dehydrogenase 10(Hsd17b10)
	B0BNA5	coactosin-like F-actin binding protein 1(Cotl1)
	B1H282	collagen beta(1-O)galactosyltransferase 1(Colgalt1)
	B1WC34	protein kinase C substrate 80K-H(Prkcsh)
	B2RYP4	sorting nexin 2(Snx2)
	B2RYP6	LUC7-like 2 pre-mRNA splicing factor(Luc7l2)
	B2RZ78	VPS29 retromer complex component(Vps29)
	B2RZD6	NADH:ubiquinone oxidoreductase subunit A4(Ndufa4)
	C0JPT7	filamin A(Flna)
	C0KUC5	LIM zinc finger domain containing 1(Lims1)
	D3Z9Z0	ankyrin 1(Ank1)
	D3ZAS9	DDRGK domain containing 1(Ddrgk1)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	D3ZCT7	Sec23 homolog B, coat complex II component(Sec23b)
	D3ZF39	UDP-N-acetylglucosamine pyrophosphorylase 1(Uap1)
	D3ZH41	cytoskeleton-associated protein 4(Ckap4)
	D3ZQ25	fibulin 1(Fbln1)
	D3ZQ74	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1(Plod1)
	D3ZTX0	transmembrane p24 trafficking protein 7(Tmed7)
	D3ZZC1	thioredoxin domain containing 5(Txndc5)
	D4A8T3	coatomer protein complex, subunit zeta 1(Copz1)
	D4A9A6	erythrocyte membrane protein band 4.1(Epb41)
	D4A9Y0	stromal cell-derived factor 2-like 1(Sdf2l1)
	D4AC23	chaperonin containing TCP1 subunit 7(Cct7)
	D4AC36	eukaryotic translation initiation factor 3, subunit F(Eif3f)
	D4ACB8	chaperonin containing TCP1 subunit 8(Cct8)
	F1LM47	succinate-CoA ligase ADP-forming beta subunit(Sucla2)
	F1LMP9	DAB2, clathrin adaptor protein(Dab2)
	F1LPV8	succinate-CoA ligase, GDP-forming, beta subunit(Suclg2)
	F1LQ55	sterol carrier protein 2(Scp2)
	F2Z3Q8	karyopherin subunit beta 1(Kpnb1)
	F7FJQ3	NPC intracellular cholesterol transporter 2(Npc2)
	F8WFT7	solute carrier family 4 (anion exchanger), member 1(Slc4a1)
	G3V6E1	myosin heavy chain 2(Myh2)
	G3V6P2	dihydrolipoamide S-succinyltransferase(Dlst)
	G3V6P7	myosin, heavy chain 9, non-muscle-like 1(Myh9l1)
	G3V6S3	calumenin(Calu)
	G3V6T1	coatomer protein complex subunit alpha(Copa)
	G3V6T7	protein disulfide isomerase family A, member 4(Pdia4)
	G3V7Q7	IQ motif containing GTPase activating protein 1(Iqgap1)
	G3V852	talin 1(Tln1)
	G3V8C4	chloride intracellular channel 4(Clic4)
	G3V8D5	6-phosphogluconolactonase(Pgls)
	G3V8L7	integrin subunit alpha M(Itgam)
	G3V8Q1	coatomer protein complex, subunit epsilon(Cope)
	G3V913	heat shock protein family B (small) member 1(Hspb1)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	G3V936	citrate synthase(Cs)
	G3V9S9	SEC24 homolog D, COPII coat complex component(Sec24d)
	G3V9T7	arsA arsenite transporter, ATP-binding, homolog 1 (bacterial)(Asna1)
	O08839	bridging integrator 1(Bin1)
	O35142	coatomer protein complex subunit beta 2(Copb2)
	O35567	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase(Atic)
	O35814	stress-induced phosphoprotein 1(Stip1)
	O35828	coronin 7(Coro7)
	O88600	heat shock protein family A member 4(Hspa4)
	P00507	glutamic-oxaloacetic transaminase 2(Got2)
	P00697	lysozyme 2(Lyz2)
	P02625	parvalbumin(Pvalb)
	P02767	transthyretin(Ttr)
	P04182	ornithine aminotransferase(Oat)
	P04636	malate dehydrogenase 2(Mdh2)
	P04639	apolipoprotein A1(Apoa1)
	P04642	lactate dehydrogenase A(Ldha)
	P04762	catalase(Cat)
	P04785	prolyl 4-hydroxylase subunit beta(P4hb)
	P04797	glyceraldehyde-3-phosphate dehydrogenase(Gapdh)
	P04916	retinol binding protein 4(Rbp4)
	P05065	aldolase, fructose-bisphosphate A(Aldoa)
	P05197	eukaryotic translation elongation factor 2(Eef2)
	P05370	glucose-6-phosphate dehydrogenase(G6pd)
	P05371	clusterin(Clu)
	P06238	alpha-2-macroglobulin(A2m)
	P06761	heat shock protein family A member 5(Hspa5)
	P07150	annexin A1(Anxa1)
	P07632	superoxide dismutase 1, soluble(Sod1)
	P07895	superoxide dismutase 2, mitochondrial(Sod2)
	P09606	glutamate-ammonia ligase(Glul)
	P10111	peptidylprolyl isomerase A (cyclophilin A)(Ppia)
	P10860	glutamate dehydrogenase 1(Glud1)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	P10959	carboxylesterase 1C(Ces1c)
	P11507	ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 2(Atp2a2)
	P11598	protein disulfide isomerase family A, member 3(Pdia3)
	P11762	galectin 1(Lgals1)
	P15178	aspartyl-tRNA synthetase(Dars)
	P15429	enolase 3(Eno3)
	P16290	phosphoglycerate mutase 2(Pgam2)
	P16617	phosphoglycerate kinase 1(Pgk1)
	P17046	lysosomal-associated membrane protein 2(Lamp2)
	P18298	methionine adenosyltransferase 2A(Mat2a)
	P18418	calreticulin(Calr)
	P18484	adaptor-related protein complex 2, alpha 2 subunit(Ap2a2)
	P19804	NME/NM23 nucleoside diphosphate kinase 2(Nme2)
	P21913	succinate dehydrogenase complex iron sulfur subunit B(Sdhb)
	P23514	coatomer protein complex, subunit beta 1(Copb1)
	P23680	amyloid P component, serum(Apcs)
	P23928	crystallin, alpha B(Cryab)
	P24090	alpha-2-HS-glycoprotein(Ahsg)
	P24368	peptidylprolyl isomerase B(Ppib)
	P25113	phosphoglycerate mutase 1(Pgam1)
	P26772	heat shock protein family E member 1(Hspe1)
	P28480	t-complex 1(Tcp1)
	P31000	vimentin(Vim)
	P34058	heat shock protein 90 alpha family class B member 1(Hsp90ab1)
	P35565	calnexin(Canx)
	P39069	adenylate kinase 1(Ak1)
	P43138	apurinic/apyrimidinic endodeoxyribonuclease 1(Apex1)
	P46462	valosin-containing protein(Vcp)
	P47819	glial fibrillary acidic protein(Gfap)
	P48500	triosephosphate isomerase 1(Tpi1)
	P51583	phosphoribosylaminoimidazole carboxylase; phosphoribosylaminoimidazolesuccinocarboxamide synthase(Paics)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	P51635	aldo-keto reductase family 1 member A1(Akr1a1)
	P51673	cellular retinoic acid binding protein 2(Crabp2)
	P52555	endoplasmic reticulum protein 29(Erp29)
	P52925	high mobility group box 2(Hmgb2)
	P54001	prolyl 4-hydroxylase subunit alpha 1(P4ha1)
	P54921	NSF attachment protein alpha(Napa)
	P56574	isocitrate dehydrogenase (NADP(+)) 2, mitochondrial(Idh2)
	P60123	RuvB-like AAA ATPase 1(Ruvbl1)
	P60711	actin, beta(Actb)
	P62138	protein phosphatase 1 catalytic subunit alpha(Ppp1ca)
	P62260	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon(Ywhae)
	P62828	RAN, member RAS oncogene family(Ran)
	P62944	adaptor-related protein complex 2, beta 1 subunit(Ap2b1)
	P62963	profilin 1(Pfn1)
	P63039	heat shock protein family D member 1(Hspd1)
	P63086	mitogen activated protein kinase 1(Mapk1)
	P63102	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta(Ywhaz)
	P63245	receptor for activated C kinase 1(Rack1)
	P63329	protein phosphatase 3 catalytic subunit alpha(Ppp3ca)
	P63331	protein phosphatase 2, catalytic subunit, alpha isozyme(Ppp2ca)
	P67779	prohibitin(Phb)
	P82995	heat shock protein 90, alpha (cytosolic), class A member 1(Hsp90aa1)
	P83868	prostaglandin E synthase 3(Ptges3)
	P84079	ADP-ribosylation factor 1(Arf1)
	P85968	phosphogluconate dehydrogenase(Pgd)
	Q04462	valyl-tRNA synthetase(Vars)
	Q07936	annexin A2(Anxa2)
	Q07984	peroxiredoxin 1(Prdx1)
	Q07984	signal sequence receptor subunit 4(Ssr4)
	Q3MHS9	chaperonin containing TCP1 subunit 6A(Cct6a)
	Q3MID3	ADP-ribosylation factor GTPase activating protein 2(Arfgap2)
	Q3T1J1	eukaryotic translation initiation factor 5A(Eif5a)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	Q498E0	thioredoxin domain containing 12(Txndc12)
	Q499Q4	phosphoglucomutase 1(Pgm1)
	Q4AEF8	coatomer protein complex, subunit gamma 1(Copg1)
	Q4KLN7	ADP-ribosylation factor GTPase activating protein 3(Arfgap3)
	Q4KLZ3	DAZ associated protein 1(Dazap1)
	Q5EAJ6	IKBKB interacting protein(Ikbip)
	Q5I0E7	transmembrane p24 trafficking protein 9(Tmed9)
	Q5I0H9	protein disulfide isomerase family A, member 5(Pdia5)
	Q5I0M1	apolipoprotein H(Apoh)
	Q5M964	fumarate hydratase(Fh)
	Q5RJR2	twinfilin actin-binding protein 1(Twf1)
	Q5RJR8	leucine rich repeat containing 59(Lrrc59)
	Q5RJR9	serpin family H member 1(Serpinh1)
	Q5U2R7	mesoderm development candidate 2(Mesdc2)
	Q5U2U8	Bcl2-associated athanogene 3(Bag3)
	Q5U2V1	FK506 binding protein 10(Fkbp10)
	Q5U3Z7	serine hydroxymethyltransferase 2(Shmt2)
	Q5VLR5	endoplasmic reticulum protein 44(Erp44)
	Q5XHZ0	TNF receptor-associated protein 1(Trap1)
	Q62658	FK506 binding protein 1a(Fkbp1a)
	Q62703	reticulocalbin 2(Rcn2)
	Q62848	ADP-ribosylation factor GTPase activating protein 1(Arfgap1)
	Q63081	protein disulfide isomerase family A, member 6(Pdia6)
	Q63584	transmembrane p24 trafficking protein 10(Tmed10)
	Q63617	hypoxia up-regulated 1(Hyou1)
	Q63678	alpha-2-glycoprotein 1, zinc-binding(Azgp1)
	Q64057	aldehyde dehydrogenase 7 family, member A1(Aldh7a1)
	Q641Y0	dolichyl-diphosphooligosaccharide--protein glycosyltransferase non-catalytic subunit(Ddost)
	Q64428	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit(Hadha)
	Q66H80	archain 1(Arcn1)
	Q66H94	FK506 binding protein 9(Fkbp9)
	Q66HA8	heat shock protein family H (Hsp110) member 1(Hsph1)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	Q68FQ0	chaperonin containing TCP1 subunit 5(Cct5)
	Q68FY0	ubiquinol-cytochrome c reductase core protein I(Uqcrc1)
	Q6AYC4	capping actin protein, gelsolin like(Capg)
	Q6AYK8	eukaryotic translation initiation factor 3, subunit D(Eif3d)
	Q6AYQ9	peptidylprolyl isomerase C(Ppic)
	Q6AYS3	cathepsin A(Ctsa)
	Q6AYU5	poly(rC) binding protein 2(Pcbp2)
	Q6BBI8	ubiquitin-fold modifier conjugating enzyme 1(Ufc1)
	Q6DGG0	peptidylprolyl isomerase D(Ppid)
	Q6IN22	cathepsin B(Ctsb)
	Q6IRE4	tumor susceptibility 101(Tsg101)
	Q6IRK9	carboxypeptidase Q(Cpq)
	Q6MG49	BCL2-associated athanogene 6(Bag6)
	Q6P3V8	eukaryotic translation initiation factor 4A1(Eif4a1)
	Q6P502	chaperonin containing TCP1 subunit 3(Cct3)
	Q6P6G4	bisphosphoglycerate mutase(Bpgm)
	Q6P6R2	dihydrolipoamide dehydrogenase(Dld)
	Q6P6V0	glucose-6-phosphate isomerase(Gpi)
	Q6P7A7	ribophorin I(Rpn1)
	Q6P9Y4	solute carrier family 25 member 4(Slc25a4)
	Q6PEC4	S-phase kinase-associated protein 1(Skp1)
	Q71UF4	RB binding protein 7, chromatin remodeling factor(Rbbp7)
	Q792I0	lin-7 homolog C, crumbs cell polarity complex component(Lin7c)
	Q7TPB1	chaperonin containing TCP1 subunit 4(Cct4)
	Q91ZN1	coronin 1A(Coro1a)
	Q99N27	sorting nexin 1(Snx1)
	Q9EQS0	transaldolase 1(Taldo1)
	Q9EQX9	ubiquitin-conjugating enzyme E2N(Ube2n)
	Q9ES54	NPL4 homolog, ubiquitin recognition factor(Nploc4)
	Q9JK11	reticulon 4(Rtn4)
	Q9QXQ0	actinin alpha 4(Actn4)
	Q9R0T3	DnaJ heat shock protein family (Hsp40) member C3(Dnajc3)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	**Accession ID**	**Gene Name**
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	Q9WUC4	antioxidant 1 copper chaperone(Atox1)
	Q9Z0V5	peroxiredoxin 4(Prdx4)
	Q9Z1X1	extended synaptotagmin 1(Esyt1)
	Q9Z269	VAMP associated protein B and C(Vapb)
	Q9Z2Q1	SEC31 homolog A, COPII coat complex component(Sec31a)
	R4GNK3	thioredoxin 1(Txn1)
Calcium	P11507	ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 2(Atp2a2)
	P48199	C-reactive protein(Crp)
	O35568	EGF-containing fibulin-like extracellular matrix protein 1(Efemp1)
	Q66H94	FK506 binding protein 9(Fkbp9)
	P05964	S100 calcium binding protein A6(S100a6)
	P50115	S100 calcium binding protein A8(S100a8)
	P50116	S100 calcium binding protein A9(S100a9)
	Q9QXQ0	actinin alpha 4(Actn4)
	Q9Z1P2	actinin, alpha 1(Actn1)
	P23680	amyloid P component, serum(Apcs)
	P07150	annexin A1(Anxa1)
	Q07936	annexin A2(Anxa2)
	Q5U362	annexin A4(Anxa4)
	Q66HH8	annexin A5(Anxa5)
	P35565	calnexin(Canx)
	Q64537	calpain, small subunit 1(Capns1)
	P18418	calreticulin(Calr)
	P19633	calsequestrin 1(Casq1)
	G3V6S3	calumenin(Calu)
	A0A0G2JYW3	clathrin, light chain A(Clta)
	P18292	coagulation factor II(F2)
	Q63207	coagulation factor X(F10)
	P20909	collagen type XI alpha 1 chain(Col11a1)
	B5DEH7	complement C1r(C1r)
	G3V7L3	complement C1s(C1s)
	Q9WUW3	complement factor I(Cfi)
	Q9Z1X1	extended synaptotagmin 1(Esyt1)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Calcium (cont.)	Q7TQ70	fibrinogen alpha chain(Fga)
	P02680	fibrinogen gamma chain(Fgg)
	D3ZQ25	fibulin 1(Fbln1)
	G3V6X1	fibulin 2(Fbln2)
	Q32KJ5	glucosamine (N-acetyl)-6-sulfatase(Gns)
	A0A0A0MY09	heat shock protein 90 beta family member 1(Hsp90b1)
	P33436	matrix metallopeptidase 2(Mmp2)
	P08733	myosin light chain 2(Myl2)
	P04466	myosin light chain, phosphorylatable, fast skeletal muscle(Mylpf)
	Q63083	nucleobindin 1(Nucb1)
	P55159	paraoxonase 1(Pon1)
	P02625	parvalbumin(Pvalb)
	Q63598	plastin 3(Pls3)
	G3V6T7	protein disulfide isomerase family A, member 4(Pdia4)
	Q63081	protein disulfide isomerase family A, member 6(Pdia6)
	Q62703	reticulocalbin 2(Rcn2)
	P16975	secreted protein acidic and cysteine rich(Sparc)
	A0A0G2JX79	signal sequence receptor subunit 1(Ssr1)
	P49744	thrombospondin 4(Thbs4)
	Q642E6	tripeptidyl peptidase 1(Tpp1)
	P09495	tropomyosin 4(Tpm4)
	P63029	tumor protein, translationally-controlled 1(Tpt1)
ECM/Focal Adhesion	A0A0G2JTV2	caldesmon 1(Cald1)
	A0A0G2JUA5	AHNAK nucleoprotein(Ahnak)
	A0A0G2JVG3, P11980	pyruvate kinase, muscle(Pkm)
	A0A0G2K199	prolyl 3-hydroxylase 1(P3h1)
	A0A0G2K1L0	tenascin C(Tnc)
	A0A0G2KAJ7	collagen type XII alpha 1 chain(Col12a1)
	A0A0G2KAW7	eukaryotic translation initiation factor 4H(Eif4h)
	A0A0H2UHR7	filamin C(Flnc)
	B2GUZ5	capping actin protein of muscle Z-line alpha subunit 1(Capza1)
	B2RYP4	sorting nexin 2(Snx2)
	B4F7E8	family with sequence similarity 129, member B(Fam129b)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
ECM/ Focal Adhesion (cont.)	C0JPT7	filamin A(Flna)
	D3ZCV0	actinin alpha 2(Actn2)
	D3ZQ25	fibulin 1(Fbln1)
	D4A7U1	zyxin(Zyx)
	D4ACB8	chaperonin containing TCP1 subunit 8(Cct8)
	E9PSY8	epidermal growth factor receptor pathway substrate 15(Eps15)
	F1LR10	LIM domain and actin binding 1(Lima1)
	F1LST1, A0A096P6L8	fibronectin 1(Fn1)
	F1M748	collagen type XXIV alpha 1 chain(Col24a1)
	F7EWC1	vasodilator-stimulated phosphoprotein(Vasp)
	G3V6P7	myosin, heavy chain 9, non-muscle-like 1(Myh9l1)
	G3V7Q7	IQ motif containing GTPase activating protein 1(Iqgap1)
	G3V852	talin 1(Tln1)
	G3V940	coronin 1B(Coro1b)
	O35244	peroxiredoxin 6(Prdx6)
	O35567	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase(Atic)
	O35568	EGF-containing fibulin-like extracellular matrix protein 1(Efemp1)
	O70513	galectin 3 binding protein(Lgals3bp)
	P04466	myosin light chain, phosphorylatable, fast skeletal muscle(Mylpf)
	P05197	eukaryotic translation elongation factor 2(Eef2)
	P06761	heat shock protein family A member 5(Hspa5)
	P07150	annexin A1(Anxa1)
	P08733	myosin light chain 2(Myl2)
	P11762	galectin 1(Lgals1)
	P16975	secreted protein acidic and cysteine rich(Sparc)
	P20909	collagen type XI alpha 1 chain(Col11a1)
	P33436	matrix metallopeptidase 2(Mmp2)
	P34058	heat shock protein 90 alpha family class B member 1(Hsp90ab1)
	P47853	biglycan(Bgn)
	P52944	PDZ and LIM domain 1(Pdlim1)
	P60711	actin, beta(Actb)
	P61314	ribosomal protein L15(Rpl15)
	P61980	heterogeneous nuclear ribonucleoprotein K(Hnrnpk)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
ECM/ Focal Adhesion (cont.)	P62138	protein phosphatase 1 catalytic subunit alpha(Ppp1ca)
	P62260	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon(Ywhae)
	P62963	profilin 1(Pfn1)
	P63102	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta(Ywhaz)
	Q07936	annexin A2(Anxa2)
	Q3B7D6	spondin 1(Spon1)
	Q3KR94	vitronectin(Vtn)
	Q4KLK7	NOP56 ribonucleoprotein(Nop56)
	Q5RJR2	twinfilin actin-binding protein 1(Twf1)
	Q5U1Y2	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)(Rac2)
	Q5U2U8	Bcl2-associated athanogene 3(Bag3)
	Q5XFX0	transgelin 2(Tagln2)
	Q62920	PDZ and LIM domain 5(Pdlim5)
	Q64303	p21 protein (Cdc42/Rac)-activated kinase 2(Pak2)
	Q6AYC4	capping actin protein, gelsolin like(Capg)
	Q6MG61	chloride intracellular channel 1(Clic1)
	Q8R4I6	actinin alpha 3(Actn3)
	Q99MZ8	LIM and SH3 protein 1(Lasp1)
	Q99N27	sorting nexin 1(Snx1)
	Q9JK11	reticulon 4(Rtn4)
	Q9QXQ0	actinin alpha 4(Actn4)
	Q9QY17	protein kinase C and casein kinase substrate in neurons 2(Pacsin2)
	Q9Z1P2	actinin, alpha 1(Actn1)
	Q9Z269	VAMP associated protein B and C(Vapb)
Acute Phase Immunity	B2RYG6	OTU deubiquitinase, ubiquitin aldehyde binding 1(Otub1)
	Q6MGB8	RT1 class Ia, locus A2(RT1-A2)
	P07150	annexin A1(Anxa1)
	A0A0G2KBC4	colony stimulating factor 1 receptor(Csf1r)
	P62329	thymosin beta 4, X-linked(Tmsb4x)
	P63312	thymosin, beta 10(Tmsb10)
	A0A0G2K719	DEAD-box helicase 3, X-linked(Ddx3x)
	P20760	Ig gamma chain segment(LOC679045)

Table S3: Control versus Lengthening genes sorted into designated clusters (continued)

Cluster	**Accession ID**	**Gene Name**
Acute Phase Immunity (cont.)	P23680	amyloid P component, serum(Apcs)
	P20761	immunoglobulin heavy chain 6(Igh-6)
	Q6P734	serpin family G member 1(Serping1)
	O08629	tripartite motif-containing 28(Trim28)
	D3ZY96	neutrophilic granule protein(Ngp)
	Q63041	pregnancy-zone protein(Pzp)
	Q62658	FK506 binding protein 1a(Fkbp1a)
	Q08163	adenylate cyclase associated protein 1(Cap1)
	Q07936	annexin A2(Anxa2)
	Q5U362	annexin A4(Anxa4)
	Q66HH8	annexin A5(Anxa5)
	P04961	proliferating cell nuclear antigen(Pcna)
	Q08163	adenylate cyclase associated protein 1(Cap1)

Table S4: DAVID-generated Functional Chart terms for Graft versus Lengthening experimental condition with corresponding p-values and Benjamini-Hochberg adjusted p-values

Functional Chart Term	P-Value	Benjamini
extracellular exosome	1.30E-27	2.80E-25
blood microparticle	4.00E-27	4.20E-25
Complement and coagulation cascades	8.10E-22	8.10E-20
extracellular space	2.40E-20	1.70E-18
Secreted	8.50E-19	1.60E-16
Signal	4.00E-18	3.70E-16
Blood coagulation	2.50E-14	1.60E-12
Hemostasis	2.50E-14	1.60E-12
poly(A) RNA binding	6.60E-13	1.50E-10
Ribosomal protein	9.60E-13	4.50E-11
negative regulation of endopeptidase activity	1.60E-12	1.20E-09
extracellular matrix	2.90E-12	1.50E-10
Ribosome	4.50E-12	2.20E-10
Glycoprotein	5.70E-12	2.10E-10
Ribonucleoprotein	4.00E-11	1.30E-09
Acetylation	5.40E-11	1.40E-09
focal adhesion	8.00E-11	3.40E-09
endoplasmic reticulum lumen	1.20E-10	4.10E-09
fibrinolysis	1.40E-09	5.60E-07
serine-type endopeptidase inhibitor activity	2.50E-09	2.80E-07
Disulfide bond	3.00E-09	7.00E-08
blood coagulation	3.70E-09	9.80E-07
Phosphoprotein	4.80E-09	1.00E-07
signal peptide	1.20E-08	5.40E-06
liver regeneration	1.70E-08	3.30E-06
complement activation, classical pathway	2.00E-08	3.20E-06
endoplasmic reticulum chaperone complex	2.60E-08	7.70E-07
structural constituent of ribosome	4.20E-08	3.10E-06
translation	1.10E-07	1.40E-05
Calcium	1.10E-07	2.10E-06
small ribosomal subunit	1.70E-07	4.40E-06
Innate immunity	3.70E-07	6.30E-06
short sequence motif:Prevents secretion from ER	3.90E-07	8.40E-05
ribosome	4.00E-07	9.40E-06
Complement pathway	4.20E-07	6.60E-06
acute-phase response	6.70E-07	7.50E-05
endoplasmic reticulum	8.70E-07	1.80E-05
Muscle protein	9.40E-07	1.30E-05
protein polymerization	1.50E-06	1.40E-04
cytosolic large ribosomal subunit	1.50E-06	2.90E-05
Serpin family	2.20E-06	8.30E-04
Serpin domain	2.50E-06	4.70E-04
Disulphide isomerase	5.00E-06	6.20E-04
Acute phase	5.30E-06	7.10E-05
Immunity	6.90E-06	8.60E-05
ribosomal small subunit biogenesis	1.00E-05	8.90E-04
SERPIN	1.10E-05	1.00E-03
Protease inhibitor I4, serpin, conserved site	1.40E-05	1.30E-03
calcium ion binding	1.50E-05	8.30E-04
fibrinogen complex	1.80E-05	3.20E-04
negative regulation of fibrinolysis	1.90E-05	1.50E-03
Methylation	2.00E-05	2.30E-04
Protease inhibitor	2.20E-05	2.40E-04
Peptidase S1A, chymotrypsin-type	3.20E-05	2.40E-03
Hydroxylation	4.50E-05	4.70E-04
heparin binding	5.10E-05	2.30E-03
Peptidase S1	5.10E-05	3.20E-03
plasminogen activation	6.50E-05	4.70E-03
Trypsin-like cysteine/serine peptidase domain	6.80E-05	3.70E-03
membrane	7.10E-05	1.10E-03
Isopeptide bond	7.80E-05	7.70E-04
smooth endoplasmic reticulum	8.60E-05	1.30E-03
melanosome	9.40E-05	1.30E-03

Table S5: DAVID-generated Functional Chart terms for Graft versus Lengthening experimental condition sorted into clusters

Cluster/Process	**Functional Chart Terms**
Protein Folding, Processing and Sorting (Intracellular Transport)	Secreted
	Glycoprotein
	endoplasmic reticulum lumen
	endoplasmic reticulum chaperone complex
	short sequence motif:Prevents secretion from ER
	endoplasmic reticulum
	Disulphide isomerase
ECM/Focal Adhesion	extracellular space
	extracellular matrix
	focal adhesion
Calcium	Calcium
Coagulation	blood microparticle
	Complement and coagulation cascades
	Blood coagulation
	Hemostasis
	fibrinolysis
	blood coagulation
Ribosome/Translation	Ribosomal protein
	Ribosome
	Ribonucleoprotein
	structural constituent of ribosome
	translation
	small ribosomal subunit
	ribosome
	cytosolic large ribosomal subunit
	ribosomal small subunit biogenesis
	protein polymerization
Complement Cascade/Immune	complement activation, classical pathway
	Innate immunity
	Complement pathway
	acute-phase response
	Acute phase
	Immunity

Table S5: DAVID-generated Functional Chart terms for Graft versus Lengthening experimental condition sorted into clusters (continued)

Cluster/Process	**Functional Chart Terms**
Post-Translational Modifications	Acetylation
	Disulfide bond
	Phosphoprotein
mRNA Processing/Transcription	poly(A) RNA binding
Peripheral Nervous System/Myelin/Proliferation Regulator	liver regeneration
Protein Degradation/Clearance (Ubiquitin-Proteasome)	Protease inhibitor
Bioenergetics and Metabolism	Signal
	Signal peptide
Cytoskeleton/Motility	Muscle protein
	membrane
Enzymatic Activity/Serpin	negative regulation of endopeptidase activity
	serine-type endopeptidase inhibitor activity
	Serpin family

Table S6: Graft versus Lengthening genes sorted into designated clusters

Cluster	**Accession ID**	**Gene Name**
Cytoskeleton/Motility	A0A0G2JTV2	caldesmon 1(Cald1)
	G3V6F1	myosin binding protein H(Mybph)
	P04466	myosin light chain, phosphorylatable, fast skeletal muscle(Mylpf)
	P02600	myosin, light chain 1(Myl1)
	A0A0G2K7F7	tropomyosin 1, alpha(Tpm1)
	P27768	troponin I2, fast skeletal type(Tnni2)
	Q7TNB2	troponin T1, slow skeletal type(Tnnt1)
	Q6P0K8	junction plakoglobin(Jup)
	Q4QQV6	lymphocyte-specific protein 1(Lsp1)
	A0A0G2K1L0	tenascin C(Tnc)
	D3ZH41	cytoskeleton-associated protein 4(Ckap4)
Peripheral nervous system/ Myelin/ Proliferation Regulator	P04961	proliferating cell nuclear antigen(Pcna)
	Q3KR94	vitronectin(Vtn)
Bioenergetics and Metabolism	A0A0H2UHL3	AE binding protein 1(Aebp1)
	P48199	C-reactive protein(Crp)
	D3Z9M5	FK506 binding protein 7(Fkbp7)
	Q64240	alpha-1-microglobulin/bikunin precursor(Ambp)
	Q3B8R6	alpha-2-glycoprotein 1, zinc-binding(Azgp1)
	P23680	amyloid P component, serum(Apcs)
	Q5I0M1	apolipoprotein H(Apoh)
	P47853	biglycan(Bgn)
	P18418	calreticulin(Calr)
	G3V6S3	calumenin(Calu)
	F1LQT4	carboxypeptidase N subunit 2(Cpn2)
	D4A488	elastase, neutrophil expressed(Elane)
	Q7TQ70	fibrinogen alpha chain(Fga)
	P14480	fibrinogen beta chain(Fgb)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Bioenergetics and Metabolism (cont.)	P02680	fibrinogen gamma chain(Fgg)
	G3V6X1	fibulin 2(Fbln2)
	Q68FY4	group specific component(Gc)
	A0A0H2UHM3	haptoglobin(Hp)
	P06761	heat shock protein family A member 5(Hspa5)
	P20059	hemopexin(Hpx)
	A0A0G2K3G0	histidine-rich glycoprotein(Hrg)
	G3V8L7	integrin subunit alpha M(Itgam)
	D3ZBS2	inter-alpha trypsin inhibitor, heavy chain 3(Itih3)
	D3ZFH5	inter-alpha-trypsin inhibitor heavy chain 2(Itih2)
	P01048	kininogen 1(Kng1)
	P08934	kininogen 2(Kng2)
	Q5PPG2	legumain(Lgmn)
	A0A0G2K1A2	myeloperoxidase(Mpo)
	D3ZY96	neutrophilic granule protein(Ngp)
	P55159	paraoxonase 1(Pon1)
	P24368	peptidylprolyl isomerase B(Ppib)
	Q6AYQ9	peptidylprolyl isomerase C(Ppic)
	Q01177	plasminogen(Plg)
	P06765	platelet factor 4(Pf4)
	D3ZQ74	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1(Plod1)
	P54001	prolyl 4-hydroxylase subunit alpha 1(P4ha1)
	D3ZGT6	prolyl 4-hydroxylase subunit alpha 2(P4ha2)
	P04785	prolyl 4-hydroxylase subunit beta(P4hb)
	G3V6T7	protein disulfide isomerase family A, member 4(Pdia4)
	Q63081	protein disulfide isomerase family A, member 6(Pdia6)
	F1LRA5	proteoglycan 4(Prg4)
	D4A0S3	rCG29588-like(LOC100360165)
	Q62703	reticulocalbin 2(Rcn2)
	I6L9G5	reticulocalbin 3(Rcn3)
	Q6P7A7	ribophorin I(Rpn1)
	A0A0G2JVN2	secreted frizzled-related protein 4(Sfrp4)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Bioenergetics and Metabolism (cont.)	A0A0G2JY31	serpin family A member 1(Serpina1)
	Q5M8C3	serpin family A member 4(Serpina4)
	P31211	serpin family A member 6(Serpina6)
	Q5M7T5	serpin family C member 1(Serpinc1)
	F7FHF3	serpin family F member 2(Serpinf2)
	Q5RJR9	serpin family H member 1(Serpinh1)
	Q62975	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 10(Serpina10)
	A0A0G2JX79	signal sequence receptor subunit 1(Ssr1)
	D4A9Y0	stromal cell-derived factor 2-like 1(Sdf2l1)
	A0A0G2K1L0	tenascin C(Tnc)
	D3ZZC1	thioredoxin domain containing 5(Txndc5)
	P12346	transferrin(Tf)
	Q3KR94	vitronectin(Vtn)
mRNA Processing/ Transcription	A0A096MIZ8	EBNA1 binding protein 2(Ebna1bp2)
	B2RYP6	LUC7-like 2 pre-mRNA splicing factor(Luc7l2)
	G3V6P6	RNA binding motif (RNP1, RRM) protein 3(Rbm3)
	Q66H80	archain 1(Arcn1)
	P18418	calreticulin(Calr)
	Q63514	complement component 4 binding protein, alpha(C4bpa)
	D3ZH41	cytoskeleton-associated protein 4(Ckap4)
	Q5RK09	eukaryotic translation initiation factor 3, subunit G(Eif3g)
	A0A140TAJ3	far upstream element binding protein 1(Fubp1)
	Q3KRF2	high density lipoprotein binding protein(Hdlbp)
	D3ZBN0	histone cluster 1, H1b(Hist1h1b)
	Q5RJR8	leucine rich repeat containing 59(Lrrc59)
	P13084	nucleophosmin 1(Npm1)
	P24368	peptidylprolyl isomerase B(Ppib)
	P04785	prolyl 4-hydroxylase subunit beta(P4hb)
	G3V6T7	protein disulfide isomerase family A, member 4(Pdia4)
	P63245	receptor for activated C kinase 1(Rack1)
	Q6P7A7	ribophorin I(Rpn1)
	P61314	ribosomal protein L15(Rpl15)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
mRNA Processing/ Transcription (cont.)	F1LZX7	ribosomal protein L17(Rpl17)
	P62718	ribosomal protein L18A(Rpl18a)
	P84100	ribosomal protein L19(Rpl19)
	P62832	ribosomal protein L23(Rpl23)
	P61354	ribosomal protein L27(Rpl27)
	P21531	ribosomal protein L3(Rpl3)
	P05426	ribosomal protein L7(Rpl7)
	P62919	ribosomal protein L8(Rpl8)
	P62250	ribosomal protein S16(Rps16)
	A0A0H2UHQ8	ribosomal protein S17(Rps17)
	A0A0H2UHH9	ribosomal protein S24(Rps24)
	Q71TY3	ribosomal protein S27(Rps27)
	P62859	ribosomal protein S28(Rps28)
	A0A0H2UHX3	ribosomal protein S4, X-linked(Rps4x)
	P29314	ribosomal protein S9(Rps9)
	O88453	scaffold attachment factor B(Safb)
	A0A0G2K2M9	serine/arginine repetitive matrix 2(Srrm2)
	Q5RJR9	serpin family H member 1(Serpinh1)
	D3ZMS1	splicing factor 3b, subunit 2(Sf3b2)
	O35814	stress-induced phosphoprotein 1(Stip1)
Protein Degradation/ Clearance (Ubiquitin-Proteasome)	A0A0G2JY31	serpin family A member 1(Serpina1)
	Q5M8C3	serpin family A member 4(Serpina4)
	P31211	serpin family A member 6(Serpina6)
	Q5M7T5	serpin family C member 1(Serpinc1)
	F7FHF3	serpin family F member 2(Serpinf2)
	Q5RJR9	serpin family H member 1(Serpinh1)
	D4A488	elastase, neutrophil expressed(Elane)
Coagulation	P20760	Ig gamma chain segment(LOC679045)
	Q64240	alpha-1-microglobulin/bikunin precursor(Ambp)
	P23680	amyloid P component, serum(Apcs)
	P11517	beta-globin(LOC689064)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	**Accession ID**	**Gene Name**
Coagulation (cont.)	F1LQT4	carboxypeptidase N subunit 2(Cpn2)
	P18292	coagulation factor II(F2)
	Q7TQ70	fibrinogen alpha chain(Fga)
	P14480	fibrinogen beta chain(Fgb)
	P02680	fibrinogen gamma chain(Fgg)
	Q68FY4	group specific component(Gc)
	A0A0H2UHM3	haptoglobin(Hp)
	P20059	hemopexin(Hpx)
	A0A0G2K3G0	histidine-rich glycoprotein(Hrg)
	D3ZFH5	inter-alpha-trypsin inhibitor heavy chain 2(Itih2)
	P01048	kininogen 1(Kng1)
	P08934	kininogen 2(Kng2)
	P55159	paraoxonase 1(Pon1)
	Q01177	plasminogen(Plg)
	Q5M7T5	serpin family C member 1(Serpinc1)
	F7FHF3	serpin family F member 2(Serpinf2)
	P12346	transferrin(Tf)
	Q3KR94	vitronectin(Vtn)
	P16296	coagulation factor IX(F9)
	Q63207	coagulation factor X(F10)
	D3ZTE0	coagulation factor XII(F12)
	A0A0G2JY31	serpin family A member 1(Serpina1)
	Q62975	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 10(Serpina10)
	Q5I0M1	apolipoprotein H(Apoh)
Ribosome/ Translation	P61314	ribosomal protein L15(Rpl15)
	F1LZX7	ribosomal protein L17(Rpl17)
	P12001	ribosomal protein L18(Rpl18)
	P62718	ribosomal protein L18A(Rpl18a)
	P84100	ribosomal protein L19(Rpl19)
	B2RZD5	ribosomal protein L22 like 1(Rpl22l1)
	P62832	ribosomal protein L23(Rpl23)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Ribosome/ Translation (cont.)	P61354	ribosomal protein L27(Rpl27)
	P21531	ribosomal protein L3(Rpl3)
	P05426	ribosomal protein L7(Rpl7)
	P62919	ribosomal protein L8(Rpl8)
	P62250	ribosomal protein S16(Rps16)
	A0A0H2UHQ8	ribosomal protein S17(Rps17)
	A0A0H2UHH9	ribosomal protein S24(Rps24)
	Q71TY3	ribosomal protein S27(Rps27)
	P62859	ribosomal protein S28(Rps28)
	A0A0H2UHX3	ribosomal protein S4, X-linked(Rps4x)
	P29314	ribosomal protein S9(Rps9)
	A0A0G2K6I0	similar to ribosomal protein S15a(LOC691716)
	G3V6P6	RNA binding motif (RNP1, RRM) protein 3(Rbm3)
	P63245	receptor for activated C kinase 1(Rack1)
	P13084	nucleophosmin 1(Npm1)
	P48199	C-reactive protein(Crp)
Complement Cascade/Immune	P48199	C-reactive protein(Crp)
	P20760	Ig gamma chain segment(LOC679045)
	Q811M5	complement C6(C6)
	P55314	complement C8 beta chain(C8b)
	F7F389	complement C9(C9)
	Q63514	complement component 4 binding protein, alpha(C4bpa)
	P08649	complement component 4A (Rodgers blood group)(C4a)
	Q9WUW3	complement factor I(Cfi)
	P50115	S100 calcium binding protein A8(S100a8)
	P50116	S100 calcium binding protein A9(S100a9)
	Q7TQ70	fibrinogen alpha chain(Fga)
	P14480	fibrinogen beta chain(Fgb)
	P18292	coagulation factor II(F2)
	A0A0H2UHM3	haptoglobin(Hp)
	P01048	kininogen 1(Kng1)
	A0A0G2JY31	serpin family A member 1(Serpina1)
	P12346	transferrin(Tf)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Complement Cascade/Immune (cont.)	Q5I0M1	apolipoprotein H(Apoh)
	D4A488	elastase, neutrophil expressed(Elane)
	A0A0G2K3G0	histidine-rich glycoprotein(Hrg)
	G3V8L7	integrin subunit alpha M(Itgam)
	A0A0G2K1A2	myeloperoxidase(Mpo)
	P06765	platelet factor 4(Pf4)
	Q5M7T5	serpin family C member 1(Serpinc1)
	Q62975	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 10(Serpina10)
	Q3KR94	vitronectin(Vtn)
	D3ZY96	neutrophilic granule protein(Ngp)
	Q63041	pregnancy-zone protein(Pzp)
Enzymatic Activity/Serpin	Q64240	alpha-1-microglobulin/bikunin precursor(Ambp)
	D3ZBS2	inter-alpha trypsin inhibitor, heavy chain 3(Itih3)
	D3ZFH5	inter-alpha-trypsin inhibitor heavy chain 2(Itih2)
	P01048	kininogen 1(Kng1)
	P08934	kininogen 2(Kng2)
	Q5M8C3	serpin family A member 4(Serpina4)
	P31211	serpin family A member 6(Serpina6)
	Q5M7T5	serpin family C member 1(Serpinc1)
	F7FHF3	serpin family F member 2(Serpinf2)
	Q5RJR9	serpin family H member 1(Serpinh1)
	Q62975	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 10(Serpina10)
	Q3KR94	vitronectin(Vtn)
	A0A0G2JY31	serpin family A member 1(Serpina1)
Post-Translational Modifications	P62961	Y box binding protein 1(Ybx1)
	P18418	calreticulin(Calr)
	Q68FQ0	chaperonin containing TCP1 subunit 5(Cct5)
	P23514	coatomer protein complex, subunit beta 1(Copb1
	A0A140TAJ3	far upstream element binding protein 1(Fubp1)
	Q3KRF2	high density lipoprotein binding protein(Hdlbp)
	D3ZBN0	histone cluster 1, H1b(Hist1h1b)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Post-Translational Modifications (cont.)	Q6LED0	histone cluster 1, H2ai-like1(Hist1h2ail1)
	P13084	nucleophosmin 1(Npm1)
	P04182	ornithine aminotransferase
	P04785	prolyl 4-hydroxylase subunit beta(P4hb)
	P63245	receptor for activated C kinase 1(Rack1)
	Q6P7A7	ribophorin I(Rpn1)
	G3V6P6	RNA binding motif (RNP1, RRM) protein 3(Rbm3)
	A0A0G2JTV2	caldesmon 1(Cald1)
	G3V6S3	calumenin(Calu)
	Q4AEF8	coatomer protein complex, subunit gamma 1(Copg1)
	Q5RK09	eukaryotic translation initiation factor 3, subunit G(Eif3g)
	D3ZLZ7	inosine monophosphate dehydrogenase 1(Impdh1)
	A0A0G2JX79	signal sequence receptor subunit 1(Ssr1)
	O35814	stress-induced phosphoprotein 1
	P61314	ribosomal protein L15(Rpl15)
	P12001	ribosomal protein L18(Rpl18)
	P62718	ribosomal protein L18A(Rpl18a)
	P84100	ribosomal protein L19(Rpl19)
	P62832	ribosomal protein L23(Rpl23)
	P21531	ribosomal protein L3(Rpl3)
	P05426	ribosomal protein L7(Rpl7)
	A0A0H2UHQ8	ribosomal protein S17(Rps17)
	A0A0H2UHH9	ribosomal protein S24(Rps24)
	Q71TY3	ribosomal protein S27(Rps27)
	P62859	ribosomal protein S28(Rps28)
	P29314	ribosomal protein S9(Rps9)
Protein Folding, Processing and Sorting (Intracellular Transport)	A0A0G2JX79	signal sequence receptor subunit 1(Ssr1)
	A0A0G2JY31	serpin family A member 1(Serpina1)
	A0A0H2UHM3	haptoglobin(Hp)
	D3Z9M5	FK506 binding protein 7(Fkbp7)
	D3ZGT6	prolyl 4-hydroxylase subunit alpha 2(P4ha2)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	**Accession ID**	**Gene Name**
Protein Folding, Processing and Sorting (Intracellular Transport) (cont.)	D3ZH41	cytoskeleton-associated protein 4(Ckap4)
	D3ZQ74	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1(Plod1)
	D3ZZC1	thioredoxin domain containing 5(Txndc5)
	D4A9Y0	stromal cell-derived factor 2-like 1(Sdf2l1)
	G3V6S3	calumenin(Calu)
	G3V6T7	protein disulfide isomerase family A, member 4(Pdia4)
	P04785	prolyl 4-hydroxylase subunit beta(P4hb)
	P06761	heat shock protein family A member 5(Hspa5)
	P18418	calreticulin(Calr)
	P23514	coatomer protein complex, subunit beta 1(Copb1)
	P24368	peptidylprolyl isomerase B(Ppib)
	P54001	prolyl 4-hydroxylase subunit alpha 1(P4ha1)
	Q5RJR8	leucine rich repeat containing 59(Lrrc59)
	Q5RJR9	serpin family H member 1(Serpinh1)
	Q62703	reticulocalbin 2(Rcn2)
	Q63081	protein disulfide isomerase family A, member 6(Pdia6)
	Q66H80	archain 1(Arcn1)
Calcium	P48199	C-reactive protein(Crp)
	P50115	S100 calcium binding protein A8(S100a8)
	P50116	S100 calcium binding protein A9(S100a9)
	P23680	amyloid P component, serum(Apcs)
	P18418	calreticulin(Calr)
	G3V6S3	calumenin(Calu)
	P18292	coagulation factor II(F2)
	P16296	coagulation factor IX(F9)
	Q63207	coagulation factor X(F10)
	P20909	collagen type XI alpha 1 chain(Col11a1)
	Q9WUW3	complement factor I(Cfi)
	Q7TQ70	fibrinogen alpha chain(Fga)
	P02680	fibrinogen gamma chain(Fgg)
	G3V6X1	fibulin 2(Fbln2)

Table S6: Graft versus Lengthening genes sorted into designated clusters (continued)

Cluster	Accession ID	Gene Name
Calcium (cont.)	P04466	myosin light chain, phosphorylatable, fast skeletal muscle(Mylpf)
	P55159	paraoxonase 1(Pon1)
	G3V6T7	protein disulfide isomerase family A, member 4(Pdia4)
	Q63081	protein disulfide isomerase family A, member 6(Pdia6)
	Q62703	reticulocalbin 2(Rcn2)
	A0A0G2JX79	signal sequence receptor subunit 1(Ssr1)
ECM/ Focal Adhesion	A0A0G2K1L0	tenascin C(Tnc)
	A0A0G2KAJ7	collagen type XII alpha 1 chain(Col12a1)
	A0A0H2UHL3	AE binding protein 1(Aebp1)
	D3ZH41	cytoskeleton-associated protein 4(Ckap4)
	F1LR10	LIM domain and actin binding 1(Lima1)
	F1M265	palladin, cytoskeletal associated protein(Palld)
	G3V6X1	fibulin 2(Fbln2)
	P04785	prolyl 4-hydroxylase subunit beta(P4hb)
	P05426	ribosomal protein L7(Rpl7)
	P06761	heat shock protein family A member 5(Hspa5)
	P13084	nucleophosmin 1(Npm1)
	P18292	coagulation factor II(F2)
	P18418	calreticulin(Calr)
	P20909	collagen type XI alpha 1 chain(Col11a1)
	P21531	ribosomal protein L3(Rpl3)
	P23680	amyloid P component, serum(Apcs)
	P24368	peptidylprolyl isomerase B(Ppib)
	P29314	ribosomal protein S9(Rps9)
	P47853	biglycan(Bgn)
	P50116	S100 calcium binding protein A9(S100a9)
	Q3KR94	vitronectin(Vtn)
	Q5I0M1	apolipoprotein H(Apoh)
	Q5U1Y2	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)(Rac2)
	Q6P0K8	junction plakoglobin(Jup)

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